

**Principles of  
PEDIATRIC AND  
NEONATAL EMERGENCIES**



# Principles of PEDIATRIC AND NEONATAL EMERGENCIES

**Third Edition**

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# Foreword

The subspecialty of Pediatric and Neonatal Emergencies has seen tremendous growth in the last few years. This is one field where the treating physician is running against time. The timely treatment is vital for intact survival of sufferers.

The Indian Pediatrics Book *Principles of Pediatric and Neonatal Emergencies* has addressed this issue very well in its last two issues. There is a need to improve the understanding about the very basic behind handling these emergencies. The third edition of this book published by Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India has included recent developments in this field.

Contributors of this book are well-known experts from respective subspecialties and from various parts of our country. Editor-in-Chief, Dr Panna Choudhury, has done a great job in putting together all articles in a common editorial style. I congratulate other editors Dr Arvind Bagga, Dr Krishan Chugh, Dr Siddarth Ramji and Dr Piyush Gupta also in bringing out this book which covers all aspects of emergency pediatrics. There is a good combination of evidence and experience in dealing with all topics included in this book.

The book is written to be relevant to the needs of the hour. It is reasonably detailed and is a good blend of latest developments in the management approach in various pediatric and neonatal emergencies within the constraints of resources and equipment faced at most of the places.

I am sure this book will fulfill all needs of both, the practicing pediatricians and postgraduate students in dealing with emergencies.



**Deepak Ugra MD**  
Consultant Pediatrician  
Lilavati Hospital and Research Centre, Mumbai  
President, Indian Academy of Pediatrics – 2010



# Preface to the Third Edition

We are happy to present the third edition of *Principles of Pediatric and Neonatal Emergencies*. The present edition continues with its tradition of serving the needs of physicians involved in the immediate care of children and neonates with life-threatening illnesses. The book has been extensively revised and updated, to reflect the current standards of emergency care relevant to the needs of pediatricians working in developing countries.

This book continues to have the privilege of scholarly writings from illustrious authors, across the country. We welcome several new colleagues and express gratitude for their contributions to this edition. A number of chapters have been completely rewritten, including those on hematological disorders, upper gastrointestinal bleeding, neonatal surgical disorders, and ophthalmologic emergencies. Inputs from consensus and expert statements of the *Academy* have been incorporated for management of malaria and severe malnutrition. The emphasis continues to be on presenting management of common and important emergencies affecting children. Detailed discussions on pathophysiology have been avoided.

We hope that this text shall continue to serve the needs of pediatricians, physicians, resident doctors, other trainees and be a part of all pediatric emergency units. As before, all the royalties generated from the sale of the book shall pass onto the journal, *Indian Pediatrics*.

Finally, we thank Mr RG Bhardwaj and Ms Veena Arora for secretarial assistance and are grateful to M/s Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India for their guidance and expeditious publication.

New Delhi  
January 2011

**Panna Chaudhury**  
**Arvind Bagga**  
**Krishan Chugh**  
**Siddharth Ramji**  
**Piyush Gupta**



# Preface to the First Edition

For the practitioners of pediatric care, emergencies in children and neonates are an inescapable fact in their daily routine. Better understanding of pathophysiology and drug metabolism and availability of newer investigative and diagnostic facilities have led to the creation of new frontiers in this important subject. Prompt recognition and appropriate management of these emergencies make the difference between life and death. A variety of traditional western textbooks provide information on this topic. However, this updated knowledge is often not relevant for the developing world situation.

Inspired by the success of its earlier venture titled *Pediatric and Neonatal Emergencies*, Indian Pediatrics—the official journal of the Indian Academy of Pediatrics, took up the formidable challenge of providing comprehensive state-of-the-art information on the subject which would also be pertinent in the Indian milieu. The present publication has been extensively updated and enlarged from the earlier experiment which now appears like a distant cousin. Guidelines have also been incorporated for organization of pediatric intensive care units.

We are indebted to the group of distinguished contributors who promptly responded to our call, despite constraints of their busy schedules.

This volume is intended for pediatricians and physicians sharing initial contact with emergencies in children and neonates as well as those responsible for the subsequent critical and intensive care. Postgraduate students should find it of particular help. The book should also prove invaluable for all current and intended pediatric emergency care units.

The editors share of financial benefits from the royalties would accrue to the *Indian Pediatrics* in an attempt to make the journal self-sufficient. We are grateful to the publishers for ensuring the high quality of the book as well as its expeditious publication.

This volume is dedicated to the memory of late Dr Man Mohan, an active associate in the earlier venture.

New Delhi  
February, 1994

**HPS Sachdev**  
**RK Puri**  
**A Bagga**  
**P Choudhury**



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S e c t i o n

1



# Approach to Child in Emergency Department

Krishan Chugh

## PEDIATRICIAN'S CONTACT WITH THE SICK CHILD

The anxious family members bring children to the physician as soon as they perceive that the child has a serious illness or injury. The physician or the pediatrician may be in a sophisticated, well equipped and well managed pediatric hospital, in a general hospital, a small nursing home or just an outpatient facility — the pediatrician's office or clinic. No matter where he is the responsibilities of the pediatrician go far beyond just providing the immediate medical attention to the sick child. Many a times, the family is totally unaware about the illness of the child or its true seriousness because the child may only be crying inconsolably or conversely be very lethargic. The infant may not be able to communicate at all to the parents and their anxiety, and often guilt, create a situation where by the "family is the patient" and not just the child. At such a time the pediatrician has to give a look of confidence and competence while simultaneously showing understanding and empathy. Hence, the importance of initial encounter of the pediatrician with the sick child and his family cannot be over emphasized.

The pediatrician has to understand the anxieties and fears of sick children and their families when they come to him (Table 1.1). The fears of the parents and the family may be different from that of the child. He has to formulate an approach to the child and the family taking into consideration those factors within the limits of the time and facilities available. The following basic principles facilitate the examination and treatment of the sick children:<sup>1,2</sup>

1. Remain calm and confident.
2. Establish rapport with the parent and the child.
3. Be direct and honest.
4. Do not separate the parent and the child.
5. Make as many observations as possible without touching the child.

6. Be flexible in the order and method of examination. It is not absolutely necessary to examine the child in the order taught in undergraduate teaching days. The information gathered in any practical way can later on be synthesized into a systematic outline.
7. Examination that produces pain or discomfort should be performed last of all, e.g. examination of throat with a spatula or examination of ears.
8. Keep the child and care taker informed.
9. Be kind and provide feedback and reassurance.

When applying these principles to an Indian context, the family scenario of "elders" accompanying the child must be taken into account. It must be remembered that often they and not the parents of the child are decision makers. Similarly, the importance of an individual who spends maximum time with the child as a caregiver should not be forgotten when eliciting a history.

**Table 1.1: Fears of the family and the child**

### *Fears of the family*

1. Fear of death of the child
2. Fear of serious illness
3. Fear of incurable illness
4. Fear of the unknown: What next?
5. Fear of separation of child for examination/ procedure/treatment
6. Fear of unknown and possibly not fully competent staff caring for the child
7. Fear of unfamiliar environment
8. Fear of machines/instruments
9. Fear of being told "sickness is because of your negligence"
10. Fear of economic loss because of child's illness

### *Fears of the child (are age dependent)*

1. Stranger anxiety
2. Separation from parents
3. Pain
4. Fear of the unknown
5. Fear of unfamiliar environment

### AGE-RELATED APPROACH

Optimum physical examination of an infant or child requires his co-operation. At least, he should not be crying and struggling. Hence, all efforts should be made to gain the confidence and trust of the child. The few minutes required for this purpose may not be available in a critically ill patient in whom measures for resuscitation must be instituted immediately.<sup>3</sup>

While every pediatrician develops his own methods and “tricks” for overcoming the initial resistance of the child, some general recommendations can be made. These techniques are based on an understanding of the age-related fears and the important developmental issues at that age. This developmental approach to pediatric emergency patient (Table 1.2) has been found quite useful.

Pre-school children are generally the most difficult patients. Their fears of separation and pain are particularly strong. However, they can be won over by encouraging fantasy, play and participation in examination. Simple explanation of the procedure being performed is helpful. School age children want to participate in their own care. Thus, they should be given choices. For example, when auscultating chest, the child may be asked whether he would prefer examination lying down or sitting. Each step must be explained to them and then their co-operation can be sought more easily.

In contrast to these age groups, the two extremes of pediatric age groups are easier to examine. For neonates, a comfortable environment and warm hand are all that is required. Over the next few months the infants can be engaged by sounds produced by the examiner or some bright colored objects or toys shown to them. Similarly, adolescents do not offer any difficulty in examination provided they are assured of confidentiality and autonomy. Respect for their privacy must be fully honored. If the pediatrician’s gender is not same as that of the adolescent, it may be a good idea to have a paraclinical worker or a colleague of the adolescent patient’s gender to be inside the examination room. Choice of having the parents inside should be left to the adolescent patient.

At all other ages it is preferable to have the parents/ caregivers around when the patient is being examined. In fact, as much of the examination as possible should be performed with the child in the mother’s custody. At times it may become necessary to examine a restless child when being given breast feed. For this, it is our duty to provide privacy to the mother.

### THE COMPLETE PHYSICAL EXAMINATION

The importance of a complete head to toe examination in the emergency room must be appreciated by all those working there (Table 1.3). This is true even when an obvious diagnosis has been made and the patient is apparently improving on the immediate treatment

**Table 1.2: Development approach to pediatric emergency patient**

Age	Important development issues	Fears	Useful techniques
Infancy 0-1	Minimal language: Feel an extension of parents, sensitive to physical environment	Stranger anxiety	Keep parents in sight and touch, avoid hunger, use warm hands, keep room warm
Toddler 1-3	Receptive language more advanced than expressive, see themselves as individuals, assertive will	Brief separation pain	Maintain verbal communication, examine in parent’s lap, allow some choices when possible
Pre-school 3-5	Excellent expressive skills for thoughts and feelings, rich fantasy life, magical thinking, strong concept of self	Long separation pain	Allow expression, encourage fantasy and play, encourage participation in care
School age 5-10	Fully developed language, understanding of body structure and function, able to reason and compromise experience with self control, incomplete understanding of death	Disfigurement loss of function death	Explain procedures, explain pathophysiology and treatment, project positive outcome, stress child’s ability to master situation, respect physical modesty
Adolescence 10-19	Self-determination decision making, peer group important, realistic view of death	Loss of autonomy loss of peer acceptance, death	Allow choices and control stress acceptance by peers, respect autonomy, stress confidentiality

**Table 1.3: Commonly missed areas in a complete examination**

Area	Examples
1. Ear: otoscopic examination	- Otitis media
2. Genitalia	- Torsion testis
3. Anal region	- Anal fissure
4. Pupils	- Poisoning
5. Blood pressure	- Shock, hypertensive crisis
6. Femoral pulses	- Coarctation of aorta
7. Skin covered by undergarments	- Petechiae

provided. For example, a toddler has been brought for high fever and irritability. On examination clear evidence of upper respiratory tract infection is found. Antipyretics (which also have analgesic effects) are given along with tepid sponging. Child's fever comes down. He is not restless any more and is sent home. Such a child is likely to return back if the associated acute otitis media was missed.

In the same context, unclothing the child is an important step to facilitate examination of the covered areas, especially the genitalia. Again, for such an examination, especially for adolescents, adequate privacy must be provided.

There is a general tendency of the parents to over clothe their young children, more so during winter months. This could hinder optimum examination of even the chest or the abdomen.

A 6 months old child was brought to the casualty department for fever and excessive crying. He had 'neck-stiffness'. All arrangements for performing a lumbar puncture were made. Child's high-neck pullover was removed for doing the lumbar puncture and he suddenly stopped crying and became cheerful. Gone was his 'neck-stiffness'.

Many a times a complete examination is not possible during the first attempt. The child may be uncooperative or he may be having a problem that needs immediate attention, e.g. a convulsing child. Obviously, the pediatrician must return to this patient at another appropriate occasion to complete the examination.

There are other occasions when a complete examination has indeed been performed but a re-check after a few minutes may be necessary. For example, a child may have apparent tachycardia with fever raising doubts about say myocarditis. One hour later when his fever has been controlled tachycardia may settle down completely. Thus, repeated examinations may be required in some children to get the complete picture.

## IDENTIFICATION OF AN ACUTELY ILL CHILD

Experience as well as statistics show that a large number of patients coming to the emergency department do not have any life-threatening problem. Afterall, unlike the pediatric intensive care units (PICUs), emergency departments (EDs) are for sick or injured children and not necessarily for dying children. However, this at times puts the personnel of the ED into 'complacency'. They may fail to respond with appropriate speed and urgency when a patient requiring say cardiopulmonary resuscitation, arrives in the ED. Thus, it is important to train all those involved in the care of acutely sick children to recognize life-threatening situations.

To identify an acute emergency the pediatrician has his usual tools of history taking, observation of the child's behavior, physical examination, bedside monitors and judicious use of laboratory parameters. These when collated together and analyzed may enable the pediatrician to institute appropriate therapeutic measures. At times those results may prompt him to perform or prescribe further tests or ask more questions in the history. Thus, dilated pupils in a child with inappropriate behavior would call for taking history about possible *dhatura* poisoning.

Change in behavior of the child or his response to stimuli given by the parents or the examiner during an examination and observation period can provide important clues to the overall degree of sickness of the child. Consolability of a child who is irritable is an example. If the child who was crying and fussing as his first response on contact with a doctor can be quietened down and made to submit to an examination would indicate a normal behavioral response and would generally go against an immediately serious illness. However, it must be remembered that the expected response would vary according to the age of the child. Certain observational scales have been developed and validated to identify serious illness in febrile children. One such scale<sup>4</sup> takes six items into consideration, viz., quality of cry, reaction to parent stimulation, variation in state of wakefulness and sleep, color, hydration and response to social overtures.

Another recently described<sup>5</sup> set of criteria has been found to be useful in evaluating children with fever and petechiae. The criteria taken into consideration were shock (capillary refill time greater than 2 seconds and/or hypotension), irritability (inconsolable crying or screaming), lethargy (as determined subjectively by the carer, nursing or medical staff), abnormality of the peripheral blood white cells count (< 5,000 or > 15,000 per cumm) and elevation of C-reactive protein (CRP) (>5 mg/l). These criteria were labeled as "ILL- criteria"

(irritability, lethargy, low capillary refill) and were found to have a high sensitivity for identifying children with positive blood cultures. Sensitivity was good even when CRP was not included. It has been shown in several earlier studies that taken individually these criteria have limitations.<sup>6-8</sup>

Age considerations in assessing a child with fever are also important. Thus, febrile young infants less than 3 months age are more likely to have serious illness than an older child. Although, it is well known that the common viral fever can also cause high fever, generally the risk of bacteremia increases as the degree of fever increases, but even at  $> 40^{\circ}\text{C}$  the risk is only 7 percent.<sup>9</sup>

### CPR IN EMERGENCY DEPARTMENT

Cardiopulmonary resuscitation (CPR) performed in a child who has already had cardiac arrest is a labor intensive, tension producing procedure that more often than not is a frustrating exercise. Chances of intact survival are abysmally low.<sup>9-13</sup> Thus, it is very important to recognize life-threatening illness immediately and intervene rapidly. Unlike the methods described above for identification of an acutely sick child, recognition of a life-threatening emergency has to be done quickly. There may be only minimal time to ask a focussed history with the details left to a later point of time. Examination also has to be performed in a short period of time. It is better to have a structured approach. The standard alphabetical order of A for airway, B for breathing and C for circulation is the most appropriate method. These are followed by D for disability prevention and E for exposure (Table 1.4).

### THE DEATH OF A CHILD IN THE EMERGENCY DEPARTMENT

After a child has died, emergency physicians must rapidly transit from treating the patient to caring for the survivors. The success of this transition is dependent on many variables, including the demands of other patients in the department, the circumstances surrounding the death, and the physician's level of skill, sensitivity, and experience. Additional demands on the physician might include notifying the proper authorities in the case of violent death or child maltreatment, the discussion of a postmortem examination, and the request for tissue or organ donation. The physician should speak with the family, if at all possible, during resuscitation to establish contact before informing them of the death of their child.<sup>14</sup> If the family arrives after the patient is pronounced dead, the physician should inform the

**Table 1.4: Pediatric primary survey and resuscitation measures**

- A. Airway/Cervical Spine Control
  - Assess airway patency
    - If patient conscious-maintain position of comfort
    - If compromised-position, suction oral airway
    - If unobtainable-oral endotracheal intubation
  - Maintain cervical spine in neutral position with manual immobilization, if head/facial trauma or high-risk injury mechanism
- B. Breathing
  - Assess respiratory rate, color, work of breathing, mental status
  - If respiratory effort adequate-administer high-flow supplemental oxygen
  - If respiratory effort inadequate—bag-valve-mask ventilation with 100 percent oxygen, naso/orogastric tube, consider intubation
- C. Circulation/Hemorrhage Control
  - Assess heart rate, pulse quality, color, skin signs, mental status
  - If perfusion adequate-apply cardiac monitor, establish IV access, direct pressure to bleeding sites
  - If signs of shock-establish vascular access (IV / IO), isotonic fluid bolus, baseline laboratory studies, cardiac monitor, urinary catheter
  - If ongoing hemorrhage suspected and continued signs of shock-blood transfusion and surgical consultation
- D. Disability (Neurologic Status)
  - Assess pupillary function, mental status (AVPU)
  - If decreased level of consciousness—reassess and optimize oxygenation, ventilation, circulation.
  - If increased ICP suspected—elevate head of bed, consider mild hyperventilation, neurosurgical consultation
- E. Exposure
  - Remove clothing for complete evaluation. Prevent heat loss with blankets, heat lamps, radiant warmer

AVPU = alertness, response to voice, response to pain, unresponsive; ICP = intracranial pressure; IO = intraosseous; IV = intravenous

family of the child's death and of the resuscitative efforts that were made. It is important that no conflicting information be given to the family by the emergency care team.

### Family Presence in Resuscitations

A study of family presence during resuscitation attempts showed that 97% would choose to witness it again, 76% believed their grieving was made easier, 67%

thought their presence was a benefit to the patient, and 100% felt confident that everything possible had been done to save their family member.<sup>15</sup> Although some health care providers feel at ease when family members are present, ED staff, if aware of these statistics, might understand the importance of offering families the option of being present in these situations, although some might decline to attend.

### Notification of Death

Before declaring death of a child always identify yourself the family members present. Attempt to have parents together. Sit down and physically place yourself in the proximity of the family unless the situation appears hostile. Always have support personnel with you. Have a scripted sentence that you feel comfortable with that clearly states that the child “died” or was pronounced dead. An example is, “Despite everything we could do, we couldn’t save your child’s life. He/she (use the child’s name here) died a few moments ago.” Avoid language such as “passed on,” “didn’t make it,” or “they’re with God now.” These euphemisms might not be understood by family and can create confusion and ultimately suspicion of the credibility of the medical staff. If the child is alive on arrival in the ED, family should be informed of the patient’s progress frequently or as often as deemed appropriate and staff is able. More importantly, if the child is expected to die, family should be informed that resuscitation efforts are proceeding but that the child is not expected to survive.<sup>16</sup> Allow grief response and facilitate grief. If you are comfortable, give physical support (hold hands, touch the shoulder) to family members. Stay close and supportive.

According to a survey,<sup>17</sup> after unexpected death of an infant in family interventions that were found useful in counseling were:

1. Openly accept an individual’s grief reactions.
2. Allow the family an opportunity to vocalize their feelings.
3. Clarify misconceptions.
4. Allow the family to hold or to be in the room alone with their dead infant.
5. Provide a private place for the family to gather.
6. Provide an explanation for the cause of the death and help them with funeral arrangements.

Allow the family to decide whether to view the child’s body at this time. Respect their decision if they choose not to view the body but also realize that seeing their child before and after death can help parents begin

grieving and reach closure. Prepare the body for viewing in a private viewing area with consideration for what the medical examiner might require to preserve potential evidence. Prepare the family for what they will experience and ensure that a qualified ED staff member will assist them.

As each life is unique, so is each death. Not unlike every other aspect of emergency medicine, individualized family-centered care during the death of a child calls for compassion, tact, and flexibility overlying the template of medical and procedural responsibility. Emergency caregivers are not immune to grief and stress responses and must avail themselves of opportunities to promote the best personal grieving and healing while providing the best care to survivors on the death of a child.

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# Ethical and Legal Issues in Emergency Care

Krishan Chugh

## ETHICS

Ethics has been defined as moral beliefs and rules about right and wrong. It is important to consider the ethical issues because values of patients, families, doctors, other health care professionals and those of the society as a whole have profound influence on the practice of pediatric emergency medicine.

### Medical Ethics is based on Sound Principles

1. *Do well*: The care that the physician provides to the patient should benefit the patient.
2. *Do no harm*: Under this principle the physician should ensure that his actions would not harm the patient.
3. *Respect autonomy*: All individuals are not alike. They may differ in their beliefs and respond differently to the same situation. Thus, the patient and his family should be allowed to decide what is good for them.
4. *Be just and fair*: The physician should not deny or institute treatment on the basis of factors (e.g. paying capacity) other than the actual medical condition of the patient.

All attempts should be made by the physician to follow these principles at all stages of care in the pediatric emergency department. In order to properly care for patients, the emergency physician has an obligation to understand ethical principles and the reasoning process one must go through to resolve an ethical dilemma. Emergency physicians face such complex decisions on a routine basis. Ethical reasoning skills are obviously a core competence in emergency medicine, even if easy answers are elusive.<sup>1</sup>

## LEGAL RESPONSIBILITIES

In the process of providing emergency medical service to a patient, pediatrician has to keep in mind his legal duties towards the patient. The basic principles are:

1. Physician cannot refuse emergency treatment to a patient, irrespective of his cast, creed, geographical

placement, ability to pay, etc. This is in contrast to the practice of medicine in his clinic in a non-emergency situation where the physician can choose his patients, say according to their capacity to pay his fee.

2. The physician may still be held responsible for not having provided the emergency treatment even when the patient (in pediatrics, the parents of the child patient) refused to be treated by him. The argument runs that the patient would not have refused treatment had he understood the seriousness of his illness. Thus, recording of vital signs and general condition remains the responsibility of the emergency department physician even if the patient is waiting for a senior doctor or his private doctor to arrive.
3. When an individual brings a case against a physician, it is the responsibility of that individual (the plaintiff) to prove negligence, etc. by the physician (defendant).
4. It is the responsibility of the emergency physician to ensure that the patient gets definitive care after the emergency care. Thus if, the emergency physician terminates the physician-patient relationship without the patient's consent and without giving the patient sufficient opportunity to secure the services of another competent physician, it will be considered as a case of abandonment. This also applies to transfer of the patient from one emergency department to another.
5. The physician has a duty to report certain diseases to the authorities, like designated infectious diseases.
6. The physician may be called upon to testify in the court in a case where he was the examining physician when the patient was brought to the emergency department.

## TYPES OF LEGAL RISKS

Both civil and criminal cases may be brought against the emergency pediatrician. Civil suits generally are brought for procuring compensation for a death or

disability caused during treatment. Criminal charges may be leveled against the physician for negligence resulting in death or disability. If found guilty, the physician may have to serve a term in jail.

The individual suing the physician has to first prove that the physician did not follow the 'standard of care'. This would amount to negligence. Then, it has to be established that this negligence was the cause of the injury or disability suffered by the patient.

### LEGAL RISK FACTORS

Pediatricians who care for children requiring emergency treatment are at a greater risk for being dragged to the court by the family. This is because of several reasons:

1. Chance of death or permanent disability is more in children brought to the emergency department by virtue of greater seriousness of the illness.
2. The medical problems brought to the emergency physician are complex. Often, he is working under stress, may be for long hours and under inadequate conditions, e.g. too much noise and disturbance, too many serious patients to be looked after simultaneously, etc. These factors increase the chances of error.
3. There is no previous, ongoing patient-doctor relationship before the emergency encounter. Thus, the family may not have the same 'faith' in the emergency pediatrician, which it has in the regular pediatrician. In fact, in general the speciality of emergency medicine and the emergency medical specialist is not well understood by our patients.<sup>2</sup>
4. The family members are under stress and they may have a guilt-complex. They may feel responsible for their child's critical condition. This provokes them to retaliate and put the blame on the most obvious person across, i.e. the physician.
5. The parents may have waited for long before the physician could attend to them as he was looking after other seriously ill patients. The anger is directed towards the physician. Thus, it is important for the nurses and other paramedical staff to recognize a critically ill child as soon as he is brought to the emergency department or even a pediatrician's clinic so that he gets top priority.
6. The courts may allow large sum of money as compensation to the family taking into consideration the long years that the child may have lived. This fact may also induce the parents to proceed against the pediatrician in the court.

### LEGAL AND ETHICAL ISSUES IN CONSENT

When a patient approaches a physician, consent for physical examination is implied, provided this does not harm the patient. Thus, when a child is brought to the emergency pediatrician, he goes ahead and performs a physical examination without getting a signed consent. A written consent, however, becomes necessary when the physician is going to perform a procedure or hospitalize the child. Generally, blanket consent is not considered sufficient legally, nor is it ethical. Thus "I am willing for the hospitalization and treatment, including diagnostic and therapeutic procedures on my child" is not a complete consent. These words did not name the procedure nor did they explain the risks involved. Insufficient information invalidates the consent.

From such discussions, concept of "informed consent" took birth. The quality of the consent given by the parents or guardian became the focus of attention. Patient's parents have to be regarded as informed consumers. An informed consent is expected to cover the following:

- Diagnosis
- Nature and purpose of proposed procedure or treatment
- Risks, side effects and consequence of the proposed procedure
- Reasonably available alternatives and their risks
- Expected outcome without the procedure.

Such a consent form would obviously be quite long. But, it should not contain any technical language and medical terms, which an ordinary person cannot understand. Further, an informed consent should be in the language that the patient's parents can understand.

Consent can be given/signed by any one of the parents and in their absence by the guardian. The guardian may be a relative, a neighbor, a teacher or the child's incharge in the daycare center. However, it is essential that the person giving the consent should be an adult. Minors cannot give consent- neither for themselves nor for others.

In a life-threatening situation the physician may not wait for a formal consent and may institute the essential measures immediately. In such a situation the pediatrician is more likely to be sued for withholding the life saving treatment rather than for providing them without parental consent.

An informed consent has four essential features: Competency, information, understanding and voluntariness.<sup>3</sup> Competency implies that the person

giving consent has medical decisional capacity. Disagreement with the physician's decisions does not necessarily mean incompetency. Thus, a reasonably intelligent father who is not under the effect of alcohol/drugs, who refuses a lumbar puncture to "rule out" meningitis in a child with seizures and fever is not incompetent.

Once it is presumed that the parent is competent his consent is based mainly on the information provided regarding the disease, procedures, risks, side effects and need of the procedure. The information may need to be presented repeatedly or even in an audiovisual form.<sup>4</sup>

It has been found that physicians generally overestimate the capability of their patients to fully understand the information provided.<sup>5</sup> It is the duty of the physician to be reasonably sure that the parent understands and comprehends the information provided to him regarding his child's treatment.

Finally, the consent should not be given under any direct or indirect pressure from the physician to accept the treatment that is the physician's favorite when other equally good alternatives exist. The parents should be given sufficient time to understand and digest the information provided. However, time may be a constraint in some acute emergencies.

### ETHICAL AND LEGAL ISSUES IN TRAINING AND RESEARCH

Unique situations are encountered in the pediatric emergency department with regard to ethical conduct of research.<sup>6</sup> There are fears in the minds of many parents and relatives that their child is being made a subject of some experiment when being treated in a large hospital, especially, a teaching hospital. This indeed may be true. However, the important issue is somewhat different: Are the child's interests being harmed by being enrolled in the "study" or the 'experiment' (in the parent's language). If the answer to this question is in the affirmative an ethical wrong is being done—the harm may be only financial. Thus, no patient can be denied a treatment or a procedure that is the 'standard of care' in similar circumstances in other institutions. Yes, an additional mode of treatment may be given to some and denied to others. Here too, this treatment should be reasonably safe.

The senior doctors often encourage their junior colleagues to 'practice' procedures in dead or dying patients. Endotracheal intubation is one such example. It is agreed by all that the newcomers have to be given "hands on training" and a recently dead patient

provides such an opportunity. However, the sensitivities of the family should be taken into consideration even at this stage. It must be ensured that they are not watching the 'trials' by a new resident doctor on their child's dead body directly or through a window or a displaced curtain.

The issue of using a dying (but not dead) patient for a similar purpose is more complex. A new inexperienced resident doctor may be assigned the duty of inserting a central venous catheter in a child who is dying and has no reasonable chance of survival. Again, the sensitivities of the family should be respected and the procedure performed only under direct supervision of the experienced senior physician. Mercifully, with the availability of manekins and models such situations arise much less frequently now.

Ethically, it is agreed that training must occur and education must go on. Otherwise, after a period of time we would have no trained personnel at all. Benefits of an academic program are tremendous to the patient community also. But, we must ensure that concerns of the family in this regard are adequately addressed.

### ETHICAL AND LEGAL ISSUES IN CPR

Cardiopulmonary resuscitation (CPR) in a patient who has suffered cardiorespiratory arrest is a very difficult area from ethical and legal angles. Decisions must be made rapidly and often must be based on suboptimal levels of information available at the time.<sup>7</sup> When a child is 'brought dead', i.e., heartbeats are not audible and there is no respiration, should the emergency pediatrician carry out CPR in every single case? The body may be cold, suggesting long delay, CPR is likely to be futile. However, the body may be cold because of exposure to cold environment or drowning in cold water. Next, should the treating physician ask almost whole of his team to come and participate in CPR even when there are more easily salvageable patients needing immediate attention in the emergency ward. Further, once CPR has been started, how long should it be continued if there is no response at all. And, what about the situation where momentarily an apparently perfusing cardiac rhythm appears repeatedly. Well, most studies show that continuation of CPR beyond 25 minutes is futile in such circumstances.<sup>8</sup>

During CPR or as it is being started it is advisable to keep the family informed as best as possible. There have been instances where parents have blamed the CPR for their child's death. A few minutes spent in explaining why and how of CPR by one of the medical staff members will virtually eliminate the chances of such an occurrence.

### ETHICAL AND LEGAL ISSUES IN WITHHOLDING LIFE SUPPORT

Doctor is expected to 'give life' and not 'take it away'. Hence, physicians are inclined to continue life support measures even when chance of survival is virtually zero. Law does not empower the physician to withhold or withdraw life support. Till this stage, the decisions to be made by the physician are based on clear enunciation. But, beyond this the lines get blurred. What should the answer be to the question of such a child's father: "Should I take the child home". Best way out is to discuss all the aspects with the family members, give them time to again think over the matter in the light of the discussion and again sit down with the family to help them reach a decision.

### ETHICAL AND LEGAL ISSUES IN DEATH

Organ transplant has raised several legal and ethical issues related to death in the hospital or to patients brought dead to the hospitals. In our country law is silent regarding withdrawal of life support in a patient who is brain dead. However, ethically it is considered fair. But, all attempts should be made to explain the circumstance to the parents and make them a part of the decision making.<sup>9</sup> Once they are convinced the subject of organ donation can be broached. Only when the parents are willing can the subject be discussed any further. It is generally agreed that physicians are not making sufficient efforts to get the parents of dying and dead children to donate the organs of their child.

### HOSPITAL ETHICS COMMITTEES

Most large hospitals have their own ethics committees which help in providing guidelines about the 'grey areas' of medical practice. The assumption is that the emergency physician by virtue of basic human nature and because of direct involvement in a particular situation may get carried away and make a biased decision. On the other hand a group of dispassionate but well-informed individuals who constitute the ethics committee can guide that individual through the difficult situations. Such committees develop consensus on contentious issues. In recent years their functions have been evaluated in USA. It has been observed that they have decreased the problem of undertreatment and replaced it by the problem of over treatment.<sup>10,11</sup>

### THE MEDICAL RECORD

The case sheet, as the medical record is often called, is an important document for the treatment of the child

in the emergency department as well as in the court of law, should a legal dispute arise. The record should have the name, address, father's name and the hospital number on each page. All entries should be dated and timed. The condition of a seriously ill child changes quite rapidly and the medical record should be able to reflect that clearly. Sweeping statements like on examination nothing abnormal diagnosed (O/E-nad) in seriously ill child give an impression of being careless in both examining the child as well as recording. Some important positive as well as negative findings should always be recorded. The physician's notes should not be at variance with that of the nurse or of another physician/specialist. All major events during the patient's stay in the emergency department should be recorded with time and date clearly mentioned. In a busy emergency department it is acceptable to write a detailed note at periodic intervals in which all that has been observed and done is noted with time of each action and observation clearly recorded.

In the court of law, the battle is fought almost entirely on the basis of the entries made in the medical record. Hence, its legal importance cannot be over emphasized. It has been said that a good medical record is the physician's best defence. Indeed, the law suit may be filed several months or even years later and the physician may remember very little about the case. Even the plaintiff's lawyer is likely to look at the case record and then decide whether there are enough lacunae for him to offer a reasonable chance of success to his client. A complete, well documented record that convincingly gives the diagnosis and records actions which are appropriate for the diagnosis and the clinical condition of the patient suggests to the lawyer not to proceed any further.

No attempt should be made to "doctor" or "enhance", i.e., change, add or delete entries in the record at a later stage. The judges tend to take this seriously. The lawyers argue that only the guilty conscience would attempt to alter the record. Even at the time when physician was writing the record in the emergency department any 'corrections' should be neatly made. The part/word to be deleted should be struck off by one single line only and no attempt should be made to completely conceal what was originally written.

### STEPS FOR SUIT PREVENTION

1. Follow the three D's carefully—duty, dialogue (communication with the patient's family) and documentation.

2. Keep yourself informed about the legal aspects of medicine.
3. Perform chart review with pre-established medical and legal criteria.
4. Know how to contact the administrator and a lawyer 24 hours a day, 7 days a week.
5. Know how to obtain a court order 24 hours a day 7 days a week or what to do if an order cannot be obtained.
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# Organization of Pediatric Emergency Services

Krishan Chugh

Emergency medical services for children is an all-encompassing, multidisciplinary system that includes parents, primary care providers, prehospital care providers and transport system, community hospital care and tertiary care referral center emergency departments, and pediatric in-patient units including critical care facilities.<sup>1</sup>

Assessment of emergency medical care in New Delhi<sup>2</sup> and Chennai<sup>3</sup> in India confirmed the general impression that the organized prehospital care is scanty and that the development of emergency medicine is still in its earliest stages.

Organization of such comprehensive pediatric emergency services at a national level or community level is a task that requires planning, resources, manpower and political will. Many models are available from the western countries, which can be adopted for our country with suitable modifications. However, for the present, limitation of resources would not permit us to take any such exercise at a large scale. But an attempt can be made to interconnect and link the centers where such facilities are available with each other and with other smaller centers in the peripheral places so as to provide a better service to people within the given resources. Thus, large hospitals with well equipped pediatric emergency departments can be encouraged to form linkages with the smaller centers as well as individual private practices within their area. Referral from them, especially during 'non-working hours' and nights can serve as the admission base of the larger hospital. This will be a welcome step for the large private sector hospitals whose pediatric departments rarely have a high bed occupancy ratio.

While the organization of pediatric emergency services at the national level will have to be done by the health administrators, all pediatricians have a role to play in the development of these services within their own institutions.

## PEDIATRIC EMERGENCY SERVICE IN A GENERAL/PEDIATRIC HOSPITAL

The services to be provided by an Emergency Department (ED) should be planned according to the needs of the community that it proposes to serve. Thus, it is important to study the epidemiology of diseases in the area. The size of population is a determinant of the expected patient number. Sociocultural factors, customs and beliefs of the population should also be taken into consideration when planning a pediatric emergency department.<sup>4</sup> There are very few hospitals where services are provided exclusively to children. Such hospitals are the centers where an 'ideal' pediatric emergency department can be set up. It can be safely assumed that pediatricians, who have adequate training in pediatrics, will manage medical services in such a hospital and its emergency department. However, that may not be enough. The medical personnel directly involved in the care of sick children should have a special training in pediatric emergency management and in pediatric advanced life support (PALS). Core knowledge for these can be obtained from standardized courses like PALS course of the American Heart Association or the APLS (Advanced Pediatric Life Support) course of the American Academy of Pediatrics and the American college of Emergency Physicians. These courses also provide an opportunity to practice the skills required in the emergency departments on manikins. Having acquired the core knowledge and the skills these pediatricians can further improve their performance by an analysis of the management they provided when dealing with emergencies in their own department. These specialists should take recertification in such courses at recommended intervals to maintain their skills and be aware of the latest developments in this field.

While a dedicated team should continue to 'man' the emergency department twenty-four hours, it is understandable that new resident doctors and postgraduate students will be added at regular

intervals in such institutions. These students and residents should be fully supervised at least in the initial weeks of their posting in the ED. Ongoing educational sessions should be a regular feature in the department. They should be taught the skills like endotracheal intubation, etc., within the first few days of their posting. Till they are reasonably well trained the senior, more skilled pediatricians should continue to perform the life saving procedures themselves.

Nurses are the most important personnel in any emergency department since they are involved in the care of sick children in the ED at all stages. Indeed, they may be the first ones to look at the sick child and start providing the care till the pediatrician arrives. Hence, it is equally important that they are well trained in important life saving procedures. They may not have the skills to do endotracheal intubation but they should certainly be able to clear the airway and maintain it clear by head tilt-chin lift or jaw-thrust maneuvers and perform the bag-valve mask ventilation. These should be taught to them and the knowledge and skills be renewed at frequent intervals.

However, more important is to identify an acutely ill child, especially the one with respiratory, cardiac or neurologic life-threatening problems. Recording of vital signs like pulse, respiration, blood pressure and temperature is done quite meticulously by all nurses. However, they are often not trained to react appropriately to abnormalities in these parameters. Again, some new nurses will come on their rotation/posting. They should be adequately supervised during their initial weeks in the ED, especially when dealing with life-threatening situations.

Besides the medical staff, other helping and non-clinical staff is on duty in the ED. They are often not well educated and have no training what-so-ever in medicine. They can also be trained to recognize some of the life-threatening situations. Sometimes, in a busy ED all the trained personnel may be busy looking after the sick children and there may be many more waiting. If in such a situation another new patient arrives who has a life-threatening disorder these helpers should be able to gauge the gravity of the situation to the extent that they can inform the pediatrician about it.

There are other important issues in the working of pediatric emergency department in general hospitals. As a rule in a general hospital, adult patient gets more importance than children do and the pediatric patient does not get the same quality of service as an adult visiting the emergency department does. Often there is a common emergency department of adult and children. This is quite natural for a general hospital.

However, the needs of children are different in the ED compared to adults.<sup>5</sup> Thus, the equipment, the training of medical and paramedical staff, etc., is very different. For these reasons, it has been recommended that there should be a designated area within the general ED for pediatric patients. Further at all times adequate staff with pediatric training should be available for pediatric patients (Table 3.1).<sup>6</sup> Since medical staff in the general ED can change often, it is advisable to have written policies and protocols for the care of pediatric patient.

### PEDIATRIC EMERGENCY SERVICES IN THE CLINIC

The pediatrician's office/ clinic/out patient (OPD) is generally a lively place where not only sick children come for advice, but even normal cheerful children visit for their regular checks and immunizations. It appears an unlikely place where a critically ill child will come. However, this can happen occasionally. It is important to train staff at the reception even in a clinic to recognize a critically ill child so that the pediatrician can be informed immediately. The pediatrician also should not ignore the request by parents who insist on being attended early because their child is "very sick". One way can be for the pediatrician to send his nurse or go himself and have a quick look at that patient so that at least a life-threatening situation is not missed.

It is mandatory for the pediatrician to have adequate equipment and supplies of disposables and drugs for treatment of a child who is critically ill and requires immediate resuscitative measures (Table 3.2).<sup>7</sup> The responsibilities of the pediatrician in such a situation include providing CPR and other treatment. Further, he has to ensure safe transfer of such a child to a suitable treatment center.<sup>8</sup>

Documentation of all that the pediatrician has observed and done is absolutely essential for optimum treatment to continue as well as for legal purposes.

### PHYSICAL DESIGN OF EMERGENCY DEPARTMENT

When the hospital building is at a planning stage, the architect, administrators and a physician who is well informed about the needs and working of a pediatric emergency department should interact with each other. The area to be allocated to the ED would depend on the number of patients expected to visit the ED everyday. The total area has to be divided into many smaller areas/cubicles/rooms according to the services planned to be provided in the ED. Information which

**Table 3.1: Pediatric equipment guidelines for ED**

The following supplies and equipment are recommended by the American College of Emergency Physicians for Pediatric Patients in a general emergency department (ED).

An emergency cart or other system to house supplies, equipment, and drugs for a designated pediatric resuscitation area should be available.

*Monitoring devices*

Blood pressure cuffs (neonatal, infant, child, adult-arm, thigh) ECG monitor—defibrillation/ cardioverter with pediatric and adult-sized paddles and hard copy recording capability.  
End-tidal PCO<sub>2</sub> monitor and/or pediatric CO<sub>2</sub> detector otoscope/ophthalmoscope/stethoscope.  
Pediatric monitor, pulse oximeter with pediatric adapter sphygmomanometer and Doppler ultrasound blood pressure devices.  
Thermometer (hypothermia)  
Central venous pressure monitoring equipment  
Vascular access supplies and equipment  
Arm boards (infant, child, and adult sizes)  
Blood gas kits  
Butterfly needles (19-25 g)  
Catheter-over-needle devices (16-24 g)  
Central venous catheters (3-8 Fr)  
Infusion pumps, drip or volumetric, with microinfusion capability, with appropriate tubing and connectors  
Intra-osseous needles (16, 18 g)  
IV administration sets and extension tubing  
IV fluid/blood warmer  
IV solutions: In addition to standard solutions, the following should be readily available to the ED for the care of pediatric patients  
D10W  
D5W 0.2 percent NS  
Umbilical vein catheters (feeding tubes size 5 Fr may be used).  
Vascular access supplies utilizing the Seldinger technique

*Medications*

Activated charcoal  
Adenosine  
Antidotes immediately available:  
• Cyanide kit  
• Flumazenil  
• Methylene blue  
• Naloxone  
Antipyretics  
Atropine  
Barbiturates  
Benzodiazepines  
Beta-agonist (commonly albuterol) for inhalation  
Beta-blockers  
Bretylium  
Calcium chloride  
Dextrose  
Dexamethasone  
Dopamine  
Epinephrine (1:1,000 and 1:10,000)  
Furosemide  
Glucagon  
Hydrocortisone  
Insulin  
Isoproterenol  
Lidocaine  
Magnesium sulfate  
Mannitol  
Methylprednisolone  
Narcotics  
Neuromuscular blocking agents

*Respiratory equipment and supplies*

Bag-valve-mask resuscitator, self-inflating (child and adult)  
Clear oxygen masks  
Standard and non-rebreathing (neonatal, infant, child, adult)  
Oral airways  
Sizes : 0,1,2,3,4,5  
Suction catheters  
Sizes: 6, 8, 10, 12, 14, 16 Fr  
Tracheostomy tubes  
Shiley tube sizes: 00, 0, 1, 2, 3, 4, 6  
Endotracheal tubes  
Uncuffed sizes: 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 mm  
Cuffed sizes: 5.5, 6.0, 6.5, 7.0, 7.5, 8.0-mm  
Stylets for endotracheal tubes (pediatric and adult)

*Medications*

• Succinylcholine  
• Pancuronium and/or vecuronium  
Potassium chloride  
Phenytoin  
Procainamide  
Racemic epinephrine for inhalation  
Sodium bicarbonate  
Verapamil

*Related supplies/equipment*

Medication chart, tape, or other system to assure ready access to information on proper per-kilogram dose for resuscitation drugs and equipment sizes.

Contd...

Laryngoscope handle (pediatric)  
 Laryngoscope blades  
 Curved: 2, 3  
 Straight or Miller: 0, 1, 2, 3  
 Pediatric Magill forceps  
 Nasopharyngeal airways  
 Sizes: 12, 16, 20, 24, 28, 30 Fr  
 Nasal cannulae (child and adult)  
 NG tubes  
 Sizes: 6, 8, 10, 12, 14, 16 Fr  
 Medical photography capability  
 Oral rehydrating solution, such as Pedialyte, Ricelyte  
 Pediatric restraining devices  
 Specialized pediatric trays  
 Cricothyrotomy including needle cricothyrotomy  
 Lumbar puncture  
 Newborn kit:  
 Umbilical vessel cannulation supplies  
 Meconium aspirator  
 Obstetric pack  
 Peritoneal lavage

*Miscellaneous equipment*

Infant scale and older child scale  
 Infant formulas, dextrose in water with various nipple sizes  
 Heating source, overhead warmer preferred

Tube thoracostomy and water seal drainage  
 Thoracotomy tray with chest tubes  
 Sizes: 8-40 Fr

Urinary catheterization Sizes: 5-12 Fr  
 Venous cutdown

*Fracture management devices*

Femur splint (child and adult)  
 Semi-rigid neck collars (child and adult)  
 Spinal immobilization board

Adapted from reference 6.

would assist in the planning of an emergency department include:

- Annual census and trends
- Average daily census with peak patient volumes
- Triage categories of patient presentations
- Admission/transfer rate, including the number of cases requiring monitoring
- Average length of stay
- Turnaround times for radiology and pathology
- Additional information which pertain to the role delineation of the department, i.e. trauma service, regional referral service.

**Total Size**

The total internal area of the emergency department, excluding observation ward and internal medical imaging area if present, should be at least 50 m<sup>2</sup>/1000 yearly attendances or 145 m<sup>2</sup>/1000 yearly admissions, whichever size is greater. The minimum size of a functional emergency department that can incorporate all of the major areas is 700 m<sup>2</sup>. These figures are based upon access block being minimal. Emergency departments may take extended amounts of time from conception to completion, therefore allowances for future growth and development must be made in the design process.

**Total Number of Treatment Areas**

The total number of patient treatment areas should be at least 1/1100 yearly attendances or 1/400 yearly admissions, whichever is greater in number. Areas such as procedure, plaster and interview rooms are not considered as treatment areas nor are holding bays or observation unit beds for admitted patients. The number of resuscitation areas should be no less than 1/15,000 yearly attendances or 1/5,000 yearly admissions and at least 1/2 of the total number of treatment areas should have physiological monitoring.

**Functional Relationships**

Emergency department		
Direct Access	Ready Access	Access
Ambulance	Car parking	Inpatient wards
Medical imaging	Helipad (if applicable)	Pharmacy
Short stay unit	Coronary care unit	Outpatients
	Intensive care unit	Mortuary
	Operating rooms	
	Pathology/Transfusion service	
	Medical records	

**Table 3.2: Pediatric emergency equipment in clinics**

<i>Respiratory equipment</i>	<i>Monitoring</i>
Oxygen cylinder with flowmeter	Blood pressure cuffs—infant, child adult
Oxygen masks—neonate, infant, child, adult	Sphygmomanometer
Bag-valve-mask resuscitator, with reservoir	Cardiac monitor*
Suction machine	Pulse oximeter with infant and pediatric probe
Yankauer suction tip	ECG monitor/defibrillator with pediatric paddles*
Suction catheters—8F, 10F, 14F	
Feeding tubes—5F, 8F	
Intubation equipment	
Laryngoscope handle with	<i>Cardiac arrest board</i>
Straight blade 0, 1, 2	
Straight or curved blade 2, 3	<i>Medication</i>
Endotracheal tubes	Resuscitation
Uncuffed 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 mm ID	Epinephrine—1:1,000, 1:10,000
Cuffed 6.0, 7.0 mm ID	Atropine
Stylets—infant, adult	Sodium bicarbonate – 4.2 percent, 8.4 percent
Disposable end-tidal CO <sub>2</sub> detector	Glucose- 25 per cent solution
Nebulizer	Anticonvulsant
	Lorazepam, medazolam, diazepam
<i>Fluid management</i>	Phenobarbital
IV catheters, short, over the needle – 16, 18, 20, 22, 24 gauge	Antibiotics, parenteral
Butterfly needles – 21, 23, 25 gauge	Poisoning
IV boards, tape, povidone-iodine and alcohol swabs, tourniquet	Ipecac
Pediatric infusion set/volume control device	Activated charcoal
Intraosseous needles—15–18 gauge	Respiratory/allergic
Isotonic fluids (normal saline or lactated Ringer's solution)	Albuterol for inhalation
	Epinephrine – 1:1,000
	Methylprednisolone/prednisolone
	Diphenhydramine, parenteral
	Miscellaneous
	Naloxone

### Bed Spacing

In the acute treatment area there should be at least 2.4 meters of clear floor space between beds. The minimum length should be 3 meters.

### Lighting

It is essential that a high standard focused examination light is available in all treatment areas.

Each examination light should have a power output of 30,000 lux, illuminate a field size of at least 150 mm and be of robust construction. Clinical care areas should have exposure to daylight wherever possible to minimize patient and staff disorientation. Lighting should conform to Australian/New Zealand Standards.

### Sound Control

Clinical care areas should be designed so as to minimize the transmission of sound between adjacent treatment

areas and sound levels should conform to Australian and New Zealand Standards and World Health Organization guidelines. Distressed relatives/Interview rooms and selected offices should have a high level of sound control to ensure privacy.

### Service Panels

Service panels should be minimally equipped as follows:

- a. Resuscitation room (for each patient space)
  - 3 × oxygen outlets
  - 2 × medical air outlets
  - 3 × suction outlets
  - 16 × GPOs in at least two separate panels
  - 1 × nitrous oxide outlet (optional)
  - 1 × scavenging unit.
- b. Acute treatment bed
  - 2 × oxygen outlets

- 1 × medical air outlet
  - 2 × suction outlets
  - 8 × GPOs in two separate panels
  - 1 × nitrous oxide outlet (optional)
  - 1 × scavenging unit
- c. Procedure room/suture room/plaster room
- 2 × oxygen outlets
  - 1 × medical air outlet
  - 1 × suction outlets
  - 8 × GPOs in two separate panels
  - 1 × nitrous oxide outlet
  - 1 × scavenging unit
- d. Consultation room
- 1 × oxygen outlet
  - 1 × suction outlet
  - 4 × GPOs
- e. External service panels
- 3 × oxygen outlets
  - 2 × medical air outlets
  - 2 × suction outlets
  - 12 × GPOs in at least two separate panels
  - 1 × nitrous oxide outlet (optional)
  - 1 × scavenging unit.

### Physiological Monitors

Each acute treatment area bed, should have access to a physiological monitor. Central monitoring is recommended. Monitors should have printing and monitoring functions which include a minimum of:

- ECG
- NIBP
- Temperature
- SpO<sub>2</sub>.

Space determinants revolve around the major functional areas of the department. These may be divided broadly into:

1. *A reception area:* All patients arriving in the ED should pass by the reception. The seriously ill patients should be carried/wheeled in to the ED directly without stopping at the reception. One of the relatives can stop at the reception to make required records. This area should have appropriate registers for making manual entries as well as the computer to make electronic records.
2. A waiting hall for the patients who are waiting for their turn to be seen by the ED nurse and doctor should be located in between the reception and the nurse's desk. Another waiting or rest area is required to provide space for the relatives of children who are being looked after inside. We

must remember that it is customary in our country for a child to be accompanied by several relatives, neighbors and friends when he is brought to the ED with a serious illness. These people are often worried, tired and even agitated. A suitable place for them to sit and relax is essential. The waiting area must be of a total size of at least 5.0 m<sup>2</sup>/1000 yearly attendances in area, that includes seating, telephones, vending machines, display for literature, public toilets and circulation space. The waiting room should include one seat per 1000 yearly attendances.

3. The patient area should be divided into two distinct sections. One for children who are not seriously ill but need to be observed for next few hours, for example, a child with high fever or a child with diarrhea and vomiting who is being given oral rehydration solution (ORS). Indeed, if the number of patients with diarrhea and dehydration is high, a separate ward/unit (the diarrhea treatment unit) may be required.

The second section of the patient area can be designated for those children who are seriously ill and require intensive treatment, for example, a child with hypovolemic shock who is being given intravenous fluid boluses. This area should be fitted with electronic monitors, atleast the pulse oximeters. When a number of interventions are being performed on a critically ill child, a lot of space is required all around the child. This should be provided for. Similarly, a child who needs cardiopulmonary resuscitation (CPR) also requires extra working space. With all the emergency staff working around this patient it is not a pleasant sight for the rest of the patients and their relatives in the ED. Hence, some privacy is required. Curtains and screens can be used.

The patient area should be connected with the hospital wards and the Pediatric Intensive Care Unit (PICU) through a separate door so that the patients who are admitted to the hospital from the ED do not have to pass through the reception again.<sup>9</sup>

4. *Procedure room:* Separate room for procedures like lumbar puncture, tube thoracostomy, thoracentesis, abdominal paracentesis, bladder catheterization, suturing etc. is essential. There should be adequate space around the patient's bed for the paramedical staff and the equipment required. It requires noise insulation and must be at least 20 m<sup>2</sup> in size.

Minimal equipment and fittings include:

- Service panel as above
  - Operating theater light suspended from the ceiling with minimum 80,000 lux
  - X-ray viewing box/digital imaging system
  - Monitoring equipment—NIBP, SpO<sub>2</sub>, ECG with access to resuscitation equipment.
5. *Nebulization area*: Just as separate designated area is recommended for diarrhea treatment, an area where the child can sit with the mother for receiving nebulized medication is desirable.
  6. Central oxygen and suction should be available in all areas, which are regularly used for patient care. In fact, even those areas which are only seldom used for patient care, should have supply of central oxygen and suction.
  7. Side lab and radiology are also desirable in the emergency department itself.
  8. Nursing station and resident doctor's work area should be open areas from where they can observe all the patients in the emergency department. Retirement rooms should be provided for them, especially if they are expected to work for long hours. It must be remembered that tired, exhausted, stressed medical staff cannot be expected to make judgments correctly and quickly.
  9. Amenities like telephone for the public should be available within or just outside the ED. A play area for children is also recommended by experts.
  10. *Resuscitation room/bay*: This room is used for the resuscitation and treatment of critically ill or injured patients. It has the following requirements:
    - Minimum size for a single bed resuscitation room is 35 m<sup>2</sup> or 25 m<sup>2</sup> for each bed space if in a multibedded room (not including storage area).
    - Area to fit a specialized uninterrupted resuscitation bed.
    - Space to ensure 360° access to all parts of the patient for procedures.
    - Circulation space to allow movement of staff and equipment around the work area.
    - Space for equipment, monitors, storage, wash up and disposal facilities.
    - Appropriate lighting, equipment to hang IV fluids, etc.
    - Maximum possible visual and auditory privacy for the occupants of the room and other patients and relatives.
  11. *Acute treatment area*: This area is used for the management of patients with acute illnesses.

Its requirements are:

- Area to fit a standard mobile bed.
- Storage space for essential equipment, e.g. oxygen masks.
- Space to allow monitoring equipment to be housed.
- Minimum space between beds is 2.4 meters.
- Each treatment area must be at least 12 m<sup>2</sup> in area.

### COMPUTERS IN THE EMERGENCY DEPARTMENT

In this information age, computers are being used in all walks of life. They have invaded every area and department of the hospitals also. However, their application in patient care has not yet reached the optimum potential. The emergency department is an area where computers can be very helpful. Besides keeping records, accounts and transporting laboratory data ("the datanets") computers are a source of knowledge bank (a kind of medical library) within the ED ("the knowledge nets"). Thus, textbooks, rare medical conditions, etc. are available at the click of a mouse. The Internet makes much more information available almost at the bedside. The information is particularly useful when caring for children with poisoning. 'Computerized diagnostic referencing' is an application of computers that can provide real short cuts to difficult diagnostic problems. Softwares are available which incorporate the latest knowledge in the medical field that can be applied to patient care directly. Computer is a tool that can help the pediatrician meet the expectations of the parents who think their emergency pediatrician is providing them the best and the latest in medical knowledge.<sup>10</sup>

It has been suggested that in the setting of emergency, information needs to be delivered quickly to those who provide care. Thus, immediate information should be accessible within 15 seconds, further information within three minutes and a digest of some detail in around 10 minutes.<sup>11</sup> Further, this information should be "evidence based", informed by the most valid clinical research available. Some Internet sites use "critically appraised topics"(CATs) in a structured abstract form, which can be easily accessed without payment.<sup>12</sup>

### COST OF EMERGENCY CARE

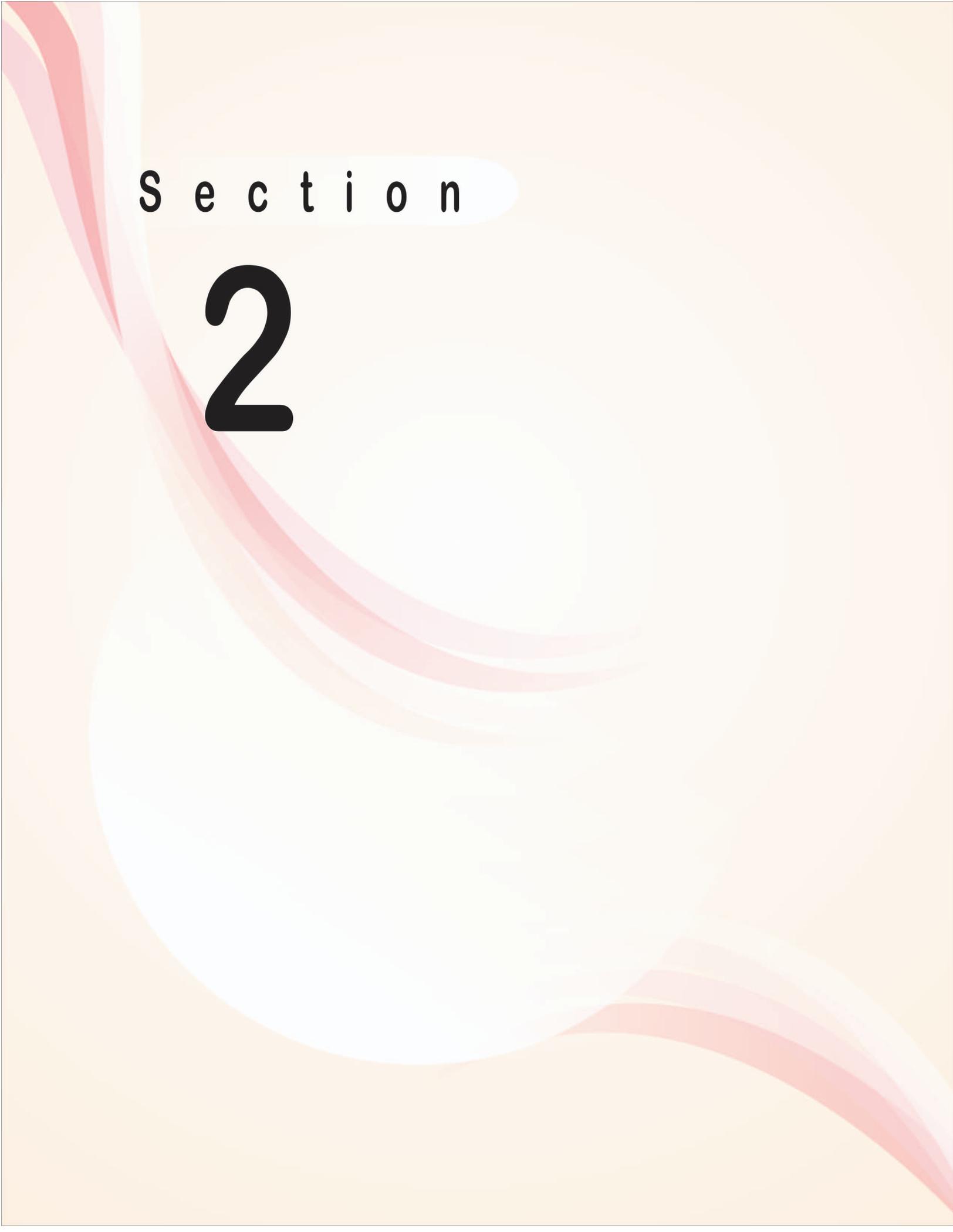
Pediatric emergency care is expensive to the state (in government run institutions) or to the individual family (in privately run institutions). In recent past costs of medical treatment, especially the emergency

care has received a lot of attention in USA. Their answer has been “managed care”. Managed care is defined as the delivery of health care with a focus on quality and cost efficiency and places importance on preventive care. Managed care aims at limiting services to “true emergencies” with follow-up directed at network care providers.<sup>13</sup> However, such networks do not exist in our country and we will have to find our own answers to cost problems.

Finally, in our efforts to provide the efficient, technology based, cost-effective services to pediatric emergency patients we must not forget the ‘ human-touch ‘. It is the lack of human touch because of poor communication that leads to dissatisfaction in the doctor-patient-family relationship.

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S e c t i o n

2



# Emergency Airway Management and Cardiopulmonary Resuscitation

S Krishnan, Sunil Dutt Sharma

The etiologies of respiratory failure, shock, cardiopulmonary arrest and dysrhythmias in children differ from those in adults. In 1988, the American Heart Association implemented the pediatric advanced life-support (PALS) program. Major revisions to the program were made in 1994, with further revisions in 1997.<sup>1-5</sup> The PALS program teaches a systematic, organized approach for the evaluation and management of acutely ill or injured children. Early identification and treatment of respiratory failure and shock in children improve survival, from a dismal 10 percent to an encouraging 85 percent.

In 1983, the American Heart Association (AHA) recommended the development of a course in pediatric advanced life support (PALS) as a means of fulfilling the need for resuscitation guidelines and training specifically for children. The first edition of the PALS manual was published in 1988, and the first PALS courses began that year. The PALS program underwent major revisions in 1994, a subsequent revision in 1997 and 2000 and now in 2005.<sup>6-16</sup>

In India, the first PALS courses were initiated under the auspices of the Indian Academy of Pediatrics (IAP) in 1994, and are now a successful training course. Emphasis is on hands-on-training and effective communication between resuscitators. The overall effect of these courses on patient outcome in India is unknown; however, anecdotally, more arrests are being successfully resuscitated and mortality is lower.

This chapter summarizes the changes contained in the 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, published in the December 13, 2005, issue of the American Heart Association journal *Circulation*, now also reviewed in 2008 and 2009.<sup>10-16</sup> It highlights major changes and provides background information and detailed explanations.

## Airway and Ventilation

Respiratory problems are common in infants and children and are the predominant cause of in and out

of hospital cardiopulmonary arrest in the pediatric age group. Assessment and treatment decisions must be made quickly to prevent progression and deterioration to respiratory failure and cardiopulmonary arrest. If respiratory failure or respiratory arrest is promptly treated, chances of intact survival of the child are high. On the other hand, once respiratory arrest progresses to pulseless cardiac arrest, outcomes are poor. Early recognition, decision making and effective management of respiratory problems are fundamental to pediatric advanced life support.

Flow chart 4.1 summarizes the approach to the child in cardiorespiratory failure and arrest.

## Management of the Pediatric Airway

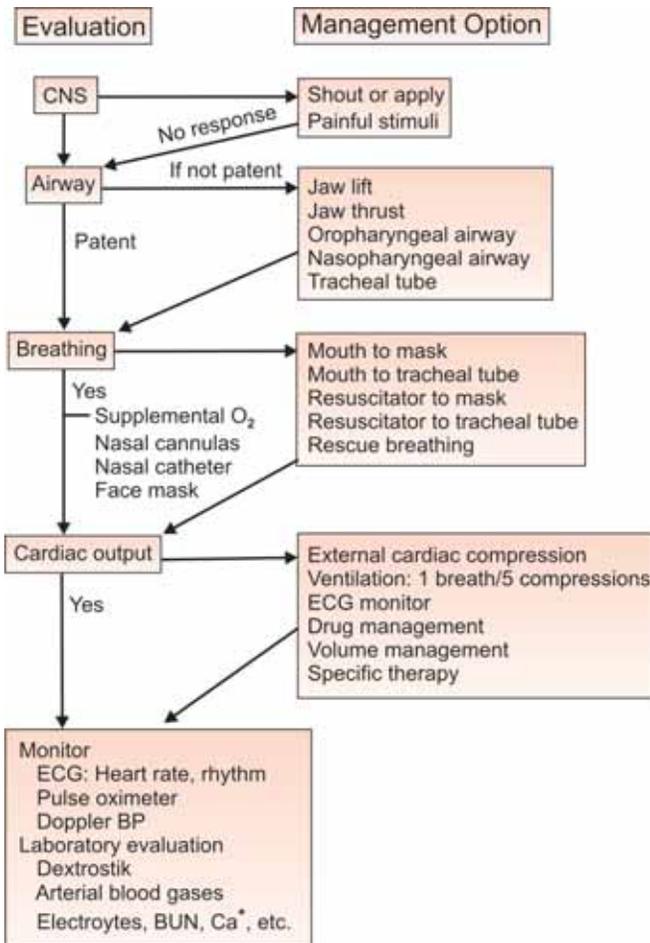
### *Anatomic and Physiologic Considerations*

The pediatric airway differs from the airway of an older child or adult. This has implications in emergency management.

Anatomic differences of the upper airway include the following: (i) The airway of the infant or child is much smaller; (ii) The tongue is larger in the infant, relative to the size of the oropharynx; (iii) The larynx in infants and toddlers is relatively cephalad in position, (iv) The epiglottis in infants and toddlers is short, narrow, and angled away from the trachea; (v) The vocal cords are lower and anterior; (vi) In infants and young children, the narrowest portion of the airway is below the vocal cords at the level of the cricoid cartilage, and the larynx is funnel shaped. In contrast, in older children, the narrowest portion of the airway is at the glottic inlet and the larynx is cylinder shaped.

These differences have the following clinical implications: (i) Relatively smaller amounts of edema or obstruction can significantly reduce the airway diameter and increase the work of breathing; (ii) Posterior displacement of the tongue which is not uncommon in an obtunded child may cause severe airway obstruction; (iii) The tongue and epiglottis may

**Flow chart 4.1:** Approach to the child in cardiorespiratory failure and arrest



be difficult to control during tracheal intubation; (iv) The cephalad larynx makes the angle between the base of the tongue and the glottis more acute. As a result, straight laryngoscope blades are more effective than curved blades in creating a direct visual plane from the mouth to the glottis; (v) Tracheal tube size should be selected based on the size of the cricoid ring rather than the glottic opening. An air leak is usually observed after intubation if the tube size is appropriate; (vi) Even a minor reduction in diameter of the small pediatric airway (by mucus, blood, or pus; edema; active constriction; external compression) results in a clinically significant reduction in cross sectional area and a concomitant increase in airway resistance and work of breathing; (vii) Resistance to airflow is inversely proportional to the fourth power of the airway radius when laminar flow is present (i.e. during

quiet breathing). However, when airflow is turbulent, e.g. during crying, resistance to airflow is inversely proportional to the fifth power of the radius. Therefore, the infant or child with airway obstruction should be kept as calm and quiet as possible to prevent generation of turbulent airflow, and markedly increased work of breathing; (viii) In infants the chest wall is highly compliant. As a result, functional residual capacity is reduced when respiratory effort is diminished or absent. In the child with obstructed airway, active inspiration often results in paradoxical chest movement rather than chest and lung expansion; (ix) The tidal volume of infants and toddlers almost totally depends on the diaphragm. When diaphragm movement is impeded (pulmonary hyperinflation, e.g. asthma or by gastric distention), respiration could be hampered; (x) The highly compliant pediatric airway makes it very susceptible to dynamic collapse in the presence of airway obstruction; (xi) The pediatric patient has a higher oxygen demand because the metabolic rate is high. Thus, in the presence of apnea or inadequate alveolar ventilation, hypoxemia could develop more rapidly in the child.

### Airway Adjuncts<sup>1,8,9</sup>

#### *Spontaneously Breathing Patient in Respiratory Distress: General Principles*

In an emergency, determining the cause of respiratory dysfunction may be impossible and even unnecessary before initiating the steps of emergency airway management.

Oxygen, in the highest possible concentration, should be administered to all seriously ill or injured patients with respiratory insufficiency, shock, or trauma, even if  $PO_2$  or  $O_2$  saturations are high. In some of these patients, oxygen delivery to tissues may be limited and can be enhanced by increasing the  $O_2$  carrying capacity.

Humidification should be added as soon as practical to prevent obstruction of the small airways by dried secretions and the adjunctive gas.

Conscious and alert children in distress should be allowed to remain in a position of comfort that they choose that promotes optimal airway patency and minimizes respiratory effort.

Oxygen should be administered in a non-threatening manner. If one method of oxygen delivery is not optimal for that child (such as a mask), alternative methods (e.g. a face tent or a "blow-by") could be attempted.

In the unconscious child, airway obstruction can be caused by a combination of excess neck flexion, jaw relaxation, posterior displacement of the tongue, and hypopharyngeal collapse. Noninvasive methods of airway opening should be attempted before use of adjuncts. Some of the pitfalls are described in the Figures 4.1A to E.<sup>8</sup>

If spontaneous breathing is inadequate despite a patent airway, assisted ventilation may be needed. In most respiratory emergencies, infants and children can be successfully ventilated with a bag-valve-mask device. Every pediatric practitioner, should be skilled

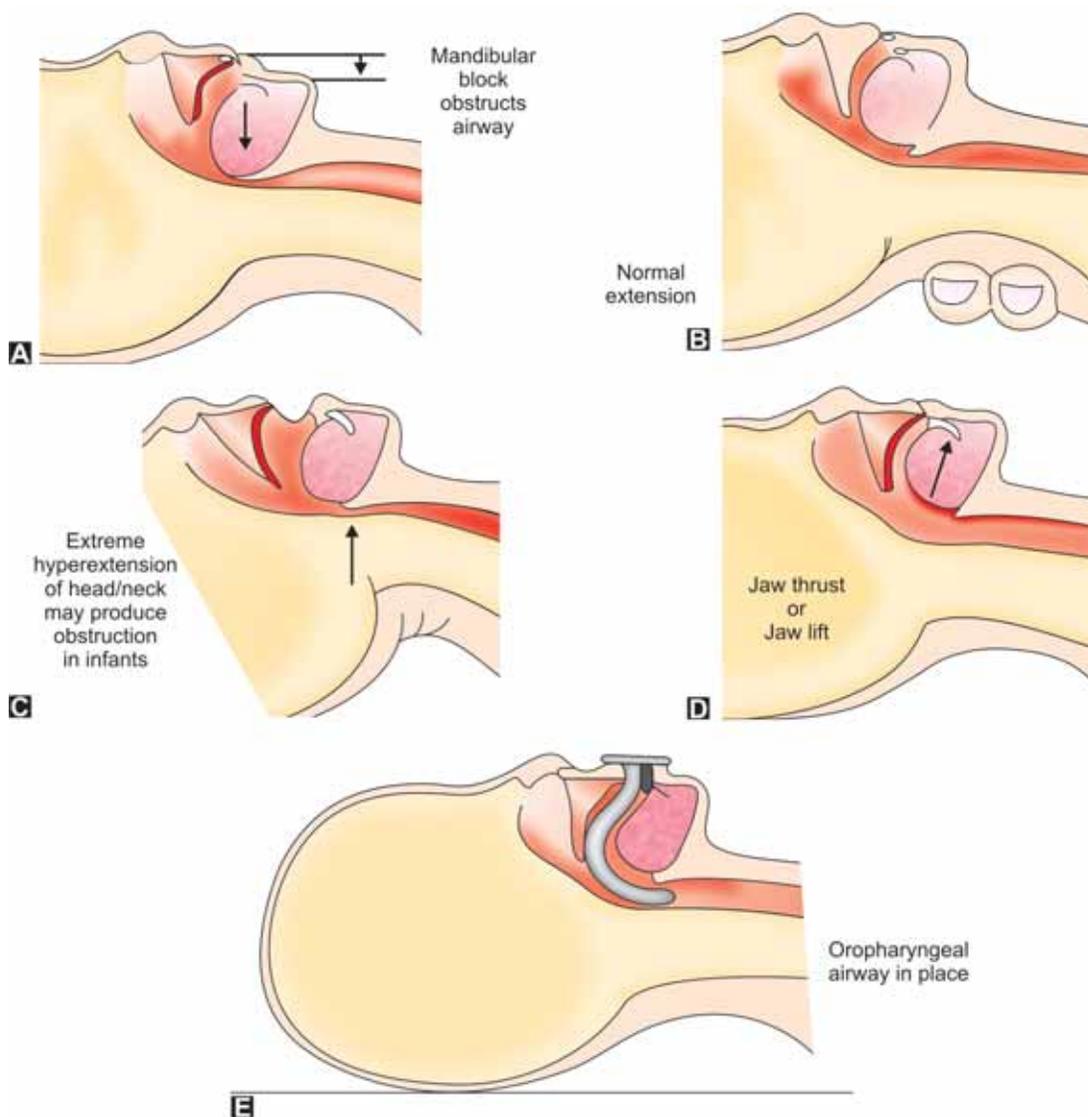
in this technique as it could be life-saving and could buy time until an experienced "intubator" arrives.

Finally, intubation should be attempted if all above measures fail, so that oxygenation and ventilation could be restored and progression to cardiac arrest may be prevented.

### Airway Protection

#### Oropharyngeal Airway

An oropharyngeal airway consists of a flange, a short bite-block segment, and a curved body usually made



**Figs 4.1A to E:** Summary of pitfalls. (A) Upper airway obstruction related to hypotonia. (B) Partial relief of airway obstruction by means of head extension (danger of cervical spine injury in cases of trauma). (C) Extreme hyperextension causing upper airway obstruction. (D) Fully open airway through use of jaw thrust or jaw lift. (E) Oropharyngeal airway stenting mandibular block off posterior pharyngeal wall

of plastic and shaped to provide an air channel and suction conduit through the mouth. The curved body of the oropharyngeal airway is designed to hold the tongue and the soft hypopharynx away from the posterior pharyngeal wall. The oropharyngeal airway is indicated for the unconscious patient only to maintain airway patency. Airway sizes may be estimated by placing the oropharyngeal airway next to the face. With the flange at the corner of the mouth, the tip of the airway should reach the angle of the jaw. Appropriate placement is essential. If the airway is too large, it may obstruct the larynx, and traumatize laryngeal structures. If it is too small or inserted improperly, it will push the tongue posteriorly and obstruct the airway. The head and jaw must be positioned to maintain a patent airway even after insertion of an oropharyngeal airway using the head-tilt, jaw-thrust, chin-lift maneuvers.

#### *Nasopharyngeal Airway*

This is a soft rubber or plastic tube that provides a conduit for airflow between the nares and the posterior pharyngeal wall in a responsive patient. A shortened endotracheal tube may also be used as a nasopharyngeal airway. The proper airway length is equal to the distance from the tip of the nose to the tragus of the ear. The airway should be lubricated before insertion. The smaller internal diameter of a nasopharyngeal airway can become easily obstructed, so its patency must be frequently evaluated.

### Management of Respiratory Failure or Arrest

If potential respiratory failure is identified, the approach to treatment of respiratory failure is: (i) Open the airway; (ii) Support breathing using an appropriate device that delivers optimal  $\text{FiO}_2$  and maintain adequate ventilation;<sup>17-20</sup> and (iii) Assess circulation.

Potential respiratory failure may not always be apparent. Physical examination and laboratory data should be interpreted in the context of previous examinations and past history. As soon as respiratory failure or inadequate ventilation is identified clinically or by blood gas analysis, rapid initiation of assisted ventilation should be undertaken. Recognition and treatment of respiratory failure is discussed in greater detail in a subsequent chapter.

## 2

### Self-inflating Bag-valve Ventilation Devices

A self-inflating bag-valve device (Fig. 4.2) with a face mask provides a rapid means of ventilating a patient

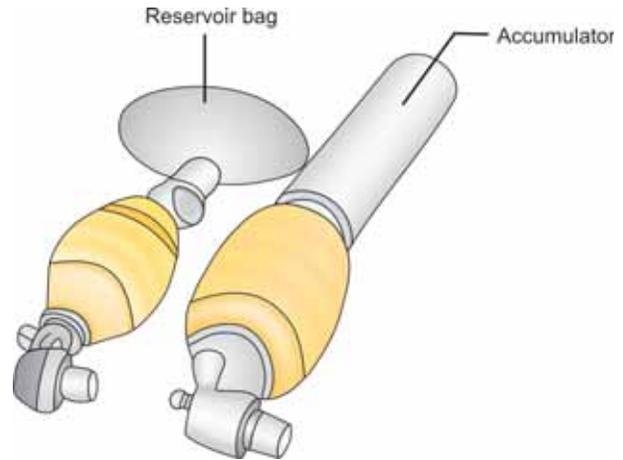


Fig. 4.2: Self-inflating resuscitation bags

in an emergency even without an oxygen source. The self-inflating bag refills independently by recoil. During reinflation the intake valve entrains room air or  $\text{O}_2$ . During bag compression the valve closes and a second valve opens to permit gas flow to the patient. When the patient exhales the outlet closes and the patients exhaled gases are vented to the atmosphere. Self-inflating bags are available in a variety of sizes-adult (1500 ml), pediatric (450 ml) and infant (250 ml). A self-inflating bag-valve device delivers room air unless supplemental oxygen is provided. At an oxygen inflow of 10 L/min, pediatric self-inflating bag-valve devices without oxygen reservoirs deliver 30 percent to 80 percent oxygen which can be increased to 100 percent with a reservoir. Many self-inflating bags are equipped with a pressure-limiting pop-off valve set at 35 to 45 cm  $\text{H}_2\text{O}$  to prevent barotrauma. Occlusion of the pop-off valve may be required in some patients if lung compliance is markedly reduced. Positive end-expiratory pressure (PEEP) can be provided during assisted ventilation by adding a PEEP valve to the bag-valve outlet.

#### *Technique of Bag-valve-mask Ventilation*

Two hands must be used to provide bag-valve-mask ventilation. The mask is held on the face with one hand which also performs the head tilt-chin lift, while other hand is used for compressing the ventilation bag. In infants and toddlers, the jaw is supported with the base of the middle or ring finger. In older children, the fingertips of the third, fourth, and fifth fingers are placed on the ramus of the mandible to hold the jaw forward and extend the head, while the index and thumb holds the mask in position. If a single operator

cannot effectively maintain the seal, two rescuers may be needed.

**Position of head and neck:** A neutral sniffing position, without hyperextension of the head, is recommended for infants and toddlers. In older children some anterior displacement of the cervical spine can be achieved by placing a folded towel under the neck and head. If unable to ventilate easily, the head should be repositioned, and airway patency should be rechecked. Also ensure that the bag (and O<sub>2</sub> source) is functioning properly. Gastric distention is common during this maneuver and should be avoided or promptly treated. Gastric inflation and passive regurgitation in the unconscious infant or child may be minimized by applying cricoid pressure (Sellick maneuver)—by compressing the esophagus between the cricoid ring and the cervical spine.<sup>19</sup> Excessive pressure must be avoided because it may produce tracheal compression and obstruction in infants.

#### Anesthesia Bag Ventilation Systems

Anesthesia bag ventilation systems (Fig. 4.3) consist of a reservoir bag, an overflow port, a fresh gas inflow port, and a standard 15 mm/22 mm connector for mask or tracheal tube. The overflow port usually includes an adjustable valve. The reservoir bag volume for infants is 500 ml, and for children, 1000 to 2000 ml. Experience is required to effectively control the ventilation devices by adjusting the fresh gas flow, the outlet control valve, and a proper face mask fit. The composition of inspired gas is determined by fresh gas flow in the absence of a non-rebreathing valve. An in-line pressure manometer may be used as a guide to prevent barotrauma. Effective ventilation is determined by observation of adequate chest movement rather than by reading a pressure manometer. The anesthesia bag

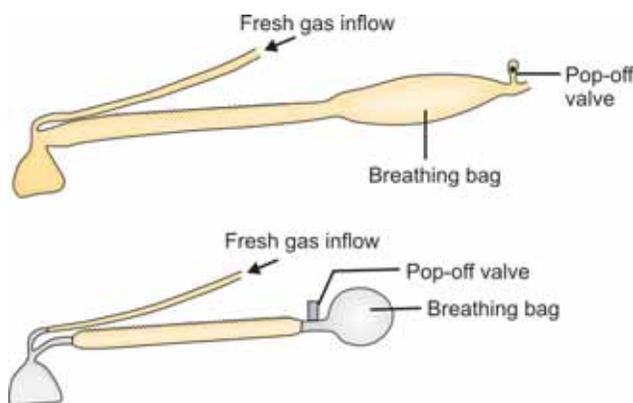


Fig. 4.3: Conventional anesthesia bags with fresh gas flow

is ideal for sedated or obtunded patients with spontaneous respiration. The fresh gas flow rate must be at least three times the patient's minute ventilation to ensure appropriate removal of exhaled CO<sub>2</sub>. PEEP or CPAP can be provided through this bag by partial closure of the adjustable pop-off valve.

#### Endotracheal Tube Ventilation

The advantages of endotracheal tube ventilation are: (i) The airway is controlled and isolated, ensuring adequate oxygenation and ventilation; (ii) Potential regurgitation and aspiration is diminished; (iii) In the arrest scenario, it is easier to coordinate ventilation with external cardiac compression; and (iv) PEEP can be delivered if needed.

Indications for endotracheal intubation include: (i) Respiratory failure or arrest; (ii) Inadequate central control of respiration; (iii) Airway obstruction; (iv) Excessive work of breathing, anticipated respiratory muscle fatigue; (v) Loss of protective airway reflexes; (vi) Prolonged need for bag-valve-mask ventilation; (vii) Need for mechanical ventilatory support; (viii) Anticipated transport of a patient in potential respiratory failure.

The technique of tracheal intubation is discussed in detail in the PALS course.<sup>4,8,20</sup>

Table 4.1 describes guidelines for the equipment used for tracheal intubation.

#### PALS and NALS Guidelines 2005<sup>10-16,21-31</sup>

The International Liaison Committee on Resuscitation (ILCOR) is responsible for coordinating the development of new guidelines distributing new information throughout the world. We now discuss some of the updates in the "new" PALS and NRP(NALS) courses based on the AHA's Guidelines 2005 conference.

Implementing the international guidelines has required adopting universal terminology to improve communication and understanding among all ILCOR participants. What was once called an endotracheal tube, for example, is now a "tracheal tube," and a bag-valve-mask device is called a "manual resuscitator." Revised age definitions have been introduced as well to emphasize and clarify the unique anatomy and physiology of children as they grow. "Newly born" (replacing newborn) refers to the first minutes or hours following birth. "Neonate" encompasses the first 28 days of life beyond the newly born period. "Infant" includes the neonatal period and extends to 1 year of age. From 1 year to 8 years of age a patient is a "child." Patients 8 years and older are classified as adults.

**Table 4.1: Guidelines for the equipment used for tracheal intubation***Some formulae:*

Selecting size of tracheal tube:

$$\text{Tracheal tube (mm ID)} = \text{Age (yrs)}/4 + 4$$

Or

$$\text{Tracheal tube (mm ID)} = \text{Age (yrs)} + 16/4$$

*Depth of insertion:*

$$\text{Age (yrs)}/2 + 12$$

Or

$$\text{ID} \times 3$$

**Note:**

- Always select tracheal tubes one size smaller and larger along with the appropriate size
- Intubation should be performed by the most experienced person on site of arrest
- Bag-valve-mask ventilation is usually an effective temporary measure until experienced personnel are available for intubation
- In presence of suspected or confirmed upper airway obstruction, use one or two sizes smaller size tracheal tube than that determined by the formula
- In specific situations, rapid sequence intubation is the recommended method for tracheal intubation and practitioners caring for sick infants and children should familiarize themselves with this technique.

Conditions requiring rapid cardiopulmonary assessment and potential cardiopulmonary support:

- Respiratory rate >60 breaths/min
- Heart rate ranges (if associated with poor perfusion)
  - Child <8 years of age: <80 bpm or >180 bpm
  - Child >8 years of age: <60 bpm or >160 bpm
- Poor perfusion, with weak or absent distal pulses
- Increased work of breathing (retractions, nasal flaring, grunting)
- Cyanosis or a decrease in oxyhemoglobin saturation
- Altered level of consciousness (unusual irritability or lethargy, or failure to respond to parents or painful procedures)
- Seizures
- Fever with petechiae
- Trauma
- Burns involving >10% BSA.

**Basic Life Support**

For the purposes of these guidelines, an "infant" is less than approximately 1 year of age. This section does not deal with newborn infants. For lay rescuers the "child" BLS guidelines should be applied when performing CPR for a child from about 1 year of age

to about 8 years of age. For a healthcare provider, the pediatric ("child") guidelines apply from about 1 year to about the start of puberty. Area should be safe for rescuer and victim both. Risk of infection disease transmission is low while performing CPR.

**Check for Response**

- Victim should be gently tapped and asked loudly, "Are you okay?" called by name if known.
- Child should be looked for movement. If the child is *responsive*, he or she will answer or move. Child should be quickly checked to see if it has any injuries or needs medical assistance. Allow the child with respiratory distress to remain in a position that is most comfortable.
- If the child is *unresponsive* and is not moving, start CPR, continue CPR for 5 cycles (about 2 minutes). One cycle of CPR for the lone rescuer is 30 compressions and 2, get an automated external defibrillator (AED). If the child must be moved for safety reasons, support the head and body to minimize turning, bending, or twisting of the head and neck.

**Position the Victim**

If the victim is unresponsive, victim should be in a supine (face up) position on a flat, hard surface, such as a sturdy table, the floor, or the ground. If turned, minimize turning or twisting of the head and neck.

*Open the Airway*

A health care provider should use the head tilt-chin lift maneuver to open the airway of a victim without evidence of head or neck trauma. If cervical spine injury suspected, open the airway using a jaw thrust without head tilt, use a head tilt-chin lift maneuver if the jaw thrust does not open the airway. The jaw thrust is no longer recommended for lay rescuers because it is difficult to learn and perform, is often not an effective way to open the airway, and may cause spinal movement.

*Check Breathing*

While maintaining an open airway, take no more than 10 seconds to check whether the victim is breathing: Look for rhythmic chest and abdominal movement, listen for exhaled breath sounds at the nose and mouth, and feel for exhaled air on cheek. Periodic gasping, also called *agonal gasps*, is not breathing. If the child is *breathing* and there is no evidence of trauma: child

should be turned on side. This helps maintain a patent airway and decreases the risk of aspiration.

### Give Rescue Breaths

If the child is *not breathing or has only occasional gasps*:

- **For the lay rescuer:** Open airway maintained and given 2 rescue breaths.
- **For the health care provider:** Open airway maintained and give 2 rescue breaths. Surety of effectiveness of breaths is checked (i.e., the chest rises). If the chest does not rise, head is repositioned, better seal made, and again tried. It may be necessary to move the child's head through a range of positions to obtain optimal airway patency and effective rescue breathing. In an infant, a mouth-to-mouth-and-nose technique is used; in a child, a mouth-to-mouth technique is used.

### Bag-Mask Ventilation (Health Care Providers)

Bag-mask ventilation can be as effective as endo-tracheal intubation and safer when providing ventilation for short periods. Self-inflating bag with a volume of at least 450 to 500 mL is used. To deliver a high oxygen concentration (60 to 95%), an oxygen reservoir to the self-inflating bag is attached. Oxygen flow should be of 10 to 15 L/min into a reservoir attached to a pediatric bag. Hyperventilation should be avoided; the force and tidal volume necessary to make the chest rise should be used. Each breath should be given over 1 second.

### Oxygen

Health care providers should use 100% oxygen during resuscitation. Once the patient is stable, supplementary oxygen should be weaned but adequate oxygen delivery should be ensured by appropriate monitoring. Whenever possible, oxygen should be humidified to prevent mucosal drying and thickening of pulmonary secretions. Masks provide an oxygen concentration of 30 to 50% to a victim with spontaneous breathing. For a higher concentration of oxygen, use a tight-fitting nonrebreathing mask with an oxygen inflow rate of approximately 15 L/min that maintains inflation of the reservoir bag. Infant and pediatric size nasal cannulas are suitable for children with spontaneous breathing. The concentration of delivered oxygen depends on the child's size, respiratory rate, and respiratory effort. For example, a flow rate of only 2 L/min can provide young infants with an inspired oxygen concentration of about 50%.

### Pulse Check (for Health Care Providers)

Pulse should be palpated—brachial in an infant and carotid or femoral in a child. Not more than 10 seconds should be wasted. If despite oxygenation and ventilation the pulse is <60 beats per minute (bpm) and there are signs of poor perfusion (i.e., pallor, cyanosis), chest compressions should be started.

### Rescue Breathing Without Chest Compressions (for Health Care Providers Only)

If the pulse is <60 bpm but there is no spontaneous breathing or inadequate breathing, rescue breaths should be given at a rate of about 12 to 20 breaths per minute (1 breath every 3 to 5 seconds) until spontaneous breathing resumes. Each breath should be given over 1 second. Each breath should cause visible chest rise. During delivery of rescue breaths, pulse reassessed about every 2 minutes, but no more than 10 seconds should be spent in doing so.

### Chest Compressions

For chest compression the lower half of the sternum should be compressed but xiphoid should never be compressed. The following are characteristics of good compressions:

- "Push hard": push with sufficient force to depress the chest approximately one third to one half the anterior-posterior diameter of the chest.
- "Push fast": push at a rate of approximately 100 compressions per minute.
- Release completely to allow the chest to fully recoil.
- Minimize interruptions in chest compressions.

In an *infant victim*, compress the sternum with 2 fingers placed just below the intermammary line. The 2 thumb-encircling hands technique is recommended for health care providers when 2 rescuers are present. In a *child*, compress the lower half of the sternum with the heel of 1 hand or with 2 hands (as used for adult victims) but should not press on the xiphoid or the ribs. It is most important that the chest be compressed about one third to one half the anterior-posterior depth of the chest.

### Coordinate Chest Compressions and Breathing

For lay rescuers, a single compression-ventilation ratio (30:2) for all age groups and for 2-rescuer CPR one provider should perform chest compressions while the other maintains the airway and performs ventilations

at a ratio of 15:2 with as short a pause in compressions as possible. Ventilation and compression of the chest should not be done simultaneously with either mouth-to-mouth or bag-mask ventilation. Once an advanced airway is in place; the compressing rescuer should deliver 100 compressions per minute continuously without pauses for ventilation and the rescuer delivering the ventilations should give 8 to 10 breaths per minute. Two or more rescuers should rotate the compressor role approximately every 2 minutes to prevent compressor fatigue and deterioration in quality and rate of chest compressions and should be accomplished as quickly as possible (ideally in less than 5 seconds) to minimize interruptions in chest compressions.

### Foreign-Body Airway Obstruction (FBAO) (Choking)

Less than 5 years children are more susceptible; 65% victims being infants. Most common cause is liquids followed by balloons, small objects and foods. Signs of FBAO include a *sudden* onset of respiratory distress with coughing, gagging, stridor (a high-pitched, noisy sound), or wheezing. The characteristics that distinguish FBAO from other causes (e.g. croup) are sudden onset in a proper setting and the absence of antecedent fever or respiratory symptoms. In severe airway obstruction victim may not cough or make sound.

### Relief of FBAO

- If FBAO is mild, do not interfere. Allow the victim to clear the airway by coughing while you observe for signs of severe FBAO.
- If the FBAO is severe (i.e. the victim is unable to make a sound):

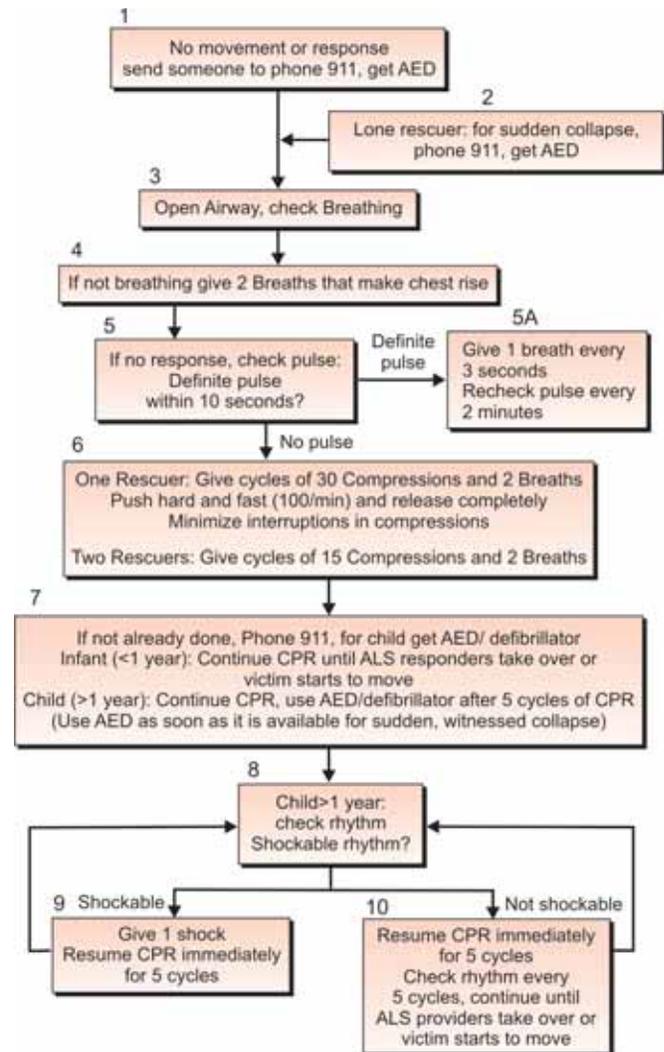
For a child, subdiaphragmatic abdominal thrusts (Heimlich maneuver) should be performed until the object is expelled or the victim becomes unresponsive. For an infant, 5 back blows (slaps) should be delivered followed by 5 chest thrusts repeatedly until the object is expelled or the victim becomes unresponsive. Abdominal thrusts are not recommended for infants because they may damage the relatively large and unprotected liver. If the victim becomes unresponsive, lay rescuers and health care providers should perform CPR but should look into the mouth before giving breaths. If a foreign body is seen, it should be removed. Blind finger sweeps should not be performed because this may push obstructing objects further into the pharynx and may damage the oropharynx. Object should be attempted to remove only if it is in the

pharynx. And then ventilation and chest compression should be attempted.

### Summary of BLS (Flow chart 4.2)

- No movement or response
- Send someone to call 911
- Open airway and check breathing
- Provide two breaths (chest should rise)
- Check pulse (no longer than 10 seconds)
- One rescuer: perform CPR cycles of 30:2
- Two rescuers: perform CPR, cycles of 15:2
- Push hard and fast (100/min)/allow full chest recoil
- If not already done, call 911

**Flow chart 4.2:** Pediatric health care provider BLS algorithm. Note that the boxes bordered by dotted lines are performed by health care providers and not by lay rescuers



- AED/defibrillator for child
- Defibrillator for infant
- Analyze and defibrillate ASAP for witnessed arrest, if VF/PVT
- Analyze and defibrillate after 5 cycles of CPR for unwitnessed arrest, if VF/PVT
- Give one shock 2 J/kg
- Resume CPR for 2 minutes
- Give one shock 4 J/kg
- Resume CPR.

### New PALS

Besides incorporating a new approach to teaching advanced life support, the revised PALS course places increased emphasis on special resuscitation circumstances that require immediate intervention (such as hypothermia, anaphylaxis, and electrical injuries) and includes optional teaching modules on such topics as pediatric sedation, children with special health care needs (those on home respirators and those with tracheostomy tubes, for example), coping with death, and toxicology for special circumstances (such as overdoses involving cocaine, tricyclic anti-depressants, narcotics, calcium-channel blockers and beta-adrenergic blockers). It also provides instruction in the use of innovative advanced life support technologies, including exhaled and end-tidal carbon dioxide detectors, the laryngeal mask airway (LMA), and the AED.

In adults, cardiopulmonary arrest is typically sudden and primarily cardiac in origin. In contrast, arrest in children usually follows progressive shock and respiratory failure. Arrest in a young child is most often associated with sudden infant death syndrome, sepsis, or trauma. Trauma is the most common cause of arrest in children older than 6 months. The success of any advanced life support intervention depends on early recognition of respiratory and circulatory compromise combined with aggressive management of the airway, treatment of rhythm disturbances, and expeditious fluid resuscitation.

The latest PALS guidelines recommend that the self-inflating bag be used for pediatric resuscitation (the flow-inflating bag can be used as an alternative by properly trained personnel to resuscitate a newly born). Rescuers should use a self-inflating bag with a minimum volume of 450 ml for full-term newborns, infants, and children. Neonatal-sized (250 ml) manual resuscitators are no longer recommended because they may not support effective tidal volume and longer inspiratory times in full-term neonates and infants.

In regard to intubated pediatric patients, the new guidelines recommend confirming tracheal tube placement by using exhaled or end-tidal carbon dioxide detectors.

The new guidelines also address the use of the laryngeal mask airway in young children. Many believe that an LMA can be inserted more readily than a tracheal tube. LMAs do not protect the airway from aspiration, and medications cannot be administered through them. They should not be used in a child with an intact gag reflex.

Vagal maneuvers have been added to the treatment algorithm for supraventricular tachycardia in children with milder symptoms who are hemodynamically stable. They may also be tried during preparation for cardioversion or drug therapy. A 12-lead ECG should be obtained before and after performing a vagal maneuver, and the ECG should be monitored continuously during the maneuver.

**Medications:** To manage unresponsive asystolic and pulseless arrest, epinephrine is initially administered intravascularly or intraosseously in a dose of 0.01 mg/kg (0.1 mL/kg of 1:10,000 solution). The latest PALS guidelines recommend the same amount of epinephrine for second and subsequent doses instead of "high dose" epinephrine. Although high dose epinephrine is no longer recommended, it still may be considered in refractory arrest situations.

Bretylium is no longer recommended for managing ventricular fibrillation or pulseless ventricular tachycardia because of the risk of hypotension and the drug's lack of documented effectiveness in pediatric patients. Amiodarone, in a dose of 5 mg/kg, is now considered the drug of choice for ventricular fibrillation or pulseless ventricular tachycardia unresponsive to three initial defibrillation attempts. It can also be used to manage hemodynamically stable ventricular tachycardia refractory to cardioversion.

### Pediatric Advanced Cardiac Life Support Helpful Information

**Weight:** (Age in years × 2) + 8 = wt in kg

**Blood pressure:**

Bare bones minimum

Birth to 1 month = 60 systolic

1 month to 1 year = 70 systolic

1 year to 10 years = (Age in years × 2) + 70

**Heart rate limits for ST vs SVT:**

ST < 220 in infants, variable with a specific history

SVT > 220 in infants, regular without a specific history

ST < 180 in children (1-5 yrs) variable with a specific history

SVT > 180 in children (1-5 yrs) regular without a specific history

*ETT size:*

(Age in years + 16) ÷ 4

Tube size × 3 = depth of insertion

*Fluid resuscitation:*

Neonate (0-30 days) 10 mL/kg

Infants and children 20 mL/kg

Infuse over 10-20 minutes

Use normal saline for resuscitation

Use D<sub>5</sub> ¼ NS for maintenance

*Common resuscitation medications:*

Epinephrine 0.1 mL/kg 1:10,000 IV/IO (1:1,000 ET) for cardiac arrest and bradycardia

Adenosine 0.1 mg/kg RIVP for SVT

Naloxone 0.1 mg/kg for narcotic OD

Lidocaine 1 mg/kg for VF arrest and VT

Sodium Bicarbonate 1 mEq/kg for TCA OD

Atropine 0.02 mg/kg as a #2 medication in bradycardia

Amiodarone 5 mg/kg for tachycardias

*Electrical therapy:*

Cardioversion 0.5-1 j/kg

Defibrillation 2 j/kg initially, followed by single shocks at 4 j/kg.

**Major changes in basic life support (BALS) affecting all rescuers**

1. *Emphasis on effective chest compressions*

- Push hard and push fast (at 100 per minute).
- Allow chest to recoil completely.
- Try to limit interruptions in compression.

Chest compressions that are too shallow or too slow do not deliver much blood flow to vital organs. The first few compressions are not as effective as later compressions. When chest compressions are interrupted, blood flow stops and coronary artery perfusion pressure falls. The more the interruption in chest compressions, the worse the victim's chance of survival. Half the chest compressions given by professional rescuers are too shallow and no compression was provided during 24 to 49% of CPR time. If chest is not allowed to recoil, blood flow during next compression will be reduced because of reduced filling of heart.

2. *One universal (30:2) compression-to-ventilation ratio for all lone rescuers*

The AHA recommends a compression-to ventilation ratio of 30:2 for all lone (single) rescuers to

use for all victims from infants (excluding newborns) through adults.

3. *Recommendations for 1-second breaths during all CPR*

- Each rescue breath should be given over 1 sec.
- Each breath should make the chest rise.
- Recommended number of breaths should be given.
- Avoid giving too many-too large-too forceful breaths.

During CPR, blood flow to lungs is 25 to 33%, so the victim needs less ventilation than normal. It is also important to limit the time used in rescue breath to reduce interruptions in compressions. Hyperventilation is harmful because it decreases venous return to heart and so limits refilling and eventually reduces the blood flow generated by next chest compressions.

4. *Attempted defibrillation: One shock, then immediate CPR*

- Deliver one shock followed by immediate CPR, beginning with chest compressions.
- Check the victim's rhythm after giving about 5 cycles (about 2 minutes) of CPR.

The rhythm analysis by AED results in 37 sec delay, such interruptions can be harmful. Moreover the 1st shock eliminates VF 85% of time. In case it fails resumption of CPR has more value than another shock. Even when shock eliminates VF, it takes several minutes to return of normal heart beat. During this brief period CPR is useful.

5. *Reaffirmation of 2003 ILCOR statement: AEDs recommended for children >1 year*

The evidence is insufficient to recommend for or against the use of AEDs in infants under one year of age. However, AEDs are recommended for children over one year of age.

**Pediatric advanced life support**

1. *Use of advanced airways*

- Verify correct tube placement with clinical examination and capnography.
- Use of cuffed endotracheal tubes: In the in-hospital setting, a cuffed endotracheal tube is as safe as an uncuffed tube for infants (except the newborn) and children. In certain circumstances (e.g., poor lung compliance, high airway resistance, or a large glottic air leak) a cuffed tube may be preferable, provided that attention is paid to endotracheal tube size, position, and cuff inflation pressure. Keep cuff inflation pressure < 20 cm H<sub>2</sub>O. The formula

used for a Cuffed endotracheal tube size (mm ID) = (age in years/4) + 3.

- *Laryngeal mask airway (LMA)*: When endotracheal intubation is not possible, LMA is an acceptable adjunct for experienced providers, but it is associated with a higher incidence of complications in children.
  - *CPR with advanced airway*: Rescuer will no longer perform "cycles" of CPR. Compress chest at rate of 100 bpm without pause for ventilation.
2. *Vascular (IV or IO) preferred to ETT drug administration*  
Intravenous (IV) or Intraosseous (IO) drug administration is preferred. But if you cannot establish vascular access, you can give lipid-soluble drugs such as lidocaine, epinephrine, atropine, and naloxone ("LEAN") via the endotracheal tube, although optimal endotracheal doses are unknown.
  3. *Routine use of high-dose epinephrine not recommended*  
Use a standard dose (0.01 mg/kg IV/IO) of epinephrine for the first and for subsequent doses. If epinephrine is administered by endotracheal route, use a dose of 0.1 mg/kg. There is no survival benefit from routine use of high-dose (0.1 mg/kg IV/IO) epinephrine, and it may be harmful particularly in asphyxia.
  4. *Timing of drug administration during pulseless arrest*  
CPR-1 Shock-CPR. Give Drug during CPR: Drug delivery should not interrupt CPR (5 Cycles or 2 min). Check rhythm after 5 cycles. A drug may be administered during the CPR that is performed while the defibrillator is charging, or during the CPR performed immediately after the shock is delivered. These revisions were proposed to minimize interruptions in chest compressions during attempted resuscitation.
  5. *Rhythm disturbances and defibrillation*
    - Deemphasize the value of lidocaine compared with amiodarone in treating ventricular arrhythmias. "Give amiodarone or lidocaine (if you do not have amiodarone)."
    - Tachycardia with adequate perfusion does not require resuscitation.
    - The superiority and greater safety of biphasic over monophasic shocks for defibrillation is emphasized.
  6. *Postresuscitation care*
    - *Hypothermia*: There is possible benefits of induced hypothermia (32 to 34°C) for 12 to

24 hours for patients who remain comatose after resuscitation from cardiac arrest.

- *Role of inodilators*: There is a probable beneficial effect of vasoactive medications, including inodilators, to treat post resuscitation myocardial depression.
- Things that have not changed in PALS.
- Shock doses for VF/VT (note that the second dose was 2 to 4 J/kg and is now 4 J/kg).
  - Shock doses for cardioversion.
  - Major steps in bradycardia and unstable tachycardia algorithm.
  - Most drug doses.
  - Appreciation that most cardiac arrests in infants and children result from a progression of shock or respiratory failure.
  - Most recommendations for treatments of poisonings and drug overdose.

### Introducing the New NRP<sup>15,16</sup>

The Neonatal Resuscitation Program (NRP) has been extensively revised to reflect the latest neonatal research. Previously NRP assessment steps were performed in sequence that is, respirations were assessed and treated, then heart rate was assessed and treated, and so on. Now, the NRP guidelines recommend that, after performing the initial stabilization steps (positioning, clearing the airway, drying, and administering oxygen), the resuscitator evaluate respirations, heart rate, and color simultaneously. This change more closely reflects the real world situation.

Perhaps the most striking new recommendation concerns management of a newly born infant delivered in meconium stained amniotic fluid. Previously meconium was suctioned from the infant's trachea with a tracheal tube if respiratory efforts were depressed at birth or the amniotic fluid contained thick, particulate meconium. Under the new guidelines, the need for tracheal suctioning is determined not by the consistency of the meconium but by whether the baby has strong respiratory effort, good tone, and a heart rate over 100/mm. Babies who do not meet any of these criteria should undergo suctioning. As in the past, the guidelines call for reintubation and suctioning until "little additional meconium is recovered" or "the heart rate indicates that resuscitation must proceed without delay."

The guidelines recommend that the heart rate be determined by palpating the umbilical cord. If an umbilical pulse is absent, then a stethoscope should be used to listen to the chest.

Recommendation is to ventilate with oxygen for a full 30 seconds initially and then proceed with chest compressions if the heart rate remains below 60/min. Depress the sternum to a depth equal to 1/3 of the anterior-posterior diameter of the chest. Another new recommendation calls for the rescuer to pause chest compressions, but not ventilation, long enough to determine the heart rate by palpating the umbilical cord. Isotonic crystalloid solution (such as normal saline or Ringer's lactate) has replaced 5 percent albumin as the recommended volume expander. Epinephrine is now indicated only if the heart rate remains below 60/min after 30 seconds of assisted ventilation with 100 percent oxygen and an additional 30 seconds of ventilation accompanied by chest compressions.

The new changes are summarized below:

1. **Initial steps/Routine care:** If answer to any of these questions is no then proceed to initial steps. If answer to all is yes, then provide routine care. Ask 4 questions
  - Full term?
  - Clear of meconium and no evidence of infection?
  - Breathing or crying?
  - Good muscle tone?
 Initially color was also a question which has been removed, so now 4 instead of 5 questions.
2. **Temperature control in preterm neonates:** VLBW neonates likely to be hypothermic despite use of conventional techniques. Additional warming techniques should be used like plastic wrapping and monitor for development of hyperthermia. Avoidance of hyperthermia is particularly important in hypoxic-ischemic event. There is insufficient data to recommend routine use of modest systemic or selective cerebral hypothermia after resuscitation of infants with suspected asphyxia.
3. Initial steps do not include giving supplemental oxygen. Highlighted as a separate next step. If cyanosis persists despite free flow oxygen give positive pressure ventilation.
4. **Meconium stained liquor:** Routine intrapartum oropharyngeal and nasopharyngeal suctioning of babies born through meconium stained liquor no longer advisable.
5. **Oxygen:** For term babies use of 100% oxygen is recommended when baby is cyanotic or when positive pressure ventilation is required during neonatal resuscitation. If oxygen is needed during resuscitation, one may begin with less than 100% oxygen or room air. If so, supplementary oxygen

should also be available to use if there is no appreciable improvement within 90 seconds after birth. Use of variable concentration of oxygen guided by pulse oximetry may improve the ability to achieve normoxia more quickly. In situations where supplementary oxygen is not readily available positive pressure ventilation should be started with room air. For very preterm babies (less than 32 weeks gestation, use an oxygen blender and pulse oximeter during resuscitation. Begin PPV with oxygen concentration between room air and 100% oxygen. Increase oxygen concentration up or down to achieve saturation between 90 and 95%. If heart rate does not respond by increasing rapidly to >100 per minute correct any ventilation problem and use 100% oxygen. Oxygen should be available if there is no appreciable improvement within 90 seconds, if no facility of blender use 100% oxygen.

6. **Positive pressure ventilation (PPV) devices:**

- Flow controlled pressure limited mechanical devices (e.g. T-piece resuscitator) also an acceptable method of administering PPV especially in preterm babies.
- Laryngeal mask airway (LMA) is effective for ventilating term and near term babies.
- LMA should not to be used in the setting of meconium stained amniotic fluid, when chest compression is required, in VLBW babies and for delivery of medications.

Effectiveness is checked by primary measure of improvement by increasing heart rate and if the heart rate is not improving assess chest movements and check breath sounds.

7. **Medications:** Higher epinephrine IV doses are not recommended. While vascular access is being obtained, administration of a higher dose (up to 0.1 mg/kg) through the endotracheal tube may be considered. Naloxone administration is not recommended during the primary steps of resuscitation, and endotracheal naloxone is not recommended.
8. **Endotracheal intubation:** Capnography (exhaled CO<sub>2</sub>) recommended primary method of confirming tube placement, or when a prompt increase in heart rate does not occur after intubation. This may have no role in brief period of intubation for clearing meconium from trachea. Evidence is insufficient to recommend for or against use of esophageal detector device.
9. **Discontinuation:**
  - After 10 minutes of continuous and adequate efforts if there are no signs of life (no heart rate

and no respiratory effort) discontinue the resuscitative efforts.

- Non-initiation of resuscitation in following conditions—
  - In conditions with almost certain death or unacceptable high morbidity in the survivors as in following conditions
  - Confirmed gestation less than 23 weeks or birth weight < 400 g
  - Anencephaly
  - Babies with confirmed trisomy 13
  - In conditions associated with high rate of survival and acceptable morbidity resuscitation always indicated (gestation of 25 weeks or more).
  - In conditions with uncertain prognosis in which survival is borderline take into account parental desires.

We now discuss other techniques useful in management of the pediatric airway in the ED setting.

### Rapid Sequence Induction (RS)<sup>32-41</sup>

Rapid sequence induction refers to the rapid, uninterrupted injection of preselected dosages of an induction agent and a muscle relaxant.

In general, the three basic *indications* for tracheal intubation of pediatric patients in the emergency department are:

1. Airway protection from aspiration or obstruction.
2. Facilitation of positive pressure ventilation for the treatment of cardiovascular or respiratory failure.
3. Optimal airway control and conditions for diagnostic or therapeutic interventions.

Establishing the indication for tracheal intubation is the first step in advanced airway management; selection of the appropriate intubation technique after careful medical evaluation is the second critical step in the evaluation process.

Rapid sequence intubation is indicated in pediatric patients who require tracheal intubation but are considered at high risk for pulmonary aspiration of gastric contents ("full stomach"). The technique has three specific objectives:

1. Rapid induction of general anesthesia to attenuate autonomic reflex responses to direct laryngoscopic tracheal intubation (DLTI).
2. Rapid onset of optimal conditions to facilitate DLTI.
3. Reduction of risk for pulmonary aspiration through cricoid pressure, minimizing the duration of time that the airway is unprotected (induction to

confirmed tracheal intubation) and complete muscle relaxation to prevent vomiting.

In general, some of these clinical situations include: (i) Head injury patients at increased risk of raised intracranial tension; (ii) Combativeness; (iii) Prolonged seizures; (iv) Drug overdosages; (v) Respiratory failure; (vi) Near drowning; (vii) Burns; (viii) Sepsis; (ix) Pneumonia with compromise of airway; and (x) Ventilation.

Contraindications include clinical conditions precluding intubation like facial edema, trauma or fracture, distorted laryngotracheal anatomy or airway anomalies.

### General Order of Rapid Sequence Intubation

A specific team leader should direct the sequence. All medications should be mixed and ready to administer before proceeding. The following sequence is recommended.

1. Brief history and anatomic assessment
2. Preparation of equipment and medications
3. Preoxygenation
4. Premedication with adjunctive agents (atropine, lignocaine and defasciculating agents)
5. Sedation and induction of unconsciousness
6. Cricoid pressure (Sellick's maneuver)
7. Muscle relaxation
8. Intubation
9. Verification of ET tube placement
10. ET tube to be secured
11. Mechanical ventilation initiated, chest X-ray ordered
12. Placement of nasogastric tube
13. Medical record documentation.

**Remember:** All drugs must be drawn up and ready before starting RSI proper suction must be ready and easily accessible. Do not use muscle relaxants unless confident of intubating.

The equipment required for rapid sequence intubation includes:

1. Uncuffed and cuffed ET tubes-appropriate sizes
2. Laryngoscope handles in good working condition, with working, strong batteries
3. Laryngoscope blades-straight (Miller) and curved (Mcintosh)-appropriate sizes
4. Oral and nasal airways
5. Magill forceps (child and adult)
6. Non-rebreather oxygen mask (adult and pediatric)

7. Ventilation masks-all sizes, for bag-valve-mask ventilation
8. Self-inflating ventilation bags (250-1500 ml) with oxygen reservoir and PEEP valve
9. Oxygen sources
10. Suctioning source
11. Large bore suction (Yankauer)
12. Flexible suction catheters-appropriate sizes
13. Nasogastric tubes appropriate sizes
14. Pulse oximeter
15. Cardiorespiratory monitor
16. Cricothyrotomy/Tracheostomy sets on standby
17. End tidal CO<sub>2</sub> monitor.

#### *Drugs that are used for Sedation and Induction of Unconsciousness*

Sedatives are administered during RSI to eliminate the sensation of paralysis and decrease the sympathetic tone (Table 4.2).

**Table 4.2: Drugs used for sedation**

Agent	Dose IV	Onset of action	Duration
Thiopental	3-6 mg/kg	10-30 sec	10-30 min
Ketamine	1-2 mg/kg	1-2 min	10-30 min
Diazepam	0.1-0.3 mg/kg	1-2 min	30-90 min
Midazolam	0.05-0.2 mg/kg	1-2 min	30-60 min
Fentanyl	2-10 mcg/kg	1 min	30-60 min
Propofol	2.5 mg/kg	20 sec	10-15 min
Etomidate	0.2-0.3 mg/kg	30-60 sec	3-10 min

#### *Muscle Relaxation*

The ideal paralytic should have rapid onset, short duration minimal side effects and be reversible. Selection of agent depends upon clinical condition, age, volume status, ICP and other underlying medical conditions. Muscle relaxants (Table 4.3) used for

**Table 4.3: Muscle relaxants**

Agent	Dose IV	Onset of action	Duration
Succinylcholine	1-2 mg/kg (<10 kg)	30-45 s	4-10 min
	1.5-2 mg/kg (>10 kg)		
Rocuronium	0.8-1.2 mg/kg	45-60 s	30-45 min
Vecuronium	0.2-0.3 mg/kg	60-90 s	90-120 min
	0.001 mg/kg (defasc. dose)		
Pancuronium	0.1 mg/kg	2-3 min	45-90 min

intubation usually allows easier intubation and ventilation. These are usually administered along with sedative.

#### **RSI Drugs**

##### *Pharmacology*

Pharmacologic agents can be organized into three basic groups: (i) RSI, (ii) resuscitation, and (iii) post-intubation sedation medications. The RSI group consists of an anesthetic induction agent and rapid onset muscle relaxant. Agents for maintenance of sedation or anesthesia after intubation include narcotics, benzodiazepines, and an intermediate duration muscle relaxant.

##### *Premedication*

Intravenous lidocaine (1-1.5 mg/kg) or fentanyl (2 mcg/kg) 3 to 5 minutes before induction is advocated by many authors. Topical lidocaine has been used to blunt adverse airway reflexes and may be as effective as IV lidocaine. This technique, combined with conscious sedation, is preferable for the management of patients with anticipated difficult airways. Atropine (10 mcg/kg) is recommended in infants for reducing the risk for arrhythmias or reflex bradycardia from laryngoscopy and succinylcholine.

##### *Ketamine*

Derivative of phencyclidine, is a dissociative anesthetic agent. It produces analgesia, amnesia and dissociation from environment, maintenance of reflexes and cardiorespiratory stability.

The effects of Ketamine are: (i) Increased oral secretions; (ii) Increased intragastric pressure; (iii) Increased intracranial pressure; (iv) Increased intraocular pressures; (v) Hypersensitivity; (vi) Bronchodilatation; (vii) Emergence reactions-Hallucinations and nightmares. Emergence reaction can be reduced by using short acting benzodiazepines along with ketamine; and (viii) Laryngospasm.

The advantages of Ketamine are rapid action, short duration of action, provides sedation and analgesia while preserving respiratory drive and airway reflexes.

The indications for use of Ketamine are: (i) Asthma, respiratory failure (intrinsic bronchodilatory activity); (ii) Shock and hypovolemia (sympathomimetic agent).

The contraindications for use of Ketamine are: (i) Increased intracranial tension; (ii) Ocular problems; (iii) Coronary artery disease; (iv) Hypertension; (v) Active pulmonary infection; (vi) Tracheal abnormalities; and (vii) Psychosis.

*Thiopental*

This is a short acting barbiturate that produces rapid sedation without analgesia. Its advantages are that it provides cerebroprotection, reduces cerebral metabolic rate, and O<sub>2</sub> consumption and acts as a free radical scavenger to decrease damage by toxic metabolites in the injured brain.

However it is a myocardial depressant and cause, hypotension. When given as infusion, we need to monitor CVP/PAWP/and do echo. Thiopental is alkaline and is not compatible with acidic drugs such as succinylcholine, vecuronium and atropine. Intravenous catheter should be flushed after thiopental administration. It should be stored in cool place and used within 24 hours of reconstitution.

The adverse effects, include: respiratory depression, decreased cardiac output, hypotension, anaphylaxis, cough, and bronchospasm. The contraindications for use are porphyria and hypersensitivity.

*Benzodiazepines (Diazepam/Lorazepam/Midazolam)*

These provides anxiolytic activity, sedation, amnesia, and anticonvulsant properties.

The adverse effects include cardiovascular and respiratory depression. However, it has a broad dosing range.

Midazolam has gained popularity over other benzodiazepines because it has a faster onset and shorter duration of action. It is lipid soluble though available as a water soluble solution. May also be administered IM, if IV access is not available.

*Fentanyl*

It is a short acting narcotic. It is usually combined with a benzodiazepine. The side effects are chest wall rigidity; with rapid injection at > 15 mcg/kg/min.

*Propofol*

This is a new anesthetic agent used for induction and sedation. It has a rapid onset of action, short duration of action and cerebroprotective effect similar to thiopentone. It depresses laryngeal reflexes and permits cough/gag-free airway manipulation. However, it can cause decrease in mean arterial blood pressure and metabolic acidosis at high doses and with prolonged infusions.

*Muscle Relaxants*

Non-competitive, non-reversible relaxants bind to the post-synaptic receptors resulting in depolarization. This

initially results in brief period of repetitive excitation causing transient fasciculations. This is followed by a block of neuromuscular transmission and flaccid paralysis. Their mechanisms are not completely understood.

*Succinylcholine*

It is the agent with the fastest onset of action (< 1 min) and recovery (within 5-10 min). As a result, and unless specifically contraindicated, succinylcholine remains the drug of choice for RSI of pediatric patients in the emergency department. Succinylcholine binds to the nicotinic receptor, causing depolarization of the muscle membrane, fasciculation, and unresponsiveness to endogenous acetylcholine. The dosage of succinylcholine is 3 mg/kg in infants less than 1 year of age or 2 mg/kg in older children. Complete neuromuscular blockade occurs within 30 ± 7 seconds in 2 to 10-year-old children, with a 25 percent recovery time of 5 ± 2 minutes.

Side effects and complications are varied. Most are related to the depolarizing effects exerted through nicotinic receptors of the autonomic nervous system and muscle membrane.

A transient increase in heart rate is common, but rare episodes of severe bradyarrhythmia occur secondary to vagal stimulation. The most devastating arrhythmias are caused by dramatic hyperkalemia, which can lead to cardiac arrest. Depolarization of the muscle membrane causes fasciculation. High risk conditions include large body surface area burns, multisystem trauma, traumatic spinal cord or other denervating injuries, extensive muscle necrosis, and selected chronic myopathies.

Succinylcholine slightly increases intracranial pressure (ICP) in lightly anesthetized patients, which is abolished by deep anesthesia, IV lidocaine, or a defasciculating dose of a non-depolarizing muscle relaxant.

The succinylcholine-induced increase in intraocular pressure is modest at most, starts at 1 minute, and lasts 5 to 7 minutes.

In general, fasciculations are less intense in children than in adults. The use of routine defasciculation doses of non-depolarizing muscle relaxants to attenuate the pathologic effects of succinylcholine on ICP and intraocular pressure in emergency patients is controversial.

The contraindications for its use include: (i) Malignant hyperthermia or associated conditions; (ii) Chronic myopathy or denervating neuromuscular disease; (iii) 48-72 hours after acute phase denervating injuries,

burns, or massive tissue injury; (iv) Pre-existing hyperkalemia (renal failure is not a contraindication); and (v) Known plasma cholinesterase deficiency (risk for prolonged duration of action only).

### Non-depolarizing Agents

These are competitive/reversible neuromuscular blockers and compete with acetylcholine for the post-synaptic receptors but do not activate them. There is absence of fasciculations at the onset of paralysis. Usually they have slower onset of action and longer duration of action than succinylcholine.

### Rocuronium

Rocuronium is a relatively new non-depolarizing muscle relaxant similar to vecuronium but with the fastest onset of action in the class. It acts by competitively blocking the interaction between acetylcholine and the nicotinic receptor. Rocuronium is the drug of choice for RSI if succinylcholine is contraindicated because of rapid onset, lack of active metabolites, paucity of side effects, and intermediate duration of action. Onset of complete neuromuscular blockade in children averages 33 seconds at a dose of 1.2 mg/kg and closely rivals succinylcholine, but the time to 25 percent recovery (41 min) is eightfold more than that for succinylcholine, which classifies the drug as intermediate duration. The major side effects after bolus administration are a transient 15 percent increase in heart rate that is of no clinical significance in children. Rocuronium similar to succinylcholine, may be administered as an IM injection in the deltoid. Non-depolarizing neuromuscular blockade induced by rocuronium may be completely antagonized by acetylcholinesterase inhibitors, such as edrophonium or neostigmine, and an anticholinergic agent (e.g. atropine or glycopyrrolate).

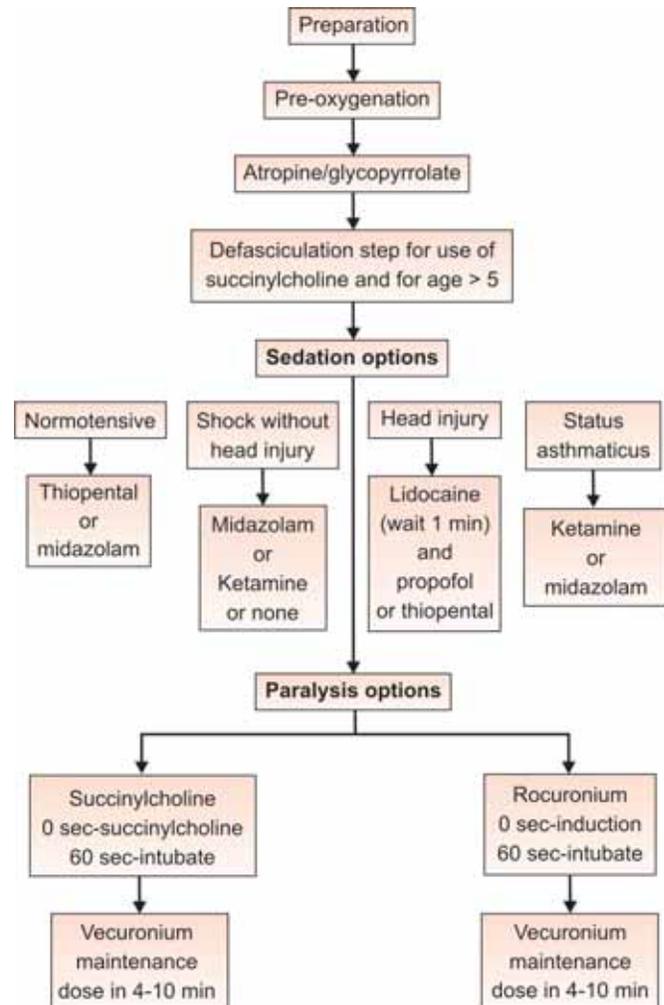
### Vecuronium

The duration of action is dose dependent for RSI. A dose of 0.2-0.3 mg/kg should be given (standard dose of 0.1 mg/kg insufficient). The onset of action is 60-90 seconds. It has a prolonged duration of action lasting 90 to 120 min. Action of these non-polarizing agents is reversed by neostigmine, pyridostigmine and edrophonium.

The clinical conditions and commonly used sequences for RSI (Flow chart 4.3) are:

- i. *Head injury (with ICP)*: Vagolytic, lignocaine, cricoid pressure, thiopentone or propofol, vecuronium/rocuronium.

Flow chart 4.3: Algorithm for RSI



- ii. *Hypotension shock*: Preoxygenate, bag-valve-mask ventilation, vagolytic, cricoid pressure, ketamine or thiopental in mild shock; none or lignocaine in severe shock, succinylcholine or vecuronium or rocuronium.
- iii. *Asthma/lower airway obstruction*: Preoxygenate (BVM), vagolytic, cricoid pressure, ketamine (+ midazolam), vecuronium or rocuronium.
- iv. *Upper airway obstruction*: Preoxygenate, vagolytic, cricoid pressure, propofol ( $\pm$  midazolam). Avoid paralysis.
- v. *Others*: Preoxygenate, vagolytic, cricoid pressure, (fentanyl+midazolam) or ketamine, vecuronium or rocuronium.

## Intubation

### *Confirmation of Tracheal Intubation*

Three critical questions must be rapidly and sequentially answered immediately after an intubation attempt:

1. Is the endotracheal tube in the trachea?
2. Is the tip of the endotracheal tube at the midtracheal location?
3. Can the lungs be ventilated?

Techniques for confirming intubation include direct observation of chest movement. Appropriate, equal air entry bilaterally on auscultation and absence of progressive gastric distention. These should be presence of "mist" in tracheal tube from the heated, exhaled air and a steady CO<sub>2</sub> level on the end-tidal CO<sub>2</sub> monitor and secondary confirmation by chest radiography.

## The Difficult Airway

### *Prediction of a Difficult Airway*

The potential for a difficult airway may be self-evident because of pre-existing or acquired conditions. However, normal individual anatomic variation may also contribute to difficulty with either tracheal intubation or mask ventilation. Various physical characteristics are associated with difficult airways: small mouth; limited mouth opening, or short interincisor distance; prominent upper central incisors with overriding maxilla; short neck or limited neck mobility; receding mandible or mandibular hypoplasia; high, arched and narrow palate; temporomandibular joint [TMJ] dysfunction; rigid cervical spine; obesity; infants, particularly those with associated congenital anomalies.

As a guide to airway evaluation, physicians should consider the steps required to visualize the larynx during laryngoscopy and the three fundamental problems that create difficult airways:

- Access:** Factors that limit access to the pharynx (i.e. trismus, large tongue, facial trauma, small mandible, morbid obesity, and C-collar)
- Visualization:** Factors that restrict or prevent visualization of the larynx (i.e. reduced mandibular space, redundant soft tissue, airway secretions, and anterior appearing larynx)
- Target:** Factors that physically distort or restrict intubation of the glottis (i.e. tumor, laryngeal displacement, subglottic stenosis, and extrinsic tracheal compression) (Flow chart 4.4).

## Laryngeal Mask Airway (LMA)<sup>42-45</sup>

The primary indication for the LMA is the need for an intermediate airway in the setting of failed intubation or mask ventilation. The Combitube is an acceptable alternative in older adolescents, but pediatric sizes are not available, and insertion is more complicated. The LMA is important as both a supraglottic ventilatory device and as a conduit for tracheal intubation in the setting of an unexpected difficult airway. It is not a replacement for the endotracheal tube and does not protect against pulmonary aspiration. The risk for gastroesophageal reflux may be increased with the LMA and general anesthesia. Cricoid pressure should be maintained during use of the LMA until the trachea is successfully intubated.

The LMA (The Laryngeal Mask Company, San Diego, US) is a reusable device, made primarily of medical-grade silicone rubber, and is entirely latex-free. Disposable devices are also currently available, but cost prohibits use, especially in our setting.

The LMA consists of three main components: An airway tube, mask and mask inflation line. The airway tube is a large-bore tube with a 15 mm standard male adaptor (Fig. 4.7). Its other end is fitted with a specially-shaped cuff which is inflated and deflated via a valve on the end of the inflation line. The mask is designed to conform to the contours of the hypopharynx with its lumen facing the laryngeal opening. The LMA is designed to be a minimally stimulating and invasive device. The LMA provides a clear upper airway if:

- Prior to insertion, it is correctly deflated to form a smooth flat wedge shape which passes easily around the back of the tongue and behind epiglottis.
- Protective reflexes are sufficiently depressed to permit smooth insertion.
- The user has acquired the necessary skill to insert the LMA.

### *Indications and Usage*

The indications include:

1. The LMA is not indicated for use as a replacement for the endotracheal tube and is best suited for use in elective surgical procedures where face masks are currently used or tracheal intubation is not necessary.
2. Known or unexpected difficult airway situation.
3. When tracheal intubation is precluded by lack of available expertise or equipment, or when attempts at tracheal intubation have failed.

Flow chart 4.4: Failed intubation algorithm

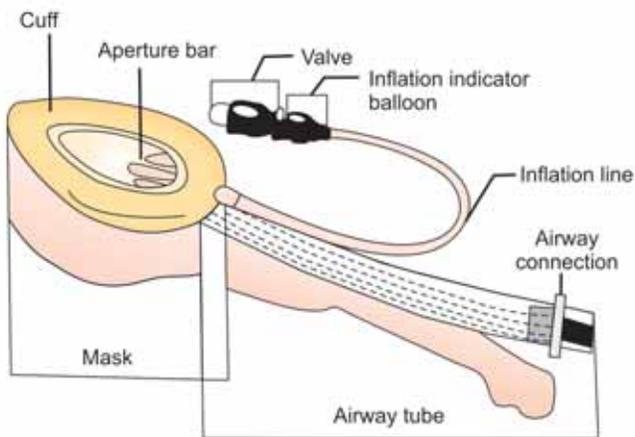
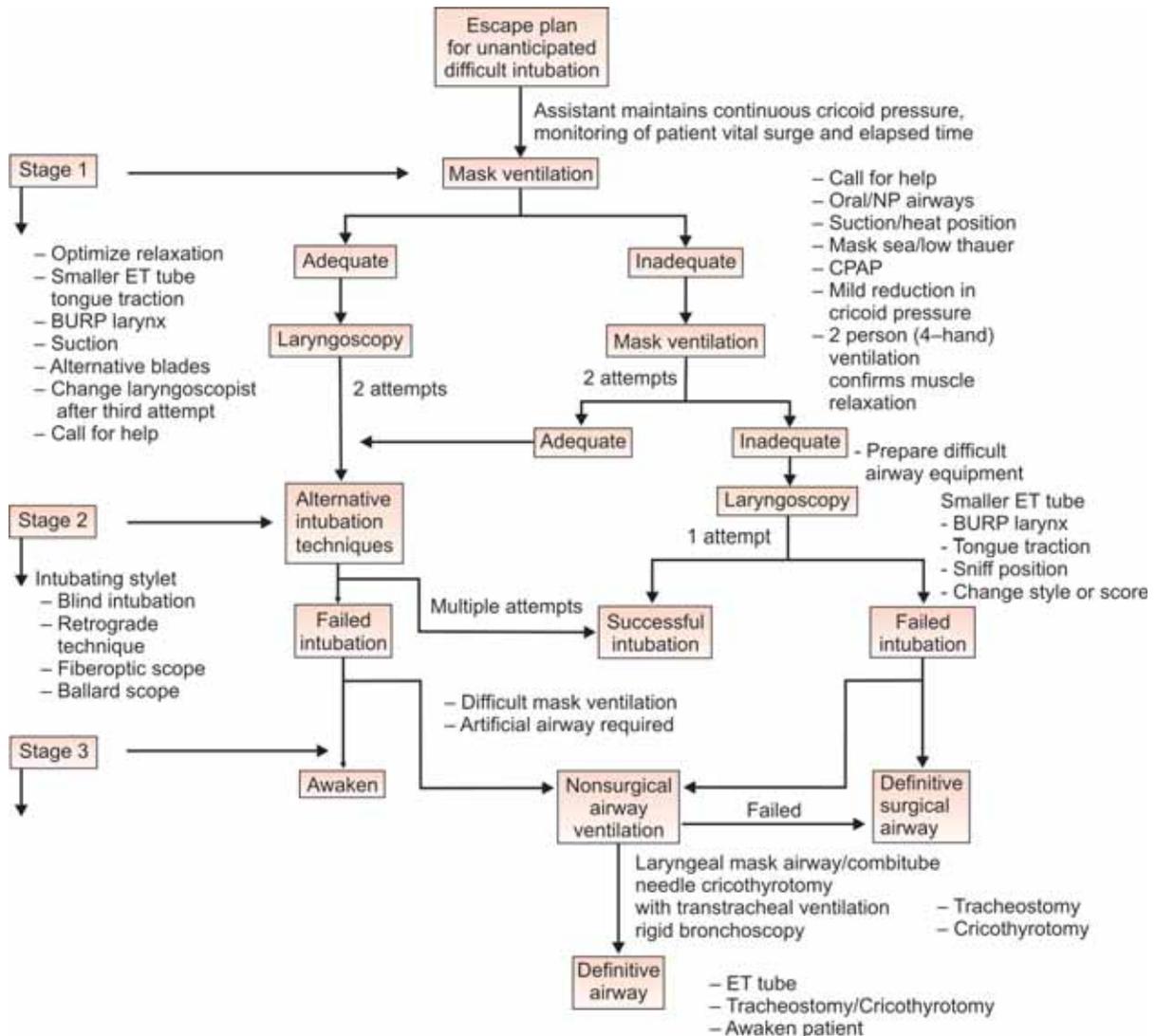


Fig. 4.4. The LMA device

### Contraindications

These include:

1. The LMA does not protect the airway from the effects of regurgitation and aspiration as described above.
2. The LMA should not be used in the resuscitation or emergency situation in patients who are profoundly unconscious (these require RSI) and in those who may resist LMA insertion.

### Precautions

1. Careful handling is essential. The LMA is made of medical grade silicone which can be torn or perforated. Avoid contact with sharp or pointed objects at all times.

- Do not expose the LMA valve to any cleaning solutions as these substances are absorbed by the LMA material resulting in premature valve failure.

#### Preparation for Use

- Thoroughly wash the LMA cuff and airway tube in warm water using a dilute 8 to 10 percent sodium bicarbonate solution.
- Clean the LMA using a small soft bristle brush. Thoroughly rinse the LMA in warm flowing tap water to remove residues.
- Steam autoclaving is the only recommended method for sterilization of the LMA. Prior to autoclaving, deflate the LMA cuff completely and ensure that the LMA valve is completely dry.

#### LMA Insertion

Lubricate only the posterior surface of the LMA mask to avoid blockage of the aperture or aspiration of the lubricant. Deflate the cuff prior to insertion. The LMA size selection guidelines are depicted in Table 4.4.

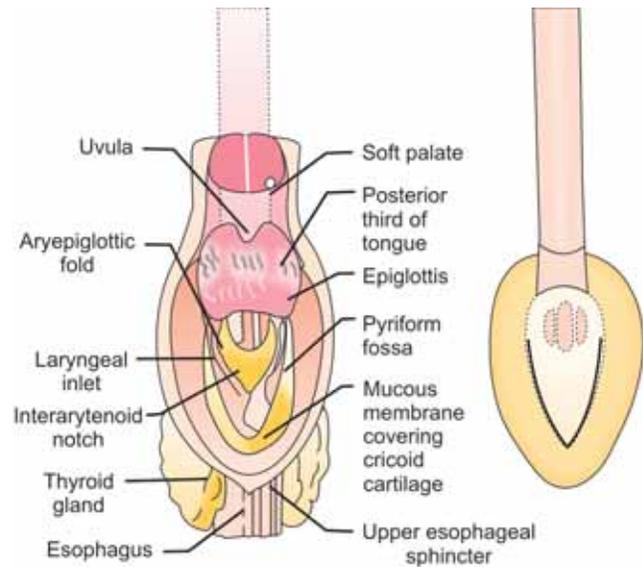
**Table 4.4: The LMA size guidelines**

Size	Patient
1	Up to 5 kg
1½	5 to 10 kg
2	10 to 20 kg
2½	20 to 30 kg
3	30 to 50 kg

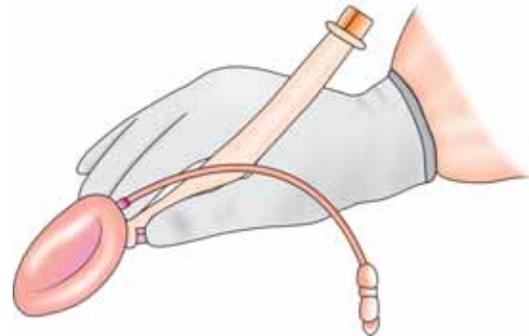
Achieve adequate level of anesthesia before inserting the LMA. Pre-oxygenate and position the head.

#### Inserting the LMA

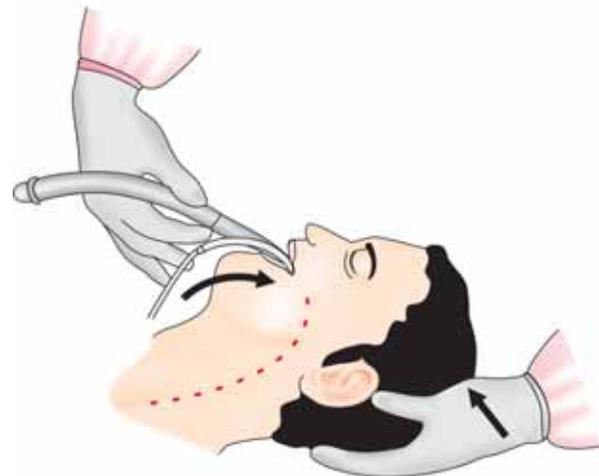
The standard technique is to hold the LMA like a pen, and with the index finger placed at the junction of the cuff and tube. The mask aperture should place forward and the black line on the airway tube should be oriented anteriorly towards the upper lip (Figs 4.5A to H). With the head extended and neck flexed, carefully flatten the LMA tip against the hard palate. Advance the LMA into the hypopharynx until a resistance is felt. The jaw may be pushed downwards with the middle finger. Check to ensure that the black line on the airway tube is oriented anteriorly towards the upper lip. Then inflate the cuff with just enough air to obtain a seal. Never over-inflate the cuff. During cuff inflation, do not hold the tube as this prevents the mask from settling into its correct location. A small outward movement of the tube is noted as the device seats itself in the hypopharynx.



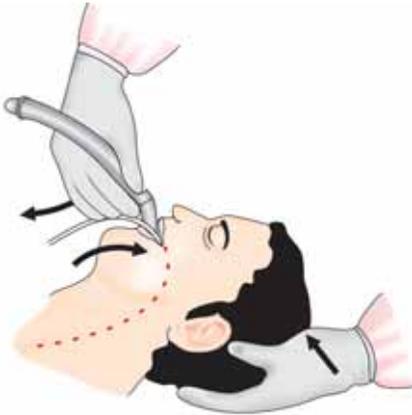
**Fig. 4.5A:** Anatomy of laryngeal region



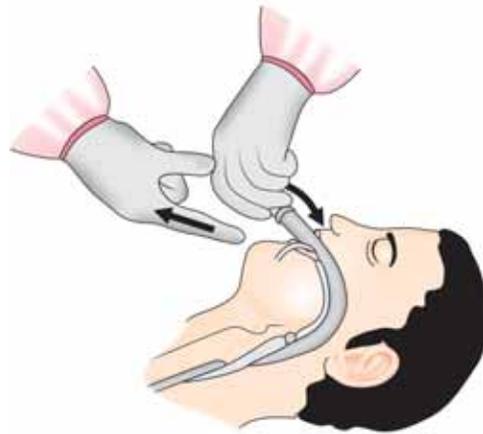
**Fig. 4.5B:** Method for holding the LMA for insertion



**Fig. 4.5C:** With the head extended and the neck flexed, carefully flatten the LMA tip against the hard palate



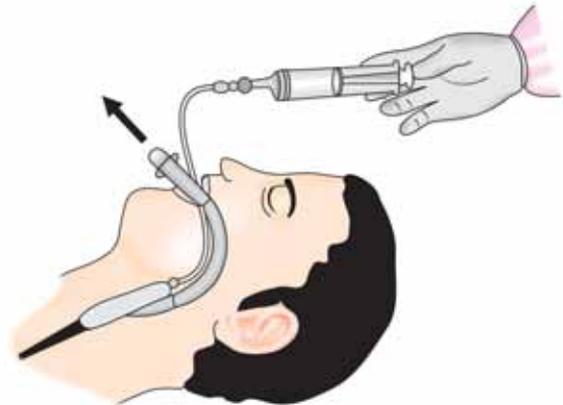
**Fig. 4.5D:** To facilitate LMA introduction into the oral cavity, gently press the middle finger down on the jaw



**Fig. 4.5G:** Gently maintain cranial pressure with the non-dominant hand while removing the index finger



**Fig. 4.5E:** The index finger pushes the LMA in a cranial direction following the contours of the hard and soft palates



**Fig. 4.5H:** Inflation without holding the tube allows the mask to seat itself optimally



**Fig. 4.5F:** Maintaining pressure with the finger on the tube in the cranial direction, advance the mask until definite resistance is felt at the base of the hypopharynx. Note the flexion of the wrist

**Figs 4.5A to H:** Technique of inserting LMA

The signs of correct placement are the slight outward movement of the tube upon inflation, the presence of a smooth oval swelling in the neck around the thyroid and cricoid area, or no cuff visible in the oral cavity.

**Gastric drainage:** Though a nasogastric tube is compatible with the LMA and does not interfere with its seal against the larynx, the nasogastric tube is best passed before LMA insertion. The presence of nasogastric tube does not rule out regurgitation. If the cuff fails to flatten or begins to curl as it is advanced, it is necessary to withdraw the mask and reinsert it. If difficulty in insertion persist, it is possible to use a

laryngoscope. To avoid trauma, force should not be used at any time.

### The Intubating LMA

This is a relatively new addition to the ED armamentarium for the difficult airway. It permits placement of a tracheal tube after appropriate positioning of the LMA. All interventions that are performed through a tracheal tube can then be undertaken, including administration of medications, ventilation, etc.

### Tension Pneumothorax

In the ED scenario, tension pneumothorax may complicate trauma or positive pressure ventilation. It should be suspected in a patient with blunt trauma or in any intubated patient who deteriorates suddenly during positive pressure ventilation. Clinical signs of tension pneumothorax include severe respiratory distress, hyperresonance to percussion and diminished breath sounds on the affected side, and deviation of the trachea and mediastinal structures away from the affected side. Treatment consists of immediate needle decompression—a large bore over-the-needle catheter is inserted through the second intercostal space, over the top of the third rib, in the mid-clavicular line. A gush of air may be heard after successful needle decompression. A chest tube should be placed as soon as it is feasible. A confirmatory chest X-ray is not needed.

### Cricothyrotomy<sup>46</sup>

It is the creation of an artificial opening in the cricothyroid membrane, may rarely be for O<sub>2</sub> administration to children with complete upper airway obstruction caused by a foreign body, severe orofacial injuries, infection, or laryngeal fracture. Cricothyrotomy facilitates effective delivery of oxygen to most patients with upper airway obstruction since the most common site of pediatric airway obstruction is at or above the glottis. Cricothyrotomy may be performed either surgically using an incision or with a needle (puncture). In the infant and toddler, risk of injury to vital structures such as the carotid arteries or jugular veins is high during surgical cricothyrotomy and must be performed only by persons with surgical training.

#### *Technique of Needle Cricothyrotomy*

A roll of sheets or towels is placed under the child's shoulders to position the larynx as far anterior as

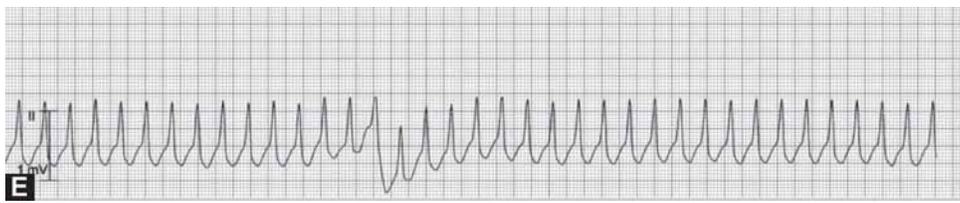
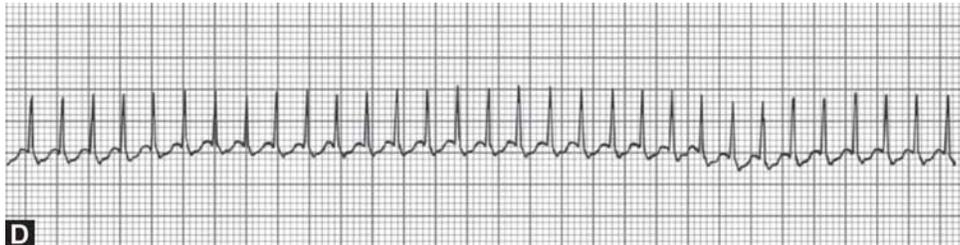
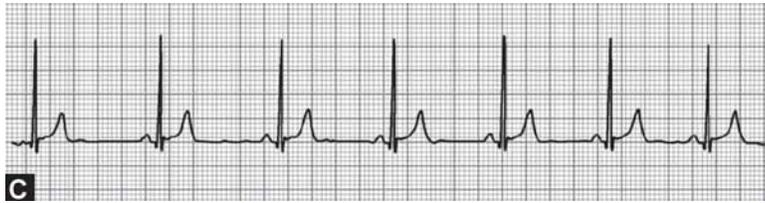
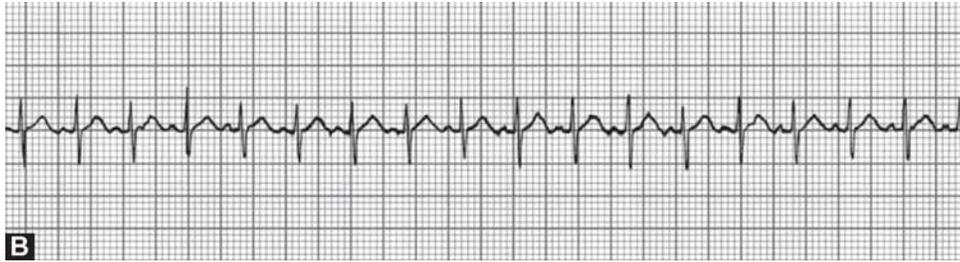
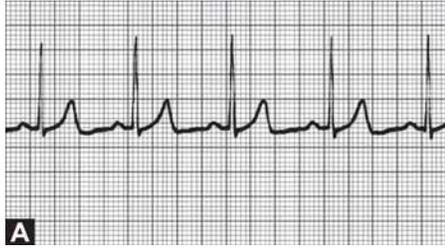
possible. The cricothyroid membrane is located. Locate an anterior and midline transverse indentation between the two cartilages.

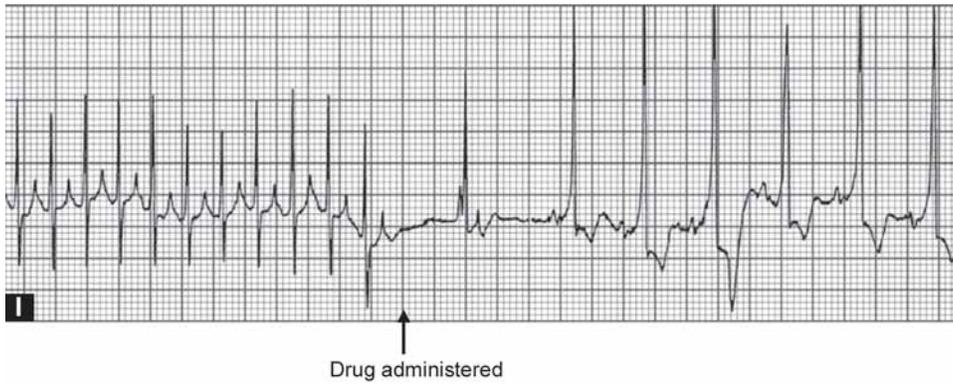
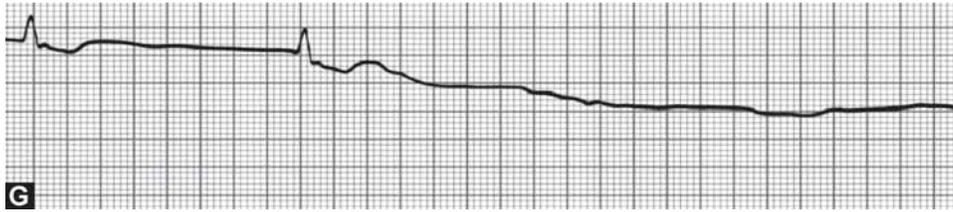
The relatively avascular cricothyroid membrane can be punctured and the underlying trachea entered percutaneously. Initially a pilot 20-gauge needle attached to a syringe is inserted and aspirated. After verifying position a large-bore cannula (at least 14-gauge) is then inserted through the cricothyroid membrane. The cannula is directed in the midline inferiorly and posteriorly at a 45 degree angle. Aspiration of air signifies entry into the trachea. The cannula is advanced into the trachea, the needle is removed, and air is again aspirated to confirm intraluminal position. The cannula is then connected to a ventilating device. An alternative method of cricothyrotomy involves a modified Seldinger technique using a guide wire. Oxygen administration may be possible through the cricothyrotomy but ventilation is limited. Ventilation is accomplished by connecting to a breathing circuit with a standard 22 mm connector. Jet ventilation may be used to ventilate, where available. Urgent evaluation by experienced personnel and permanent artificial airway placement is imperative.

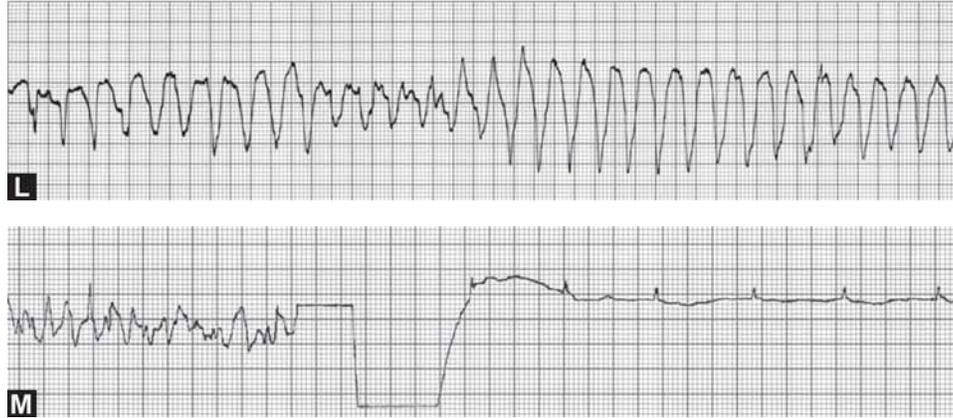
### Pediatric Arrhythmias<sup>47</sup>

Pediatric rhythms are divided into core rhythms A to H and non-core rhythms I to M:

- A. Normal sinus rhythm (Fig. 4.6A)
- B. Sinus tachycardia (Fig. 4.6B)
- C. Sinus bradycardia (Fig. 4.6C)
- D. Supraventricular tachycardia (SVT) (Fig. 4.6D)
- E. Wide-complex tachycardia; presumed ventricular tachycardia (monomorphic) (Fig. 4.6E)
- F. Ventricular fibrillation (VF) (Fig. 4.6F)
- G. Asystole (Fig. 4.6G)
- H. Pulseless electrical activity (PEA) (Fig. 4.6H)
- I. SVT converting to sinus rhythm with adenosine administration (Fig. 4.6I)
- J. Wide-complex tachycardia (in a child with known aberrant intraventricular conduction; this is SVT with aberrant conduction) (Fig. 4.6J)
- K. First-degree AV block (Fig. 4.6K)
- L. Torsades de pointes (polymorphic ventricular tachycardia) (Fig. 4.6L)
- M. VF converted to organized rhythm after successful shock delivery (defibrillation) (Fig. 4.6M)







**Figs 4.6A to M:** Core rhythms (A to H) and non-core rhythms (I to M)

- A. Normal sinus rhythm
- B. Sinus tachycardia
- C. Sinus bradycardia
- D. Supraventricular tachycardia
- E. Wide complex tachycardia; presumed ventricular tachycardia (monomorphic)
- F. Ventricular fibrillation (VF)
- G. Asystole
- H. Pulseless electrical activity (PEA)
- I. SVT converting to sinus rhythm with adenosine administration
- J. Wide-complex tachycardia (in a child with known aberrant intraventricular conduction; this is SVT with aberrant conduction)
- K. First-degree AV block
- L. Torsades de pointes (polymorphic ventricular tachycardia)
- M. VF converted to organized rhythm after successful shock delivery (defibrillation)

### Pediatric Bradycardia Algorithm

Support ABCs, as needed

Provide oxygen

Attach monitor

Perform CPR if HR <60 with signs of poor perfusion unresponsive to oxygenation and ventilation.

Give epinephrine:

- IV/IO: 0.01 mg/kg (1:10,000: 0.1 mL/kg)
- ET: 0.1 mg/kg (1:1,000: 0.1 mL/kg)

Repeat every 3-5 minutes

If bradycardia due to increased vagal tone or primary AV block

- Atropine first, 0.02 mg/kg

Consider pacing

### Pediatric Pulseless Arrest Algorithm

BLS algorithm

VF/PVT

One shock 2j/kg

Resume CPR immediately for 2 minutes

Check rhythm

Give one shock 4j/kg

Resume CPR immediately for 2 minutes

Give epinephrine

- IV/IO: 0.01 mg/kg (1:10,000: 0.1 mL/kg)
- ET: 0.1 mg/kg (1:1,000: 0.1 mL/kg)

Repeat every 3-5 minutes

Consider antiarrhythmics

- Amiodarone 5 mg/kg, or
- Lidocaine 1 mg/kg, or
- Magnesium 25-50 mg/kg for torsades de pointes

### Asystole/PEA

Perform CPR for 2 minutes

Give epinephrine

- IV/IO: 0.01 mg/kg (1:10,000: 0.1 mL/kg)
- ET: 0.1 mg/kg (1:1,000: 0.1 mL/kg)

Repeat every 3-5 minutes.

### During CPR

- Push hard and fast (100 per minute)
- Ensure full chest recoil
- Minimize interruptions in chest compressions
- Avoid hyperventilation

- Secure the airway and confirm placement
- After advanced airway is placed, CPR goes from cycles of 30:2 (1 rescuer) 15:2 (2 rescuers), to an asynchronous practice (100 cpm/8-10 bpm)

Rotate compressors every 2 minutes with the rhythm checks

- Search for and treat possible contributing causes (6 H's and 5 T's)
  - Hypovolemia
  - Hypoxia
  - Hydrogen ion (acidosis)
  - Hypo/hyperkalemia
  - Hypoglycemia
  - Hypothermia
  - Toxins
  - Tamponade (pericardial)
  - Tension pneumothorax
  - Thrombosis (coronary or pulmonary)
  - Trauma

### PEDIATRIC TACHYCARDIA WITH PULSES AND POOR PERFUSION

Assess and support ABCs as needed

Give oxygen

Attach monitor/defibrillator

#### Narrow QRS (< 0.08 sec)

##### *Sinus Tachycardia*

Compatible history with known cause

P waves present/normal

Variable RR, constant PRI

Infant rates <220 bpm

Children rates <180 bpm

Treat underlying cause

##### *Supraventricular Tachycardia*

Vague, nonspecific history

P waves absent or abnormal

Abrupt rate changes (fixed RR, PRI may be variable)

Infant rates  $\geq 220$

Children  $\geq 180$

Consider vagal maneuvers

If IV access

- Adenosine 0.1 mg/kg RIVP

- May double first dose

Or

Synchronized cardioversion 0.5-1 j/kg

If not effective, increase to 2 j/kg

Sedate if possible but do not delay cardioversion

#### Wide Complex (>0.08 sec)

##### *Ventricular Tachycardia*

Synchronized cardioversion 0.5-1 j/kg

If not effective, increase to 2 j/kg

Sedate if possible but do not delay cardioversion

Expert consultation advised

- Amiodarone 5 mg/kg over 20-60 minutes

Or

- Procainamide 15 mg/kg over 30-60 minutes

### PEDIATRIC TACHYCARDIA WITH PULSES AND ADEQUATE PERFUSION

Assess and support ABCs as needed

Give oxygen

Attach monitor/defibrillator

#### Narrow QRS (<0.08 sec)

##### *Sinus Tachycardia*

Compatible history with known cause

P waves present/normal

Variable RR, constant PRI

Infant rates <220 bpm

Children rates <180 bpm

Treat underlying cause

#### Supraventricular Tachycardia

Vague, nonspecific history

P waves absent or abnormal

Abrupt rate changes (fixed RR, PRI may be variable)

Infant rates  $\geq 220$

Children  $\geq 180$

Consider vagal maneuvers

If IV access

- Adenosine 0.1 mg/kg RIVP

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Synchronized cardioversion 0.5-1 j/kg

If not effective, increase to 2 j/kg

Sedate if possible but do not delay cardioversion

#### Wide complex (>0.08 sec)

##### *Ventricular Tachycardia*

Synchronized cardioversion 0.5-1 j/kg

If not effective, increase to 2 j/kg

Sedate if possible but do not delay cardioversion

Expert consultation advised

- Amiodarone 5 mg/kg over 20-60 minutes  
Or
- Procainamide 15 mg/kg over 30-60 minutes  
Or
- Lidocaine 1 mg/kg IV bolus

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*"From the greater strength and vivacity of the flame of a candle, in the pure air, it may be conjectured that it might be peculiarly salutary to the lungs in certain morbid cases when the common air would not be sufficient though pure oxygen might be very useful as a medicine." Joseph Priestly, the discoverer of oxygen as a therapy, thus speculated on its medicinal applications.*

Oxygen is by far, the most frequently used intervention in the management of the critically ill child; whether there is respiratory disease or not. There is often, a casual attitude towards the administration of oxygen. We forget that oxygen has well characterized and potentially toxic effects on the lungs and neonatal retina.

Oxygen therapy is the process of increasing the concentration of oxygen in inspired air, to correct or prevent hypoxia. The primary indication is the presence or risk of hypoxemia which may be from a pulmonary or extrapulmonary cause. Many biochemical reactions in the body depend on oxygen utilization. Supply of oxygen to the tissues depends on many factors like ventilation, diffusion across alveolar-capillary membrane, hemoglobin, cardiac output, and tissue perfusion. The goal of oxygen therapy is to supply adequate oxygen to the tissues. Reduced oxygen in the blood is hypoxemia, whereas reduced oxygen to the tissues is hypoxia.<sup>1</sup> For oxygen to increase  $\text{PaO}_2$ , there have to be units of low ventilation with normal or near normal perfusion. Any true extra or intrapulmonary right to left shunting will be largely unaffected by an elevation of alveolar oxygen tension ( $\text{PAO}_2$ ).

### Limitations of Oxygen Therapy<sup>1,2</sup>

The major limitation of oxygen therapy lies in the pulmonary toxicity of increased alveolar oxygen tension. This is clearly related to the duration and level of oxygen administration. An  $\text{FiO}_2$  0.6 for more than 24 hours is definitely associated with lung damage; whereas 0.4 or less can be given for prolonged periods.

Another feature that limits the usefulness of oxygen therapy in pulmonary disease is the relationship

between the  $\text{FiO}_2$  and the resultant  $\text{PaO}_2$  under conditions of varying or increasing intrapulmonary shunting (Fig. 5.1). This is akin to a certain amount of cardiac output by-passing the alveoli without getting oxygen from them. The diseased alveoli do not allow oxygen to diffuse into the capillaries that serve them. The amount of blood not getting oxygenated is expressed as a shunt fraction. Once this is in excess of 30 percent of the total cardiac output, oxygenation cannot be maintained with less than 0.5  $\text{FiO}_2$ . With a greater than 40 percent shunt, atmospheric oxygen alone will not be enough and some other means of providing oxygen under pressure will be needed-PEEP/CPAP/IPPV.

Oxygen administration for the correction of hypoxia can extend from simple tubes and masks to life support systems like ECMO.<sup>2</sup> Oxygen administration to the non-intubated patients only, is elaborated in this chapter.

### Using Oxygen

The goal of therapy is to achieve the optimal level of oxygen in the blood at the least possible concentration. Clinical assessment of oxygenation includes the five vital signs namely, heart rate, respiratory rate (including level of distress), blood pressure, temperature and  $\text{SpO}_2$  measurement. Patient assessment for distress is more important than any other parameter in deciding further therapy. Algorithms help but only as guidelines.

Oxygen should be given without wasting time and thought. Further therapy, amount, duration, etc can then be formulated. Between 0.4-0.6  $\text{FiO}_2$  is adequate in most situations.  $\text{FiO}_2$  of 1 is only needed during resuscitation. However, if needed, it should never be withheld for fear of toxicity.

If the patient is in obvious distress, a high flow system should be used. If there is no distress or cyanosis, and vitals are stable, a low flow device can be used.  $\text{SpO}_2$  monitoring is essential (5th vital sign) and should be kept above 92 percent. An increasing requirement of oxygen to maintain the same  $\text{SpO}_2$  is an ominous sign. Children should be nursed in the manner that makes them most comfortable and not by

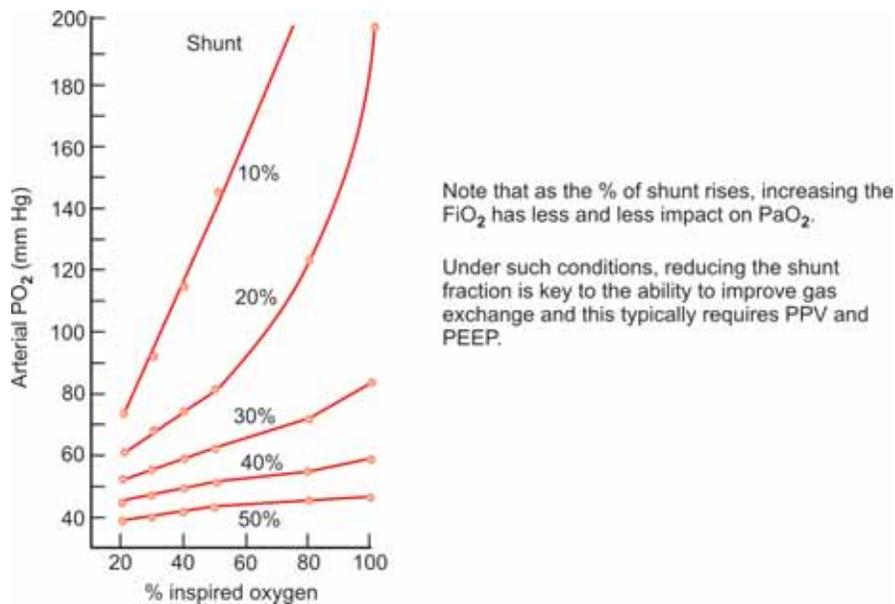


Fig. 5.1: Shunting: effects of FiO<sub>2</sub> on PaO<sub>2</sub>

any preconceived notions. Mothers are often the best administrators of oxygen. A frightened and agitated mother will result in a frightened and agitated child so a little time spent in explaining the situation may go a long way in providing comfort. If a child is upset by one method, another should be tried, including a "blow by" flow of gas.

**Caution:** If a child is seen to require O<sub>2</sub>, it is mandatory to supply the O<sub>2</sub> first and then determine the cause as quickly as possible. A rise in saturation on institution of therapy should not bring with it complacency. If there is an increasing requirement of O<sub>2</sub>, this too should be taken seriously and the flow not just dialed up to increase saturations. Very often, this is done to the point where the child's respiratory failure is recognized too late because the O<sub>2</sub> level

Table 5.1: Indications for intervention to a higher level of support

- Dropping SpO<sub>2</sub>
- Increasing FiO<sub>2</sub>
- Fatigue, confusion, agitation, drowsiness (ABG to look for PaO<sub>2</sub>, PaCO<sub>2</sub>, acidosis)
- Poor respiratory effort, obtundation
- Heart rate, BP fluctuations with diaphoresis.

delivered masked the saturation on the monitor. The indications for further intervention are summarized in Table 5.1.

A spontaneously breathing child can be delivered oxygen by any of the following systems:

#### Oxygen Delivery Devices

#### Oxygen Sources and Flow Regulators

Medical gas is provided either from a wall source or from a cylinder. A wall source should provide at least 50 psi of pressure at all times. Cylinders operate at psi of 1800-2400. This is too much even to run ventilators. This pressure cannot be delivered directly to the patients and hence, a down regulating valve before a flow meter is required. It is the flow meter and not the valve, that is used to manipulate the flow rate.

A low flow system provides FiO<sub>2</sub> that varies with the patient's inspiratory flow rates, e.g. nasal cannula, simple mask, non-rebreathing masks.

A high flow system provides fixed FiO<sub>2</sub> at flows that meet or exceed the patient's own inspiratory flow requirements. The patient's own flow requirements depend on the minute ventilation. Normal flow requirements are 3-4 times the MV and MV=Tidal Volume (Vt) × Respiratory rate (RR). Average Vt is about 6 ml/kg. Therefore a 5 kg child breathing at 60/minute needs about 6-7 l/min of an air oxygen

mixture. There are only three real high flow systems; (1) Venturi, (2) Non-rebreathing mask (sometimes), (3) Anesthesia bag and circuit with reservoir.

**Nasal cannula:** Two soft prongs in the nostrils attached to the oxygen source are attached to the nostrils. The prongs should have some space at the sides for exhalation, as there is only inflow. A single intranasal catheter has little role in any setting. The flow is directed to the nasopharynx, which continues to do the work of humidification and heat exchange. The maximum accepted flow is 2-4 l/min. Irritation and nasal obstruction may occur but these are generally well tolerated. In small premature babies, some inadvertent PEEP may be generated from close fitting prongs and although this device has been used after extubation to provide some pressure, it is inappropriate as a CPAP device and not recommended.<sup>3</sup> Neither should these prongs be substituted for the correct CPAP tubings to cut costs, as they are too narrow and offer too much resistance to air flow. The indications for this device are: (1) Minimal oxygen requirements less than 30%, (2) Weaning off from oxygen, (3) Chronic oxygen therapy on low concentrations. This device offers the single advantage of comfort and conservation of the gas.

**Simple masks:** A mask has perforations, which are exhalation ports. It fits the person's face without much discomfort. As babies vary in size, the most comfortable size must be sought and care must be taken that there are no pressure points or eye damage. Precise  $FiO_2$  is not the aim when using these masks and by their nature, they are used in conditions that are not severe. They provide a maximum of 40% oxygen but as this can vary with the flow rate provided with the inspiratory flow rate of the patient a small infant may get considerably more  $FiO_2$  than expected. Hence the importance of checking the concentration provided by using an analyzer.

**Partial rebreathing masks:** These are simple masks with an additional reservoir that allows the accumulation of oxygen enriched gas for rebreathing. A portion of the exhaled volume from the anatomical dead space is rich in oxygen. This is what enters the reservoir. Up to 60 percent can be delivered but the pitfalls are similar to those of the simple mask.

**Non-rebreathing masks:** This can work as a high flow system. These are like the above masks, but have a valve at the entry port that allows only oxygen from the source to enter the reservoir. It prevents room air from being entrained by an additional one way valve

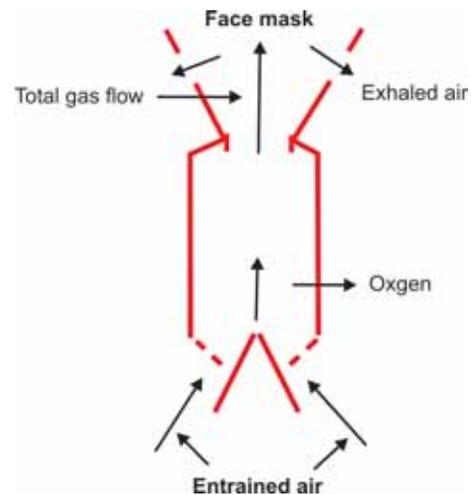
**Table 5.2:** Oxygen percentages with different systems

Litres/min	Simple	Partial rebreathing	Non-rebreathing masks
5	40%		
6	45-50%	35%	55-60%
8		45-50%	60-80%
10		60%	80-90%
12		60%	90%
15		60%	90-100%

at the exhalation port. A well-fitting mask can provide up to 100 percent oxygen. The oxygen percentages obtained with different systems are summarized in Table 5.2. When in doubt of the patient's requirements or if the patient is sick, as in the case of shock states, respiratory distress, cardiac failure; this is the mask to choose to institute  $O_2$  therapy as it will provide maximum oxygen and build reserves, even prior to intubation.

**Air-entrainment or venturi masks:** These are dilutional masks that work on the Bernoulli principle (Fig. 5.2). Oxygen is delivered through a narrow orifice at a high flow. Negative lateral wall pressure is created in the tubing system. There are openings (entrainment ports) near the nozzle that allow room air to be sucked in, diluting the oxygen. Changing the size of the nozzle, the flow rates, as well as ports, allows control of the amount of oxygen (Table 5.3).

The advantages of a venturi system include: (i) A high flow device guarantees the delivery of a fixed  $FiO_2$  the patient cannot entrain room air; (ii) The high flow comes



**Fig. 5.2:** Principle of the air-entrainment or venturi mask

**Table 5.3: Venturi devices and delivery of oxygen**

Liters/min (Oxygen/Total)	Oxygen concentration (percent)	Air: Oxygen ratio
2/53	24	25:1
4/45	28	10:1
6/47	31	7:1
8/45	35	5:1
10/33	40	3:1
12/32	50	5:3

from the air at low oxygen concentrations, therefore saving on oxygen costs; (iii) Can be used for low  $\text{FiO}_2$  also; (iv) Helps in deciding whether the oxygen requirement is really increasing or decreasing; When the  $\text{FiO}_2$  requirement is high, the flow rate of  $\text{O}_2$  required can be up to 12 l/min and this wastes a lot of  $\text{O}_2$ .

The oxygen concentrations obtained with venturi devices are depicted in Table 5.3.

Each device will have a table on the package insert as a guide to flow rates required by that particular device. This should be followed.

In children, the problem of fit and comfort is a daily issue. Infants too large for oxyhoods and too small for masks are our usual population. The average infant or even toddler is usually intolerant of a mask and will keep pulling it off. In fact, the infant that remains quiet when the mask is first fitted, is one that may be obtunded from hypoxia or too tired to fight.

**The oxyhood:** This is small baby's friend. A clear transparent hood that has enough room for the baby's head to fit comfortably and allows free neck and head movement without hurting the baby, is the correct hood size to use. At least 3-4 sizes are available and a unit should keep one of each size. Too big a hood will dilute the oxygen and too small a hood will discomfort and result in carbon dioxide accumulation. Adequate flow of humidified oxygen ensures mixing of delivered gases and flushing out of carbon dioxide. Oxygen gradients can vary as 20 percent from top to bottom. Continuous flow at 6 l/min avoids this problem. Cold air will cause heat stress and condenses on the baby's head, which will be mistaken for perspiration. Adequate flow of at least 6 l/min assures that  $\text{CO}_2$  does not accumulate and there must be an outlet for this at the top as  $\text{CO}_2$  is lighter than  $\text{O}_2$  and will rise to the top.

Face tents and oxygen tents are not used much in India. They do not provide more than about 30% oxygen and are cumbersome to use and keep clean and limit access to the child.

**Measurement of delivered oxygen:** An oxygen analyser or  $\text{FiO}_2$  meter is used to measure the concentration of oxygen actually delivered to the patient. The important part of this system is the actual sensor, its quality and accuracy is of paramount importance. It is connected to an instrument that digitally converts the sensed concentration into a reading that is displayed. The sensor has its own life of about 1000 sensing hours. It is the most expensive part of the machine. It also tells us how wrong our own rough estimates of delivered oxygen can often be. The oxyhood is the ideal place to use it but it can also be held at the mouth/nose within a mask for a quick reading. Calibration with every use is needed.

**Continuous positive airway pressure (CPAP):** This is indicated as a possible method for correcting hypoxemia when the oxygen requirement is > 60 percent with a  $\text{PaO}_2$  of < 60 mm Hg. This is the classic criterion but it must be stressed that clinical parameters and the general condition of the patient must also act as the paramount guiding force. CPAP, like background PEEP, reduces the work of breathing, increases the FRC and helps maintain it, recruits alveoli, increases static compliance and improves ventilation perfusion ratios.

Whatever the method of delivery, it is a versatile tool in the child with early, incipient or even frank respiratory failure. An easy method is to use snug fitting nasal prongs (the shortest, widest for the snuggest fit with appropriate connection tubing) with a closed mouth in small neonates <1400 grams this method can also provide non-invasive PP ventilation. A pacifier may help in keeping the mouth closed. CPAP systems vary from the unit made underwater seals, bubble CPAP systems with flow drivers readily available but more expensive, to those on ventilator systems.  $\text{FiO}_2$  will be inaccurate in the locally made systems. Stand alone CPAP systems with good oxygen blenders may be as expensive as basic ventilators. CPAP can be successfully used in RDS of prematurity, asthma, early ARDS, pneumonia, etc. It could be tried prior to conventional ventilation in any spontaneously breathing patient who does not require emergency ventilation. When using CPAP without intubating the trachea, a proper patient-system interface is important for success.

**Oxygen concentrator:** This device separates oxygen from nitrogen in the air by using adsorption and desorption over a material called zeolite, that adsorbs only the nitrogen. No ventilator or CPAP machine can run on this, as the outlet pressure is only 5 psi. The resultant  $\text{FiO}_2$  is about 0.4. This is useful in many

situations and is often used in home oxygen therapy. The device costs between Rupees 40,000 to 80,000.

**Weaning:** This is based on clinical and laboratory parameters. The SpO<sub>2</sub> levels are a boon in this phase and ABGs are usually not needed. Abrupt cessation may precipitate rises in pulmonary pressures in neonates. The flow/concentration should be gradually lowered while monitoring the child. Low flows and concentration can continue without ill effects for a long time.

A high flow system can be replaced by a low flow system, but this doubles the costs.

**Hyperbaric oxygen (HBO):** The goals are to deliver extremely high partial pressure of oxygen > 760 torr. This dissolves the plasma partial pressure and the dissociation occurs in the plasma rather than from that bound to hemoglobin.<sup>4</sup> At room air, the PaO<sub>2</sub> is 80-100 torr, at 1 ATA (atmospheric absolute) with 100 percent oxygen, it is 500+ torr. At 2ATA in 100 percent oxygen it is 1200 + torr. The indication for HBO are summarized in Table 5.4.

**Complications:** When air highly enriched with oxygen is supplied over a prolonged period of time to the alveoli, the inert gas nitrogen gets displaced and replaced by oxygen. Oxygen is absorbed out of the alveoli and this may lead to a loss of volume in the alveoli resulting in atelectasis. This is called the phenomenon of alveolar nitrogen washout.

**Hyperoxia is poorly defined:** It appears to produce cellular injury through increased production of reactive oxygen species, such as the superoxide anion, the hydroxyl radical, and hydrogen peroxide.<sup>5</sup> When the production of these reactive species increases and/or the cell's antioxidant defenses are depleted, oxygen radicals can react with and impair the function of essential intracellular macromolecules, resulting in cell

**Table 5.4: Indications approved for HBO**

Smoke inhalation	Clostridial myonecrosis
Carbon monoxide poisoning	Osteomyelitis (Refractory)
Cyanide poisoning	Acute traumatic ischemia
Thermal burns	Compromised skin grafts
Anemia due to severe blood loss	Radiation injury
Air embolism	

death. There is currently no reliably effective drug for preventing or delaying the development of oxygen toxicity in humans. Use of the lowest effective oxygen concentration, the avoidance of certain drugs, multiple transfusions and attention to nutritional and metabolic factors remain the best means currently available to avoid or minimize oxygen toxicity. Research is continuing into more effective ways to prevent, diagnose, and treat this disorder.

*Oxygen therapy saves lives. Yes, there are side effects but the advantages far outweigh the risks. Hypoxia kills more people than correctly delivered oxygen. Use but do not abuse.*

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"Shock" is a clinical syndrome that results from an acute, circulatory dysfunction and consequent failure to deliver sufficient oxygen and other nutrients to meet the metabolic demands of tissue beds.<sup>1</sup> The common final sequence of events in all forms of shock is altered cellular and subcellular metabolism and energy production. Clinically the syndrome of shock is characterized by signs of hemodynamic instability, tachycardia, poor capillary refill usually associated with relative or absolute hypotension; decreased skin temperature and evidence of major organ hypoperfusion (diminished urine output, changes in mental status, disseminated intravascular coagulation and acute respiratory distress syndrome).

A rational approach to the patient presenting with the shock syndrome not only requires a thorough understanding, of the dynamic nature of shock, but also warrants early recognition, hemodynamic monitoring and immediate provision of effective circulatory support and specific agents to combat shock syndrome. Such support is usually best provided in an intensive care unit.

### Etiology of Shock

Acute circulatory dysfunction can occur from one of the four basic abnormalities (Table 6.1).

1. **Hypovolemia:** Caused by loss of circulating volume.
2. **Cardiogenic shock:** Caused by pump failure as in myocarditis and valvular heart disease.
3. **Obstructive shock:** Caused by mechanical impediment to forward flow of blood, for example, pulmonary embolus and cardiac tamponade.
4. **Distributive shock:** Caused by inappropriate distribution of cardiac output secondary to abnormal vasodilatation.

Tissue perfusion is jeopardized by all the above etiologies but often these factors combine, that is why it is important to understand the cardiovascular variables operative in normal circulatory state.

Table 6.1: Etiology of shock

#### Hypovolemic

##### *Fluid and electrolyte loss*

Diarrhea, vomiting  
Excessive sweating

Pathologic renal loss

##### *Plasma loss*

Burns  
Leaky capillaries  
Sepsis, inflammation  
Nephrotic syndrome  
"Third space loss".  
Intestinal obstruction,  
Peritonitis

##### *Blood loss*

External-Laceration  
Internal-Ruptured  
viscera, GI bleed,  
intracranial bleed  
(neonates)

##### *Endocrine*

Diabetes mellitus  
Diabetes insipidus  
Adrenal insufficiency

#### Cardiogenic

##### *Myocardial insufficiency*

Congestive heart failure  
(Congenital, or acquired  
heart disease)  
Cardiomyopathies-Myocarditis  
Arrhythmias  
Hypothermia  
Drugs, toxins  
Myocardial depressant effect of  
hypoglycemia, acidosis, hypoxia

##### *Outflow obstruction*

Cardiac tamponade  
Pneumopericardium  
Tension pneumothorax  
Pulmonary embolism

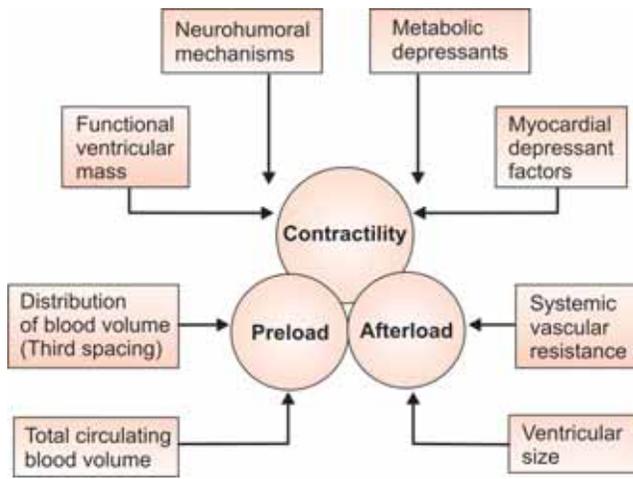
#### Distributive

Septic shock  
Anaphylaxis  
Neurogenic shock  
Drugs/toxin  
Tissue injury  
Prolonged hypoxia or ischemia

### Applied Physiology of Circulation

The basic function of circulation is delivery of oxygen and essential nutrients to peripheral tissues and removal of metabolic waste from those tissues. In most cases of shock there is either insufficient delivery or inappropriate distribution of oxygen and nutrients. An

Flow chart 6.1: Major determinants of cardiac output



understanding of pathophysiology of shock therefore requires an understanding of circulation and normal determinants of tissue perfusion.

**Cardiac output** is the most important determinant of tissue perfusion and is defined as volume of blood ejected by the heart per minute. It is the product of stroke-volume and the heart rate. The major determinants of cardiac output are depicted in Flow chart 6.1.

**Stroke volume** is the volume of blood ejected from the heart per ejection cycle. The heart increases as a result of endogenous catecholamines and increased adrenergic tone and decreases as a result of vagal tone. Within physiologic limits an increase in heart rate results in an increase in cardiac output but an excessively high heart rate may limit diastolic filling time. In young children and infants, elevations of heart rate is the most important compensatory mechanism for increasing cardiac output; therefore, one should refrain from treating the tachycardia alone without determining the underlying etiology.

The stroke volume is determined by preload, afterload and myocardial contractility.

**Preload** refers to the volume of blood filling the ventricle at the onset of diastole. It is determined by the volume of venous return to the heart and myocardial end-diastolic fiber length. Any reduction in circulating blood volume results in decreased venous return to the heart, decreased preload, decreased stroke volume and decreased cardiac output. Increase in venous capacitance as seen in distributive shock causes a relative hypovolemia, decreased venous return and decreased cardiac output. Volume replacement

improves cardiac output by increasing venous return and preload.

**Myocardial contractility** is determined by the total mass of functioning-ventricular muscle, myocardial perfusion, intrinsic and extrinsic neurocirculatory control mechanisms and the presence of physiologic and pharmacological stimulants or depressants. Acidosis, hypoxia, hypoglycemia, toxins, sepsis and primary myocardial disease all decrease contractility. Increase in contractility (positive inotropy) is affected by endogenous catecholamines and exogenous inotropic agents.

**Afterload** is best understood as the sum of forces that the ventricle must overcome in order to eject blood. It is determined by systemic vascular resistance. Increase in systemic vascular resistance causes an increase in the work of heart and a decrease in cardiac output. Afterload may be manipulated by vasodilator therapy.

### Distribution of Blood Flow

The distribution of blood flow is under local and neural control.

**Vascular factors** determine the exchange of gases and nutrients within tissue beds and the resistance to flow of blood through an organ bed. The latter depends upon the viscosity of blood and by length and cross-sectional area of blood vessels perfusing that organ.

**Neuronal control** is exercised through sympatho-adrenal discharge to the circulatory system. It is regulated by medullary neurons in the vasomotor center of the brainstem. Activity of these neurons is modulated by different impulses originating from various receptors located in strategic areas throughout the body. These are arterial and cardiopulmonary baroreceptors, chemoreceptors and somatic receptors in skeletal muscle. When cardiac output is insufficient to meet the metabolic demands of the tissues, interaction of these receptors with the sympathetic and parasympathetic output effects selective vasoconstriction which helps in shunting away the blood from less essential area such as skin (resulting in coolness, mottling, prolonged capillary refill), kidneys (resulting in decreased urine output), and gastrointestinal tract, to vital organs namely brain and heart.

A number of circulating humoral agents play an important role in cardiovascular homeostasis. These agents have direct cardiovascular and renal effects and indirect effect on central and/or peripheral adrenergic transmission. These are renin, vasopressin, adrenal steroids, prostaglandin, kinins, atrial natriuretic factor

and catecholamines. Their release is partly mediated through direct and indirect cellular effects of toxins, ischemia and antigens on various organs.

## Pathophysiology

### *Hypovolemic Shock*

Hypovolemic shock is the most common form of shock in children worldwide<sup>2</sup> and severe diarrhea which leads to hypovolemic shock is a major cause of death in India and other developing countries.<sup>3,4</sup> However, there is little data on its true incidence. It occurs due to a sudden reduction in circulating blood volume relative to the capacity of the vascular system. In true hypovolemia there is an actual loss of circulating blood volume, as a consequence of acute blood loss (internal or external) or loss of fluid and electrolytes (diarrhea, vomiting). Relative hypovolemia occurs secondary to peripheral pooling of fluid volume due to loss of vascular resistance. In children this form of hypovolemia is most often seen in septic shock, which is discussed later.

Important aspects of hypovolemic shock are the extent and the rapidity with which hypovolemia occur.<sup>5</sup> A sudden reduction in circulating blood volume of 10 percent in previously healthy individuals results in mild reduction in arterial pressure and moderate reduction in cardiac output, whereas loss of 40 percent of circulating blood volume produces reduction in arterial pressure and cardiac output. This loss of circulating blood volume is followed by a series of cardiac and peripheral homeostatic adjustments directed at restoration of systemic arterial blood pressure and perfusion of critical organs such as heart and brain. Whether these adjustments are adequate to maintain cardiovascular homeostasis is determined by patients pre-existing hemodynamic status.<sup>5</sup> The classic hemodynamic features of hypovolemic shock include tachycardia, peripheral vasoconstriction, hypotension and reduced cardiac filling pressures.

### *Cardiogenic Shock*

Cardiogenic shock in children is best viewed as a 'pump failure'. The common cause of cardiogenic shock in children is impaired cardiac performance following dysrhythmias, myocarditis, drug intoxication and metabolic derangements. The usual common denominator of this form of shock is an inadequate stroke volume, usually as a result of decreased myocardial contractility. Inadequate preload, with accompanying hypovolemia, capillary injury, vascular instability, decreased cardiac output and tissue perfusion, produce

a rapid downhill spiral of microcirculatory failure. Children rarely go through a compensated phase. A strict hemodynamic operational definition, based upon invasive hemodynamic monitoring is necessary to plan the management of cardiogenic or hypovolemic shock. It must be remembered that the end result of various types of shock is cell death.

### *Distributive Shock*

In this type of shock there is maldistribution of the blood volume. Common to all the conditions is massive injury to capillary endothelium resulting in loss of its integrity and leakage of fluid to interstitium or so-called "third-space". The classic example of distributive shock in children is septic shock; other conditions include anaphylaxis, drug intoxication and central nervous system injury.

Septic shock is a consequence of bacteremia most commonly associated with Gram negative organisms.<sup>6</sup> The condition is also seen with Gram positive infections as well as fulminant viral infection. It is more often seen in hospitalized children and is one of the common causes of mortality in pediatric intensive care units.<sup>7</sup> The etiology of sepsis varies with the age of child, presence of septic focus such as, peritonitis, pneumonitis or urinary tract infection and certain predisposing conditions that include neoplasia, immunodeficiency syndrome, immunosuppressive therapy and sickle cell disease.

Septic shock often follows a trimodal pattern of hemodynamic presentation: "warm" shock, "cold" shock and "multi" system organ failure. In the early stages, there is a decrease in systemic vascular resistance and an increase in cardiac output ("warm" shock). Hemodynamically it is characterized by low cardiac filling pressures, increased cardiac output, tachycardia, and decreased whole body oxygen consumption. The latter effect is due to impaired mitochondrial oxygen utilization and deficient oxygen delivery to cells despite an increase in overall cardiac output (maldistribution of cardiac output). Late in sequence of septic shock there is a decline in cardiac output and profound hypotension with severe acidosis, hypoxemia and hypoxia (cold shock). The end stages of septic shock are often associated with multiple organ derangements in cardiovascular, pulmonary and renal systems. Above stages are relevant to understanding of clinical severity of septic shock.

### *Mediators of Septic Shock*

The clinical manifestations of septic shock are as a result of complex interplay between microbial products and host mediator systems. Microbial factors that are

important are gram negative lipopolysaccharide (LPS), peptidoglycans from Gram-positive organisms, certain polysaccharide and extracellular enzymes (streptokinase) or toxins (enterotoxins of Staphylococci). The role of LPS as a mediator of septic shock has been studied most extensively.<sup>8</sup>

In patients with septic shock a variety of host factors have been implicated. These include activation of coagulation and fibrinolysis, complement and kinin system as well as factors released from stimulated macrophages and neutrophils like cytokines, tumor necrosis factors (TNF) and interleukin-1 (IL-1). Such patients may develop disseminated intravascular coagulation (DIC).<sup>9,10</sup> The deposition of fibrin in the microvasculature is closely linked to the development of multiple organ dysfunction syndrome (MODS).<sup>10</sup>

The hypercoagulation and associated MODS results in very poor prognosis for patients with sepsis.

A variety of host factors have been implicated in the pathogenesis of septic shock. These include components of coagulation cascade, complement and kinin systems as well as factors released from stimulated macrophages and neutrophils, like cytokines, tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), and interleukin-1 (IL-1), vasoactive peptides (histamine) and products of arachidonic acid metabolism (eicosanoids).

Interaction of host with these mediators produces a series of metabolic alterations at the cellular and sub-cellular levels, the end result of which is multiple organ system failure.

### Stages of Shock

Shock is a progressive disorder, which if unhalted, spirals down into even deeper levels of hemodynamic and metabolic deterioration. The progression may be fulminant and the patient may go into profound shock within minutes, such as after a massive hemorrhage. More often it evolves over a span of hours. The progression has been arbitrarily divided into three stages; (i) Early compensated shock; (ii) Progressive decompensated shock; and (iii) Late decompensated shock and multiorgan failure.

Early or compensated shock implies that vital organ function is maintained by intrinsic compensatory mechanisms. Venous capacitance is decreased, fluid shifts from interstitial to intravascular space and arteriolar vasoconstriction occurs. The blood flow to vital organs is normal or increased unless limited by pre-existing hypovolemia or myocardial dysfunction. At this stage symptoms and signs of hemodynamic impairment are often subtle and a high degree of

clinical suspicion is required to identify early signs of hemodynamic compromise. Arterial pressure is usually maintained, there is an increase in heart rate, narrowing of pulse pressure, early peripheral vasoconstriction (decreased skin temperature and impaired capillary refill  $\geq 3$  seconds) and mild anxiety. If shock is identified and vigorously treated at this stage, the syndrome may be successfully reversed in many cases.

The progressive decompensated stage appears with persistence of shock, especially when an additional stress is imposed on an individual in compensated shock. In this stage despite intense arteriolar constriction and increased heart rate, there is decline in blood pressure and cardiac output. This leads to lowered perfusion pressure, increased precapillary arteriolar resistance, progressive blood stagnation, anaerobic metabolism and release of proteolytic and vasoactive substances. Platelet aggregation and release of tissue thromboplastin produce hypercoagulability and DIC.

The patient may demonstrate impairment of major organ perfusion, which may manifest as altered mentation (impaired cerebral perfusion), oliguria (renal hypoperfusion) and myocardial ischemia (coronary flow impairment). The external appearance of patient reflects excessive sympathetic drive with acrocyanosis, peripheral vasoconstriction and cold and clammy extremities. It is evident at this point that the patient has deteriorated further. Rapid aggressive intervention is required to halt the progression of shock to decompensated stage.

Irreversible shock is a term applied to the clinical situation in which even correction of hemodynamic derangement does not halt the downward spiral. This stage is marked by progressive reduction in cardiac output, progressive fall in the blood pressure and worsening of metabolic acidosis. The prolonged hypoperfusion of brain, heart and kidneys leads to ischemic cell death in these organs with progressively worsening coma, renal failure and worsening pulmonary edema and acute respiratory distress syndrome (ARDS). A generalized endothelial damage disrupts the integrity of cell membrane with unrestrained shifts in fluids and electrolytes between cells and interstitial space, accounting for the often repeated statement, "shock not only stops the machine, but also wrecks machinery".

### Recognition and Assessment

The recognition of shock in a child who is lethargic, ashen gray, tachypneic and cold and has diminished peripheral pulses and low blood pressure presents no

difficulties. However, it is too late. To apply aggressive therapeutic interventions, early recognition of shock or impending shock is crucial. It requires a high index of suspicion and a knowledge of conditions predisposing to shock. The age of the child, previous medical conditions such as congenital heart disease, immunodeficiencies, suspected ingestion and a history of trauma should all raise the suspicion. Children who are febrile, have an identifiable source of infection or are hypovolemic from any cause are at a greater risk of developing shock. It may be very difficult to determine which children have crossed over from a state of being dehydrated and febrile to a state of fully developed shock.

On physical examination the most significant early physical signs of shock result from autonomic response to stress. In children, tachycardia occurs early and is often the sole mechanism to increase cardiac output. True tachycardia is noticed well before any notable alterations in blood pressure. As heart rate and respiratory rate vary considerably with age, reference to age-related standards is necessary. Blood pressure is age and weight dependent. Hypotension may be defined as systolic blood pressure < 5th centile; SBP (5th centile) :  $70 + (\text{Age in years} \times 2)$ .

The respiratory rate is usually elevated in shock. An increase in respiratory rate does not always indicate pulmonary disease but rather may be secondary to respiratory compensation for metabolic acidosis due to poor tissue perfusion.<sup>2</sup> Table 6.2 shows age-related upper limits of respiratory rate and pulse.

In a healthy child, the cardiovascular system shows extraordinary compensatory capability. Blood pressure may remain stable and heart rate may show relatively mild elevation until there is a sudden decompensation. The changes in heart rate and blood pressure also depend on the acuteness of the underlying events. An acute volume deficit of 10 percent may be marked by an increased in pulse rate by 20 beats/min and a 20 percent deficit has an associated heart rate increase of 30 beats/min with variable decrease in blood pressure. A gradual 10-15 percent loss of volume produced

minimal physiologic changes; hypotension may not occur until 30 percent volume loss.<sup>5</sup> Therefore, in the assessment of shock, blood pressure and pulse rate measurements may be helpful but cannot be overvalued as overall indicators of hemodynamic status in children.

Decreased tissue perfusion can be identified by decreased surface temperature, impaired capillary refill (> 3 seconds) and impaired function of several organs. Body surface temperature is time-honored, simple and effective method of assessing adequate tissue perfusion. Cold extremities or increased peripheral core temperature gradients (>3°C) indicate intact homeostatic mechanisms compensating for hypovolemia by cutaneous vasoconstriction.<sup>11</sup>

**Decreased capillary refill** is a sensitive indicator of tissue perfusion. The rate of refill after compression of soft tissues or nail beds for 5 sec is related to the site, temperature and the amount of circulation through the microvasculature. Normally a blanched area disappears extremely rapidly in less than 2 sec. A greater than 2 sec delay in refill is clearly abnormal. Although capillary refill is a very non-specific indicator of tissue hypoperfusion and doubts have been raised,<sup>12</sup> serial determination at frequent intervals is an excellent indicator of response to treatment. A gradual decrease in values is seen as the shock syndrome is successfully reversed.<sup>13,14</sup>

**Vital organ hypoperfusion** can be assumed to occur if oliguria from renal hypoperfusion coexists, or if child develops clouded sensorium with disorientation, lethargy, confusion or hallucinations. The temperature may be normal, low or elevated, depending upon the underlying etiology. Presence of hypothermia may be suggestive of sepsis in neonate.

The physical findings of early septic shock are different from other types of shock.

Table 6.3 summarizes clinical signs and symptoms of shock for rapid initial clinical assessment of a child in shock.

### Initial Hematologic/Biochemical Determinations

Initial laboratory determinations should include those that may alter immediate therapy. These include complete blood counts, serum electrolytes, serum calcium, blood sugar, arterial blood gases and serum lactate. Additional laboratory parameters should be obtained as warranted by the patient's condition and the most likely etiologies for shock state. Shock is a syndrome of multiple organ system failure. Directing laboratory investigations to assess the functions of

**Table 6.2: Age-related upper limits or respiratory rate and pulse**

Age	Respiratory rate (per min)	Pulse rate (per min)
Infant	50	160
Toddler	30	140
School-age child	25	120
Adolescent	20	110

**Table 6.3: Signs and symptoms of shock***Signs because of infection*

- i. Fever
- ii. Focus of infection

*Signs of autonomic response to low cardiac output*

- i. Tachycardia (most important early sign)
- ii. Tachypnea, hyperpnea
- iii. Blood pressure-normal

*Signs of decreased tissue perfusion (Helpful but cannot be relied upon)*

- i. Color: pale, ashen-gray
- ii. Capillary refilling time ( $\geq 3$  sec)
- iii. Decreased skin surface temperature
- iv. Increased difference between core and peripheral temperature  $\geq 2^{\circ}\text{C}$

*Signs of major organ dysfunction (late signs)*

*Brain:* Agitations, stupor-coma, ischemic brain injury

*Kidneys:* Acute renal failure; oliguria, anuria

*GIT:* Erosive gastritis, nasogastric aspirates decreased bowel sounds

*Liver:* Ischemic hepatitis; elevation of transaminases and bilirubin

*Hematologic:* Coagulation abnormality, elevated PT, PTTK, severe DIC and thrombocytopenia

**Table 6.4: Laboratory measurement in shock patients**

<i>Cardiovascular system</i>	<i>Gastrointestinal, liver</i>
ECG	Stool occult blood
Chest X-ray	Gastric pH
Blood gases	Liver function tests
Echocardiogram	
<i>Respiratory system</i>	<i>Metabolic</i>
Blood gases	Serum $\text{Na}^+$ , $\text{K}^+$ , $\text{Ca}^{++}$
Lung function tests	Blood glucose
	Serum lactate
	Serum proteins
<i>Renal System</i>	<i>Infection screen</i>
Urine-Sp. Gravity, $\text{Na}^+$ , sediment, protein, sugar	Cultures-Blood, CSF
Blood urea, S. creatinine	Urine, stool, pus
<i>Hematologic System</i>	
Complete blood counts	
Coagulation screen	
Platelet count, fibrinogen degradation products	
D-dimers	

**Monitoring of Shock**

Adequate monitoring of shock serves the following purpose:

1. It allows, definition of pathophysiologic stages of shock, which is helpful in diagnosis, prognosis and treatment.
2. It permits continuous assessment of vital organ function.
3. It provides a means to assess the efficacy of therapeutic intervention.
4. It prevents complications by early recognition of correctable problems.

A repeated and careful examination of the child's physiological status must be made by a competent observer. The emphasis must be on ongoing assessment of alteration in peripheral perfusion (capillary refill), color, presence of cyanosis, characteristics of the pulse, blood pressure, respiratory pattern and level of consciousness. In addition, the minimum monitoring of a child with shock or at risk for shock should include continuous monitoring of ECG, temperature (skin and core)<sup>11</sup> hourly urine output, and central venous pressure.

The central venous pressure (CVP) is principally a measure of preload. The CVP may not be useful as a single absolute value since the range of normal (5 to 15 cm) is large. However, a low CVP is an indicator of decreased preload or hypovolemia. CVP monitoring is most useful in assessing response to fluid resuscitation. The CVP of hypovolemic patient will change very little in response to an initial fluid bolus, but the CVP of a patient who is euvoletic, hypervolemic or in cardiogenic shock will have a large sustained increase to a fluid challenge.

**Invasive Hemodynamic Monitoring<sup>15</sup>**

In children with myocardial compromise, consideration must be given to invasive BP and pulmonary arterial pressure monitoring. Many invasive bedside monitoring devices are now available and are complemented by an ever widening range of laboratory measurements. Invasive pressure monitoring provides quick and accurate assessment of cardiac filling as well as right and left heart filling pressures and alteration in pulmonary vascular resistance.

The use of balloon tipped, flow directed multilumen pulmonary artery catheter (Swan-Ganz catheter) has increased our understanding of shock states. It can help in establishing the nature of hemodynamic problem, optimize cardiac output while minimizing the risk of fluid overload and allows the rational use

of inotropic and vasoactive agents. Measurement of pulmonary artery occlusion pressure in addition to CVP with these catheters adds an extra dimension of information about left ventricular function. In addition combining pressure measurements with the determination of cardiac output allows one to quantitate cardiac performance accurately.<sup>16,17</sup>

### Management of Shock

The following are major objectives in the management of shock:

1. Rapid recognition of shock and resuscitation.
2. Correction of initial insult.
3. Correction of secondary consequences of shock.
4. Maintenance of function of vital organs.
5. Identification and correction of aggravating factors.

All the objectives are approached simultaneously in an organized way so as to ensure optimal therapy as illustrated in Figure 6.3.

During the initial resuscitation in emergency room, therapy should be directed towards achievement of clinical therapeutic endpoints of shock resolution (Table 6.5).

### Oxygen Administration

The initial resuscitation involves securing a patent airway, administration of oxygen and establishment of intravenous access.<sup>19,20</sup> Oxygen is a drug, and its use should be guided by considerations applicable to the use of other drugs in treatment of shock. In general, oxygen in maximal concentration should be administered initially to all patients in shock, in view of impaired peripheral oxygen delivery.<sup>20</sup> An attempt should be made to achieve an arterial oxygen saturation of 90 percent or higher. Once stabilization is achieved, fraction of oxygen in inspired air should not exceed 0.6, to reduce the incidence of pulmonary oxygen toxicity. Oxygen may be administered through

non-rebreathing mask, nasal prong CPAP, tracheal tube with CPAP or mechanical ventilation. Mechanical ventilation is indicated in patients having hypoxemia not responding to oxygen administration by non-invasive methods, hypotension and/or clinical signs suggestive of myocardial dysfunction or pulmonary edema. Continuous assessment of oxygenation can be guided by the use of pulse oximetry, but significant alterations in management must be based upon direct assessment of arterial blood gases.

### Intravenous Access

Emergency intravenous access during the first five minutes of resuscitation of a shock patient is a difficult but a realistic goal. Standard techniques like peripheral vein catheterization either percutaneously or by venous cutdown are likely to be unsuccessful in a patient with severe shock. In such a case, intraosseous line should be established if three attempts have failed or 90 seconds have elapsed.<sup>18</sup> Using a standard protocol, IV access during pediatric resuscitation should rarely be delayed beyond fifth minute if all available techniques are utilized.<sup>20,21</sup>

### Fluid Therapy

Adequate volume resuscitation is the most important step in management of hypovolemic, septic and distributive shock.<sup>22</sup> Preload needs to be optimized to improve cardiac output and thus oxygen delivery. Although hypovolemic shock is the most common type of shock in children, the precise etiology of shock and volume status of the patient may not be completely apparent sometimes. Fluid therapy should be initiated before establishing a line for monitoring the CVP. In the case of otherwise normal cardio-respiratory function, volume overload resulting in pulmonary edema is rare. The circulating volume must be replaced in boluses of 20 ml/kg within minutes since rapid restoration of cardiac output and tissue perfusion pressure reduces the chances of serious organ damage particularly acute renal failure.<sup>17,19</sup>

**Choice of fluid:** Guidelines for the use various intravenous fluids for volume resuscitation are in Table 6.6. The available choice of fluid includes crystalloid, colloids and blood products. Recent evidence clearly supports the use of crystalloids in pediatric septic shock.<sup>23</sup> There may be a role of colloids in patients with pre-existing low plasma oncotic pressure state such as PEM, nephrotic syndrome, acute severe burns or liver disease, in patients with malaria and dengue shock syndrome.<sup>24,25</sup> Blood and blood products are not the

**Table 6.5: Therapeutic endpoints in the management of shock<sup>18</sup>**

- Normal pulses
- Capillary refill time < 2 sec
- Warm extremities
- Normal mental status
- Normal blood pressure
- Urine output > 1 ml/kg/hr
- Decreased serum lactate
- Reduced base deficit
- SvO<sub>2</sub> > 70%

**Table 6.6: Intravenous fluids for volume resuscitation**

<i>Solutions</i>	<i>Indications</i>
<b>Crystalloids</b>	
0.9 percent sodium chloride Ringer's lactate solution	<ol style="list-style-type: none"> <li>1. Initial fluid of choice for shock of undetermined etiology</li> <li>2. Can be used for up to 50 percent volume expansion</li> <li>3. Hypertonic saline used in burn patients <i>Caution:</i> Avoid excess use in severe hypo-oncotic states and cardiogenic shock</li> </ol>
<b>Colloids</b>	
Five percent serum albumin in normal saline	1. Hypovolemic-hypoproteinemic patients with renal cardiac and respiratory failure
Twenty-five percent serum albumin in normal saline	2. Refractory hypovolemic shock (in combination with crystalloids) <i>Caution:</i> Contraindicated in burns and severe capillary leaks
Ten percent dextran-40 in 5 percent dextrose Hydroxyethyl starch in normal saline	
<b>Blood products</b>	
Whole blood	1. Volume replacement in trauma or hemorrhage
Packed red blood cells	2. Packed cells in burn patients
Fresh frozen plasma	3. Plasma in coagulopathies

first choice for immediate volume expansion in children with shock. Blood is recommended for replacement of volume loss in pediatric trauma patients with inadequate perfusion despite administration of 2-3 boluses of isotonic crystalloid.

**Amount of fluid:** The amount of fluid to be administered depends upon the volume status and ongoing losses of the patient. Initial fluid resuscitation usually require 40-60 ml/kg but can be as much as 200 ml/kg in septic shock.<sup>19</sup> Response to a fluid challenge should include an improvement in capillary refill, an improvement in sensorium, a decrease in tachycardia, elevation of an initially low blood pressure and the maintenance of an adequate urine output ( $\geq 1$  ml/kg/h). If there is no response after 2 or 3 boluses, CVP measurement may be useful in evaluating the response to further fluid therapy. The CVP should be interpreted in light of serial clinical assessment, as it is likely to be influenced by rapid heart rate and increases in intrathoracic pressure.<sup>17</sup> Patient should be monitored for clinical signs suggestive of myocardial dysfunction or pulmonary edema during fluid therapy.

Every effort should be made to resolve shock in the first hour of resuscitation as it is associated with a significant decline in mortality rate in sepsis. Implementation of a time sensitive goal directed approach to the management of septic shock is of paramount importance (Flow chart 6.2).

### Cardiovascular Support

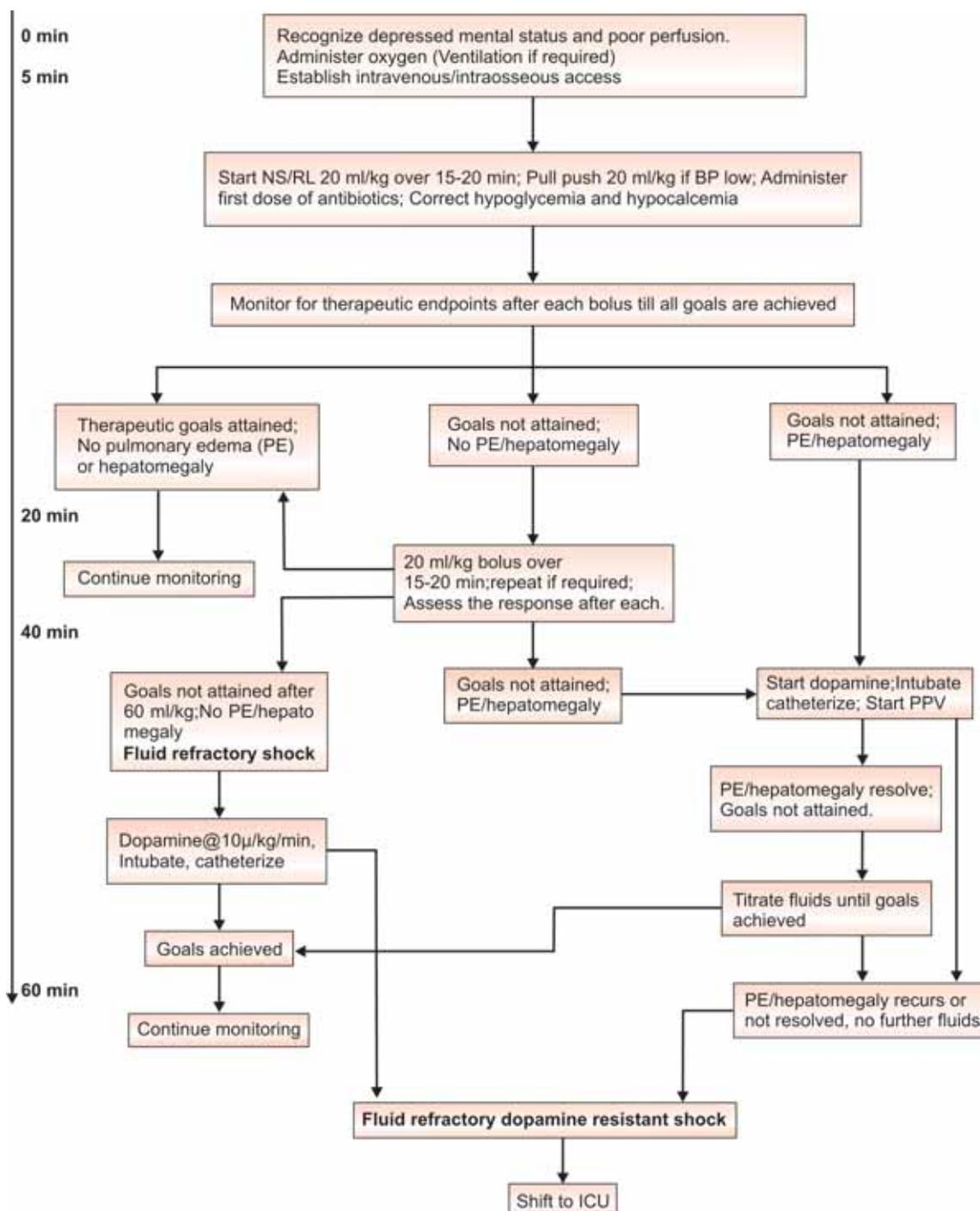
Cardiogenic shock and late stages of septic shock are characterized by impairment of myocardial function.<sup>7,27,28</sup> Hence, therapeutic endeavors to optimize cardiac output should be the cornerstone of shock therapy.

### Inotropic, Vasopressor and Vasodilator Therapy<sup>27-29</sup>

The therapy is directed towards increasing myocardial contractility and decreasing left ventricular afterload. Unfortunately, no single agent appears to produce the effects desired in all forms of shock. Proper choice of drugs requires knowledge about exact hemodynamic disturbance and pharmacology of these drugs and their hemodynamic effect at various doses, site of action and dosage, which are given in Tables 6.7 and 6.8.<sup>30,32-36</sup>

The choice of vasoactive drug used in patients with shock would depend on patient's condition after adequate volume resuscitation. Some of pediatric patients have high cardiac output, vasodilation and hypotension manifesting as tachycardia, flush CFT, low to low normal blood pressure and wide pulse pressure. *Dopamine* is generally accepted as first line vasopressor in this setting. It increases MAP through an increase in cardiac output and peripheral resistance.

Children with septic shock more often have myocardial dysfunction with compensatory vasoconstriction.

Flow chart 6.2: Management of pediatric septic shock within first hour of resuscitation<sup>26</sup>

This leads to a state of low cardiac output with high cardiac filling pressures and high systemic vascular resistance manifesting as tachycardia, prolonged CFT, cold extremities and low to low normal blood pressure

and narrow pulse pressure. *Dobutamine* is the agent of choice in this setting. However, dobutamine alone may be inadequate in a hypotensive patient. Therefore, it is usually combined with dopamine or norepinephrine.

**Table 6.7: Properties of various sympathetic receptors, their properties and effects of cardiovascular support drugs**

Receptor	$\alpha$	$\beta_1$	$\beta_2$
Receptor	1-vasoconstrictor	Heart rate	Vasodilation
Property	2-decreased central sympathetic flow, vasoconstrictor	Contractility Conduction	
Drugs			
Phenylephrine	++/+++	-	-
Nor-adrenaline	++++	++++	+ / ++
Adrenaline	++++	++++	++++
Isoproterenol	-	++++	++++
Dopamine	++/+++	++++	++
Dobutamine	+	+++++	

**Table 6.8: Cardiotonic vasodilator agents**

Drug	Dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	Predominant site of action	Comments
Dopamine	0.5-5 5-10 >10	Dopaminergic $\beta_1$ $\alpha_1$	Vasodilator to renal and cerebral beds. Inotrope dose Pressor dose, arrhythmogenic
Dobutamine	2-20	$\beta_1$ and $\beta_2$	Inotrope, weak chronotrope, selective mild vasodilator
Isoproterenol	0.1-5		Inotrope, chronotrope, vasodilator, arrhythmogenic
Nor-adrenaline	0.05-1		Strong vasoconstrictor, useful in resistant hypertension.
Adrenaline	0.03-0.1 0.01-0.2 > 0.2	$\beta$ $\alpha_1, \beta_1$ and $\beta_2$ mixed $\alpha$	Inotrope Inotrope and pressor effects, Vasoconstriction and arrhythmogenic
Amrinone	5-10		Loading dose 2-3 mg/kg IV over 30 min
Milrinone	0.75-1.0		Loading dose 75 $\mu\text{g}/\text{kg}$ , for every increase of infusion by 0.25 $\mu\text{g}/\text{min}$ extra loading dose of 25 $\mu\text{g}/\text{kg}$
Ca-chloride	10-20 mg/kg	-	
Nitroglycerin	0.75-1.0	-	Venodilator, limited experience in children
Nitroprusside	10-20 mg/kg	-	Vasodilator, arterial > venous, cyanide toxicity a problem

When a child in septic shock does not improve and the goals of treatment are not achieved even after dopamine and/or dobutamine infusion, the shock is labeled as *fluid refractory, dopamine/dobutamine resistant shock*. At this stage, children with shock can further be classified into 2 broad categories: warm shock and cold shock.

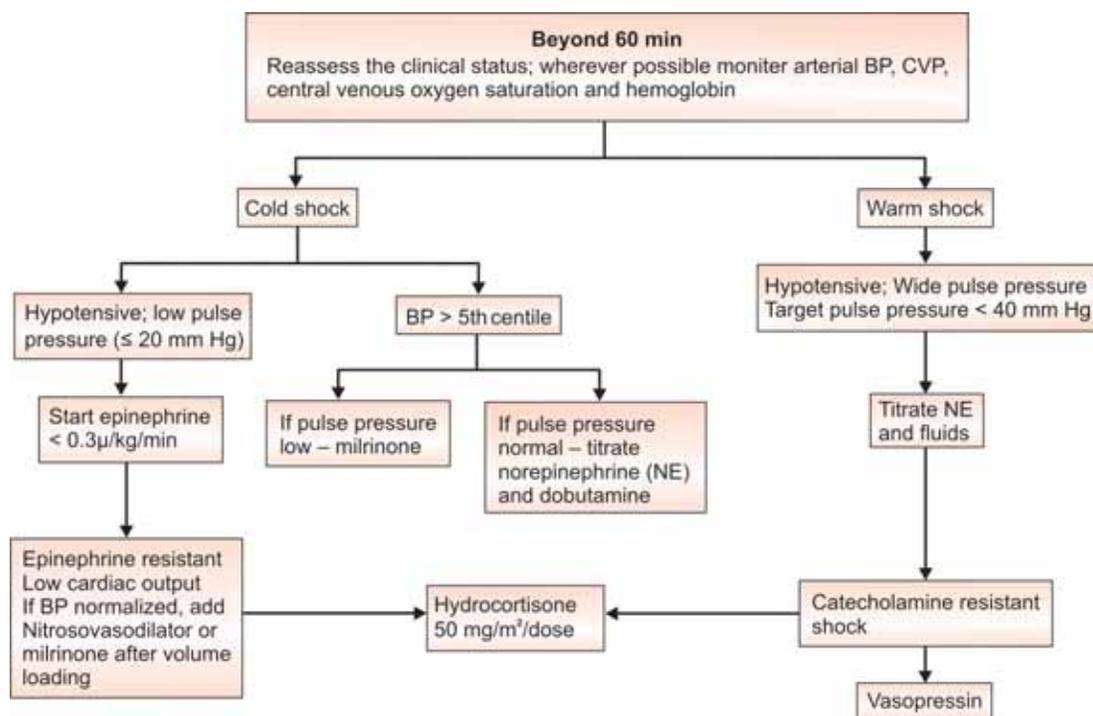
Children in cold shock may have low blood pressure. In these children, *epinephrine* should be titrated to achieve normal MAP for age. Once this is achieved but the child continues to have elevated systemic vascular resistance and low cardiac output,

*nitrosovasodilators* are warranted. *Milrinone* should be strongly considered if low cardiac output and high vascular resistance state persists in spite of epinephrine and nitrosovasodilators.<sup>36</sup>

Children with cold shock may also have normal blood pressure. In these children, milrinone would be the drug of choice if pulse pressure is low. However, if the pulse pressure is normal or high, *norepinephrine* and *dobutamine* should be titrated up.

*Norepinephrine* is the vasoactive agent of choice for the child with warm shock with poor perfusion or hypotension. It has potent  $\alpha$  adrenergic vasocons-

**Flow chart 6.3:** Management of pediatric septic shock beyond first hour of resuscitation<sup>26</sup>



tracting effects with little effect on heart rate or cardiac output. An infusion of *vasopressin* (0.3 to 2 milliunits/kg/min) may be useful in the setting of norepinephrine refractory shock. Vasopressin antagonizes the mechanisms of sepsis mediated vasodilation and acts synergistically with endogenous/exogenous catecholamines in stabilizing blood pressure.

Use of vasodilators like nitroprusside or nitroglycerine may aid children with cardiogenic shock who remain hypodynamic with high systemic vascular resistance despite fluids and inotropes. Titration of inotropes in the management of pediatric shock has been summarized in Flow chart 6.3.

All of these agents are given by continuous intravenous infusions in a central catheter. A standby peripheral catheter should be available in case of malfunction of primary catheter. Infusion should preferably be given through an infusion pump and should never be interrupted because half-life of these agents is only one or two minutes. Inadvertent flushing of catheter can be fatal because of sudden delivery of a bolus of these drugs. All infusions with their rates should be carefully labeled. The infusion rate should be calculated in micrograms/kg/minute.<sup>17,37</sup>

### Antiarrhythmic Therapy

Cardiac output in young children is highly dependent on heart rate. The wide variation in heart rates associated with metabolic derangements may significantly impair cardiac performance.

Treatment of arrhythmias includes correction of acidosis, hypoxia, hypocalcemia and hypokalemia or hyperkalemia. Specific cardio-active drugs that may be used are atropine and isoproterenol for bradyarrhythmias, adenosine, verapamil or digoxin for supraventricular tachyarrhythmias and lidocaine for ventricular ectopy (Table 6.9).

### CORRECTION OF METABOLIC ABNORMALITIES

#### Acidosis

A significant secondary complication in shock of any etiology is the development of metabolic acidosis as a consequence of tissue ischemia. Severe acidosis impairs metabolic processes, impedes normal neurovascular interactions, and may prevent effective pharmacologic actions of various vasopressor and inotropic agents administered to the patient. Correction is indicated when marked metabolic acidosis exists (arterial blood,

**Table 6.9: Antiarrhythmia drugs**

Drug	Dose	Comment
<i>For supraventricular tachycardia</i>		
Adenosine	0.1-0.2 mg/kg	
<i>For bradyarrhythmias</i>		
1. Atropine	0.01-0.03 mg/kg	Vagolytic
2. Isoproterenol	0.1 mg/kg	Vasodilator
<i>For ventricular tachycardia</i>		
1. Lidocaine	1 mg/kg bolus	20-50 µg/kg/min infusion
2. Bretylium	5 mg/kg bolus	
3. Phenytoin	15 mg/kg bolus	Rate 0.75-1 mg/kg/min
4. Cardioversion	0.5-1 J/kg	Supraventricular tachycardia: Use if hemodynamic instability

pH < 7.15). Sodium bicarbonate is usually given in an initial dose of 1 to 2 mEq/kg. Subsequent doses are based on body weight and base deficit (mEq = body weight in kilograms × base deficit 0.3). Bicarbonate should be used only to partially correct the pH to a level that does not pose a serious immediate threat to life. Care must be taken to avoid over correction as this may impair cardiac function and cause paradoxical central nervous system acidosis.

### Calcium

Sustained decrease in ionized calcium as seen in course of any acute hemodynamic deterioration is associated with depressed myocardial function, tachycardia, hypotension, alteration in sensorium and motor nerve excitability. Therapeutic intervention is justified when serum ionized calcium level falls below normal (less than 3.0 mg/dl). An intravenous infusion of 1-2 ml/kg of 10 percent calcium gluconate under cardiac monitoring is the usual dose. Hypocalcemia has been shown to be associated with poor outcome in pediatric patients.<sup>38</sup> However, careful controlled trials to test the efficacy of calcium replacement therapy are lacking.

### Phosphate

Phosphorus is essential to muscle, nervous system and functioning of blood cells. Consequences of severe hypophosphatemia include acute respiratory failure, altered myocardial performance, platelet dysfunction, hemolytic anemia, hepatocellular damage and

neurologic abnormalities. To correct hypophosphatemia, 5 to 10 mg/kg of potassium phosphate is given intravenously over six hours. Complications of phosphate therapy include hypocalcemia and hypotension.

### Blood Glucose

At the time of resuscitation, hypoglycemia is of major concern for its negative inotropic effect and associated severe neurological damage. Blood glucose ≤ 60 mg/dL can be used to define hypoglycemia (beyond the neonatal period).<sup>18</sup> Hypoglycemia should be identified rapidly and corrected immediately.<sup>27</sup> IV dextrose may be administered as 25% dextrose (2-4 ml/kg) or 10% dextrose (5-10 ml/kg). A regular monitoring protocol should then follow to maintain blood sugar around 150 mg/dL. Hyperglycemia is not a significant management issue during initial resuscitation, however, it may warrant correction with insulin infusion at a later stage especially if it is associated with polyuria.<sup>39</sup> Whether tight glycemic control with insulin therapy improves outcome in severe sepsis remains unanswered. However, hypoglycemia and fluctuating blood glucose levels should be avoided in all patients.

### Ventilatory Support

The lung is the most sensitive of the organs that is affected by shock. Respiratory failure can develop rapidly and is frequently the cause of death. In a patient with shock the work of breathing is substantially increased, which may result in respiratory muscle fatigue. Therefore, patients in shock should be intubated early and treated with positive pressure ventilation.

Indications for mechanical ventilation in the management of a patient in shock are:

1. Apnea or ventilatory failure (acute respiratory acidosis).
2. Failure to achieve adequate oxygenation with high flow oxygen-with venturi masks or nasal prongs.
3. Respiratory fatigue-for relief of metabolic stress of the work of breathing.
4. Adjunctive therapy for other interventions (post-operative state).

In a patient requiring positive pressure ventilation, an attempt should be made to achieve arterial oxygen concentration 60 torr with an FiO<sub>2</sub> of 0.6 or less. This may be facilitated by judicious use of positive end expiratory pressure. Close observations of chest movements, ventilator pressures and flow and arterial blood gases are essential to ensure adequate oxygenation and ventilation.

Air leaks and its sequelae are quite common in children on positive pressure ventilation. Frequent posture changes and vigorous physiotherapy to promote drainage of secretions and avoid atelectasis are essential.

### Prevention of Acute Renal Failure

The hypotension and hypoperfusion that are associated with shock may often lead to oliguria and renal failure. Aggressive fluid replacement is necessary to support urine output. RIFLE (Risk, Injury, Failure, Loss and End stage renal disease) criteria have been established for acute kidney injury based on declining glomerular filtration rate and urine output.<sup>40</sup> Nevertheless, should hyperkalemia, refractory acidosis, hypervolemia and altered mental status occur, renal replacement therapy should be seriously considered. Peritoneal dialysis, intermittent hemo-dialysis and continuous renal replacement therapy (CRRT) are available options. It should be remembered to avoid nephrotoxic drugs in this setting.

### Gastrointestinal Support

Gastrointestinal disturbances, as a consequence of shock, include bleeding and ileus. Ileus may result from hypokalemia and may lead to abdominal distention with respiratory compromise. Gastrointestinal blood loss can be prevented by using antacids, an H<sub>2</sub> receptor blocker, or sucralfate. However, these agents must be used with caution as raising gastric pH is associated with bacterial overgrowth in stomach which may increase the incidence of nosocomial pneumonia.

### Hematological Support

The role of blood and blood products in the initial resuscitation has already been discussed. Subsequently, packed RBCs should be transfused if SvO<sub>2</sub> is < 70% and if Hb is < 10 g% after achieving optimal CVP, urine output > 1 ml/kg/hour, age appropriate perfusion pressure and normal capillary refill.<sup>31</sup> Once tissue oxygen consumption/delivery has resolved, red cell transfusion is recommended only when hemoglobin falls to < 7g% to target hemoglobin of 7-9 g%.<sup>41</sup>

Coagulation abnormalities and thrombocytopenia are common in patients with sepsis and shock. However, fresh frozen plasma and platelet transfusion should only be used in presence of clinical bleeding or if any invasive procedure is being planned.<sup>42</sup>

### Nutritional Support

Nutritional support is a frequently overlooked but extremely important aspect of the care of the shock

patient.<sup>43</sup> Excessive catabolism with destruction of lean body mass is the most common nutritional abnormality in shock states. Nutritional support of shock patient should be started as soon as possible. In case of patients on ventilator, nasogastric tube is placed for initial gastric decompression and then is converted to gastric feeding tube.<sup>44</sup> Close monitoring of daily caloric intake and determination of serum albumin, electrolytes and liver function tests should be done.

Immunonutrition<sup>45-47</sup> has been the subject of considerable interest in the recent past. Various agents ( $\omega$ -3 polyunsaturated fatty acids, glutamine, arginine, zinc,  $\beta$ -carotene, selenium, etc) have been studied but none of them are recommended in critically ill patients at the moment pending further studies.

### Special Aspects of Management of Septic Shock

Management of septic shock deserves special mention because despite many advances in medicine it carries a mortality of 40 to 50 percent. Early recognition, appropriate therapeutic response and removal of nidus of infection are necessary for optimum outcome in pediatric sepsis.

Septic shock should be clinically suspected when a febrile child has tachycardia, tachypnea and accompanying signs of sepsis and organ hypoperfusion such as obtunded sensorium and oliguria. The key to successful intervention is recognition of septic shock before hypotension occurs; hence the urgency to treat sepsis and septic shock on the basis of clinical findings and not laboratory tests.<sup>37</sup>

Immediate resuscitation (the first hour) include establishment of adequate airway and ventilation which is required in as many as 80 percent of children with septic shock require aggressive volume resuscitation in boluses of 20 ml/kg to a total volume of 40-60 ml/kg in the first 10 minutes of arrival.<sup>48</sup> Any further fluid therapy is guided by invasive hemodynamic monitoring (CVP and pulmonary artery wedge pressure). Despite adequate volume resuscitation, most children with severe septic shock have a cardiovascular dysfunction that requires early introduction of inotropic support. The choice of appropriate agent depends upon the hemodynamic state as discussed earlier. Besides the conventional inotrope support, milrinone lactate is a novel vasodilator and inotropic agent which has proved to be very efficacious in children with refractory septic shock.<sup>34</sup>

### Increased Oxygen Delivery

Oxygen consumption in sepsis increases linearly with oxygen supply. Hence, tissue oxygenation should be

improved and lactic acidosis reduced by maximizing oxygen delivery. It has been suggested to focus the therapeutic aim on maintenance and/or increase in delivery of oxygen to tissue and increased consumption to match the increased tissue oxygen demand.<sup>49</sup> This can be achieved by increasing cardiac output and oxygenation since the hemodynamic end-points for resuscitation of septic shock are normal systolic pressure, high cardiac output, high oxygen delivery and high oxygen consumption.<sup>31</sup> Studies in adult patients have demonstrated significant benefit of achieving supranormal delivery of oxygen within 24 hours of admission in reducing mortality among critically ill patients.<sup>49</sup> However, evidence for similar benefit in children are lacking. It is now increasingly appreciated that cellular energies are deranged in septic shock, not in terms of only impaired tissue perfusion but also impaired mitochondrial respiration and/or uncoupling as a result of cytopathic hypoxia.<sup>50</sup> Efforts to improve outcome by manipulating systemic oxygen delivery are therefore unlikely to succeed.<sup>51</sup>

### Antibiotics

Therapy with antibiotics should be initiated as soon as possible, preferably after sampling for cultures. It is preferable to provide empirical broad spectrum antibiotic coverage taking into consideration the primary site of infection, local bacterial sensitivity pattern and immunocompetence of the host. In addition, pus anywhere in the body should be drained surgically.

### Corticosteroids

The role of steroids in patients with septic shock remains to be defined.<sup>52</sup> Glucocorticoids experimentally inhibit most of the acute phase reactions. They interfere with generation of various mediators of inflammation, viz, prostaglandin, bradykinin, serotonin, and histamine, block complement activation, prevent aggregation of leukocytes and decrease capillary permeability. They also blunt almost all forms of immune functions, including action of lymphokines such as gamma interferon, macrophage-stimulating factor interleukin-1 and 2, natural killer cell activity and plasminogen activator, if introduced early in the course of shock. The clear indication for use of steroids include children who have proven adrenal insufficiency or who are at risk for adrenal insufficiency. The latter group includes children who are suspected to have pituitary or adrenal abnormalities, who are on prolonged steroid therapy or those who present with

septic shock and purpura.<sup>19</sup> In these cases, it is preferable to obtain a baseline cortisol level and adrenal insufficiency may be assumed if random cortisol level is less than 18 µg/dL. Stress doses of hydrocortisone should be given intravenously (2 mg/kg or 50 mg/m<sup>2</sup>) followed by 50 mg/m<sup>2</sup>/day in four divided doses intravenously for 5 to 7 days.<sup>53</sup>

Adrenal insufficiency (absolute or relative) is common in children with severe sepsis and septic shock.<sup>54</sup> In most studies, a poor adrenal reserve or absolute adrenal insufficiency was associated with catecholamine refractory shock and/or poor outcome.<sup>19</sup> *It may be therefore acceptable to use stress doses of hydrocortisone until reversal of shock for pediatric sepsis patients with catecholamine resistant shock.*<sup>55,56</sup>

## NEWER MODALITIES FOR SEPSIS AND SEPTIC SHOCK

### Extracorporeal Therapies

Three forms of extracorporeal therapies have been reported in children with severe sepsis. Extracorporeal membrane oxygenation has been reported in pediatric sepsis with 50 percent survival rates.<sup>57</sup> Plasmapheresis has been reported in children with DIC and purpura fulminants as a measure to restore the balance of circulating antithrombotic and profibrinolytic factors to a state of normal homeostasis without causing volume overload.<sup>58</sup> Other possible pathways altered include immune modulation, apoptosis and energy metabolism. The use of whole blood exchange transfusion has also been reported to be beneficial in neonatal shock. The role and indication for extracorporeal therapy in the management of pediatric shock is evolving.

### Immune System Enhancers

Immune system enhancers like granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factors have been used to increase neutrophil counts in children with sepsis related neutropenia. Intravenous gamma globulin, specific polyclonal antibodies directed at common core LPS antigen of *E. coli*, has been shown to reduce the mortality in patients with Gram negative sepsis and even prevents the progression of shock when given prophylactically to high risk patients. Experience with anti-cytokine therapies has been disappointing. Therapies that more globally target restoration of immunologic homeostasis may hold more promise in the acute setting.

### Antithrombotic and Antifibrinolytic Factors

A number of studies have suggested that anticoagulant factors and proteins may be both markers for sepsis and its severity and replenishment of these may help reverse hypercoagulable states.<sup>59</sup> These agents include antithrombin-III, activated protein-C<sup>60</sup> and tissue factor pathway inhibitor, each of which has been shown to interrupt clotting and limit platelet aggregation, and hence prevent development of DIC.

Tissue factor inhibitor is a very appealing therapeutic agent, which affects both extrinsic and intrinsic coagulation cascade. This interruption of coagulation cascade at multiple points lead to inhibition of wide-spread coagulation and consequent deposition of microfibrin emboli in peripheral vascular beds ultimately resulting in improved survival.<sup>61</sup>

Recombinant human soluble thrombomodulin (rhm-TM) and recombinant human activated protein-C (rh-APC) are other promising agents.<sup>62</sup> rhAPC is recommended in adult patients at high risk of death such as those in septic shock, sepsis with MODS and sepsis induced ARDS. However, current data does not support its use in pediatric septic shock.<sup>63</sup>

### Prognosis and Assessing Outcome

Aggressive and early management of shock is associated with intact survival of a child. The mortality depends upon the underlying etiology. Therapeutic goals for management of shock are still being defined. Shock is a hypermetabolic state; hence merely attaining normal physiological parameters during therapy of shock may not be adequate. Outcome is improved in patients with increased cardiac output, elevated oxygen consumption and elevated oxygen extraction and without significant pulmonary disease. In septic shock goal directed therapy to achieve a mixed venous oxygen saturation ( $SvO_2 > 70\%$ ) has been shown to be the best endpoint. On the other hand low body temperature ( $< 37^\circ\text{C}$ ), pulmonary disease, low cardiac index ( $< 3.3 \text{ L/min/m}^2$ ) and decreased oxygen utilization are all poor prognostic indicators in shock.<sup>64</sup>

To manage shock to the conventional goals of resuscitation, i.e. "ABC" for airway breathing and circulation, are added "D" for increasing the delivery of oxygen to levels that meet the metabolic demands of all tissues in body specially those tissues within the splanchnic circulation and "E" for ensuring utilization of oxygen by tissues. Early detection and aggressive management of shock is likely to improve the outcome.<sup>65</sup>

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Acute respiratory failure remains a major cause of morbidity and mortality in both pediatric and adult populations. Acute respiratory failure (ARF) is the most common emergency in critically ill children. ARF can be defined as inadequate exchange of oxygen and carbon dioxide due to pulmonary or non-pulmonary causes leading to hypoxemia, hypercarbia or both. When a child presents in respiratory distress it is important to recognize tachypnea, agitation, nasal flaring, grunting, retraction and act on those findings rather than waiting for lethargy, cyanosis and bradycardia, the signs dangerously close to cardiorespiratory arrest.

#### How are Children different from Adults?

Due to high vagal tone and vagal predominance in the respiratory tract of children, the most common cause of bradycardia and cardiac arrest is secondary to respiratory causes, and therefore avoidable. Primary asystole or ventricular fibrillation is uncommon. The frequency of acute respiratory failure is higher in infants and young children than in adults for several reasons. This difference can be explained by defining anatomic compartments and their developmental differences in pediatric patients that influence susceptibility to acute respiratory failure.

The **extrathoracic airway** comprises of the area extending from the nose through the nasopharynx, oropharynx, and larynx to the subglottic region of the trachea. Differences in pediatric versus adult patients include the following:

- Neonates and infants are obligate nasal breathers until the age of 2-6 months because of the proximity of the epiglottis to the nasopharynx. Nasal congestion can lead to clinically significant distress in this age group.
- The small size of the airway is one of the primary differences in infants and children younger than 8 years compared with older patients.
- Infants and young children have a large tongue that fills a small oropharynx.
- Infants and young children have a cephalic larynx. The larynx is opposite vertebrae C3-4 in children versus C6-7 in adults.
- The epiglottis is larger and more horizontal to the pharyngeal wall in children than in adults. The cephalic larynx and large epiglottis can make laryngoscopy challenging.
- Infants and young children have a narrow subglottic area. In children, the subglottic area is cone shaped, with the narrowest area at the cricoid ring. A small amount of subglottic edema can lead to clinically significant narrowing, increased airway resistance, and increased work of breathing. Older patients and adults have a cylindrical airway that is narrowest at the glottic opening.
- In slightly older children, adenoidal and tonsillar lymphoid tissue is prominent and can contribute to airway obstruction.

The **intrathoracic airways** and lung include the conducting airways and alveoli, the interstitia, the pleura, the lung lymphatics, and the pulmonary circulation. Noteworthy differences among pediatric children include the following:

- Infants and young children have fewer alveoli than do adults. The number dramatically increases during childhood, from approximately 20 million after birth to 300 million by 8 years of age. Therefore, infants and young children have a relatively small area for gas exchange.
- The alveolus is small. Alveolar size increases from 150-180 to 250-300  $\mu\text{m}$  during childhood.
- Pores of Kohn connecting alveoli are not developed until one year of age, and channels of Lambert which connect alveoli to larger airways do not develop until 5 years of age. This results in non-uniform distribution of ventilation due to lack of collateral air circulation.
- Smaller intrathoracic airways are more easily obstructed than larger ones. With age, the airways enlarge in diameter and length.
- Infants and young children have relatively little cartilaginous support of the airways. As cartila-

ginous support increases, dynamic compression during high expiratory flow rates is prevented.

The **respiratory pump** includes the nervous system with central control (i.e. cerebrum, brainstem, spinal cord, peripheral nerves), respiratory muscles, and chest wall. Features of note in pediatric patients include the following:

- The respiratory center is immature in infants and young children and leads to irregular respirations and an increased risk of apnea.
- The ribs are horizontally oriented. During inspiration, a decreased volume is displaced, and the capacity to increase tidal volume is limited compared with that in older individuals.

Furthermore, children with hypoxemia compensate by increasing rate of respiration rather than depth of respiration therefore, tachypnea and shallow breathing are important signs of acute respiratory failure and should be taken seriously. It is also important to recognize that response to obstruction of the airway results in obstructive apnea especially in premature infants who have a poor respiratory center response to rising arterial  $p\text{CO}_2$ . Episodes of apnea and bradycardia should be taken seriously and properly investigated.

### Classification

Respiratory failure may be classified as hypoxemic or hypercapnic.

**Hypoxemic respiratory failure (type I)** is characterized by a  $\text{PaO}_2$  of less than 60 mm Hg with a normal or low  $\text{PaCO}_2$ . This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units. Some examples of type I respiratory failure are cardiogenic or noncardiogenic pulmonary edema, pulmonary hemorrhage and pneumonia.

**Hypercapnic respiratory failure (type II)** is characterized by a  $\text{PaCO}_2$  of more than 50 mm Hg. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. The pH depends on the level of bicarbonate, which, in turn, is dependent on the duration of hypercapnia. Common etiologies include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (e.g. asthma, [COPD]).

### Physiology of Gas Exchange

Respiration primarily occurs at the alveolar capillary units of the lungs, where exchange of oxygen and

carbon dioxide between alveolar gas and blood takes place. During ideal gas exchange, blood flow and ventilation would perfectly match each other, resulting in no alveolar-arterial  $\text{PO}_2$  difference. However, even in normal lungs, not all alveoli are ventilated and perfused perfectly. For a given perfusion, some alveoli are underventilated while others are overventilated. Similarly, for known alveolar ventilation, some units are underperfused while others are overperfused. The optimally ventilated alveoli that are not perfused well are called high V/Q units (acting like dead space), and alveoli that are optimally perfused but not adequately ventilated are called low V/Q units (acting like a shunt).

The efficiency of lungs at carrying out of respiration can be further evaluated by measuring alveolar-to-arterial  $\text{PaO}_2$  difference. This difference is calculated by the following equation:

$$\text{PA O}_2 = \text{FIO}_2 \times (\text{PB} - \text{PH}_2\text{O}) - \text{P}_A \text{CO}_2 / \text{R}$$

For the above equation,  $\text{P}_A \text{O}_2$  = alveolar  $\text{PO}_2$ ,  $\text{FIO}_2$  = fractional concentration of oxygen in inspired gas, PB = barometric pressure,  $\text{PH}_2\text{O}$  = water vapor pressure at 37°C,  $\text{P}_A \text{CO}_2$  = alveolar  $\text{PCO}_2$ , assumed to be equal to arterial  $\text{PCO}_2$ , and R = respiratory exchange ratio. R depends on oxygen consumption and carbon dioxide production. At rest,  $\text{VCO}_2/\text{VO}_2$  is approximately 0.8.

### Pathophysiologic Causes of Acute Respiratory Failure

Hypoventilation, V/Q mismatch, and shunt are the most common pathophysiologic causes of acute respiratory failure. These are described in the following paragraphs.

#### Hypoventilation

Hypoventilation is an uncommon cause of respiratory failure and usually occurs from depression of the CNS from drugs or neuromuscular diseases affecting respiratory muscles. Hypoventilation is characterized by hypercapnia and hypoxemia. Hypoventilation can be differentiated from other causes of hypoxemia by the presence of a normal alveolar-arterial  $\text{PO}_2$  gradient.

#### V/Q Mismatch

V/Q mismatch is the most common cause of hypoxemia. V/Q units may vary from low to high ratios in the presence of a disease process. The low V/Q units contribute to hypoxemia and hypercapnia in contrast to high V/Q units, which waste ventilation

but do not affect gas exchange unless quite severe. The low V/Q ratio may occur either from a decrease in ventilation secondary to airway or interstitial lung disease or from overperfusion in the presence of normal ventilation. The overperfusion may occur in case of pulmonary embolism, where the blood is diverted to normally ventilated units from regions of lungs that have blood flow obstruction secondary to embolism. Administration of 100% oxygen eliminates all of the low V/Q units, thus leading to correction of hypoxemia. Hypoxemia increases minute ventilation by chemoreceptor stimulation, but the PaCO<sub>2</sub> level generally is not affected.

### Shunt

The deoxygenated blood (mixed venous blood) circulating in the collapsed region of lung bypasses the ventilated alveoli and mixes with oxygenated blood that has flown through the ventilated alveoli, consequently leading to a reduction in arterial blood content. This is due to intrapulmonary shunting. Intracardiac right to left shunting (e.g. Tetralogy of Fallot, other cyanotic congenital heart diseases) leads to mixing of deoxygenated blood with left heart circulation. Here, the discussion will be particularly related to intrapulmonary shunting.

The shunt can be calculated by the following equation:

$$QS/QT = (CCO_2 - CaO_2) / (CCO_2 - CvO_2)$$

QS/QT is the shunt fraction, CCO<sub>2</sub> (capillary oxygen content) is calculated from ideal alveolar PO<sub>2</sub>, CaO<sub>2</sub> (arterial oxygen content) is derived from PaO<sub>2</sub> using the oxygen dissociation curve, and CVO<sub>2</sub> (mixed venous oxygen content) can be assumed or measured by drawing mixed venous blood from pulmonary arterial catheter assuming a normal heart with no structural heart disease.

Anatomical shunt exists in normal lungs because of the bronchial and thebesian circulations, accounting for 2-3% of shunt. Shunt as a cause of hypoxemia is observed primarily in pneumonia, atelectasis, and severe pulmonary edema of either cardiac or noncardiac origin. Hypercapnia generally does not develop unless the shunt is excessive (>60%). When compared with V/Q mismatch, hypoxemia produced by shunt is difficult to correct by oxygen administration.

### Etiology of Acute Respiratory Failure

2

These diseases can be grouped according to the primary abnormality and the individual components of the respiratory system, as follows (Table 7.1):

- Central nervous system disorders
  - CNS infection
  - Drug overdose
  - Sleep apnea
  - Stroke
  - Traumatic brain injury
- Disorders of the peripheral nervous system, respiratory muscles, and chest wall
  - Chest wall
    - Diaphragm eventration
    - Diaphragmatic hernia
    - Flail chest
    - Kyphoscoliosis
  - Respiratory muscles
    - Duchenne muscular dystrophy
    - Guillain-Barré syndrome
    - Infant botulism
    - Myasthenia gravis
    - Spinal cord trauma
    - SMA
- Extrathoracic airway
  - Acquired lesions
    - Infections (e.g. retropharyngeal abscess, Ludwig angina, laryngotracheobronchitis, bacterial tracheitis, peritonsillar abscess)
    - Traumatic causes (e.g. postextubation croup, thermal burns, foreign-body aspiration)
    - Other (e.g. hypertrophic tonsils and adenoid)
- Congenital lesions
  - Subglottic stenosis
  - Subglottic web or cyst
  - Laryngomalacia
  - Tracheomalacia
  - Vascular ring
  - Cystic hygroma
  - Craniofacial anomalies
- Intrathoracic airway and lung
  - Acute respiratory distress syndrome (ARDS)
  - Asthma
  - Aspiration
  - Bronchiolitis
  - Bronchomalacia
  - Left-sided valvular abnormalities
  - Pulmonary contusion
  - Near drowning
  - Pneumonia
  - Pulmonary edema
  - Pulmonary embolus
  - Sepsis.

**Table 7.1: Common causes of respiratory failure**

<i>Common causes of type I (hypoxemic) respiratory failure</i>	<i>Common causes of type II (hypercapnic) respiratory failure</i>
<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Pulmonary edema</li> <li>• Pneumothorax</li> <li>• Pulmonary embolism</li> <li>• Pulmonary arterial hypertension</li> <li>• Cyanotic congenital heart disease</li> <li>• Bronchiectasis</li> <li>• Adult respiratory distress syndrome</li> <li>• Fat embolism syndrome</li> <li>• Obesity</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic bronchitis and emphysema (COPD)</li> <li>• Severe asthma</li> <li>• Drug overdose</li> <li>• Poisonings</li> <li>• Myasthenia gravis</li> <li>• Polyneuropathy</li> <li>• Poliomyelitis</li> <li>• Primary muscle disorders</li> <li>• Head and cervical cord injury</li> <li>• Primary alveolar hypoventilation</li> <li>• Obesity hypoventilation syndrome</li> </ul>

### Approach to a Child with Acute Respiratory Failure

For adequate management of a child in acute respiratory failure proper detailed history, physical examination and relevant investigations are necessary. It, must however, be emphasized that establishing a detailed diagnosis may take up important initial intervention time in order of priority after quick history and rapid cardiopulmonary assessment. For example, after ensuring patent airways and breathing (ABCs), beginning oxygen therapy in a wheezing patient without waiting for a chest radiograph may be appropriate as dictated by the clinical condition.

History of onset and duration of symptoms prior to onset of respiratory distress is important. Respiratory problems at birth such as premature birth and hyaline membrane disease, apnea, stridor, asphyxia and respiratory distress or neuromuscular problems should be enquired into.

While conducting a rapid cardiopulmonary assessment for examination of a child in respiratory failure the following points must be payed attention to:

- **General condition:** Playful; toxic, drooling or continuously coughing
- **Color:** Pink, pale or cyanosed
- **Mental status:** Agitated, anxious, lethargic, comatose
- Chest deformity/scoliosis
- Hoarse voice, no voice, or croupy cough
- **Respiratory rate:** Tachypnea, bradypnea or episodes of apnea
- Audible wheeze
- **Accessory muscle use:** Head bobbing, nasal flaring, sternocleidomastoid prominence, suprasternal retractions, subcostal and intercostal retraction
- **Breath sounds:** Equal, diminished or absent, wheezes, rales (crepitation)

- **Tachycardia.**
- **Congenital** facial deformity/airway problems such as choanal atresia, short chin (mandibular hypoplasia), micrognathia or retrognathia.

#### **Simultaneous initial intervention and investigations include:**

1. Placing a pulse oximeter probe in the emergency department (casualty) to check oxyhemoglobin saturation should be a standard of care on all patients in acute respiratory failure.
2. Oxygen therapy by mask, nasal cannula or head box should be initiated at the first opportunity.
3. Position of comfort should be maintained, such as sitting position or in mothers lap to control child's anxiety. One should avoid forcefully laying down the child for examination of throat or for a neck or chest radiograph, as this can precipitate severe airway obstruction, cyanosis, bradycardia and cardiac arrest in a child with partial upper airway obstruction. If airway and breathing is maintained, aerosol therapy with a beta stimulant (salbutamol) or adrenaline nebulizer may be initiated depending upon predominant wheezing or stridor respectively.

On the other hand if the airway is not maintained or respiratory distress is severe, airway should be emergently opened with jaw thrust or head tilt and chin lift maneuver followed by bag mask ventilation with 100 percent oxygen and endotracheal intubation.

Preferably, endotracheal intubation should be performed under controlled situation in the PICU or the operation theater especially if labile upper airway obstruction is suspected, such as in cases of severe croup/epiglottitis/bacterial tracheitis, with ready availability of tracheostomy set up and an ENT surgeon available as stand by while endotracheal

intubation procedure is being performed (endotracheal intubation procedure is described elsewhere).

4. Blood for complete blood count (CBC), blood culture, and basic metabolic investigation such as sodium, potassium, urea and creatinine may be drawn. Arterial blood gas can also be drawn.
5. A good intravenous line should be established for intravenous fluid therapy, for drug therapy such as steroids and antibiotics as needed.
6. Portable upright chest and airway (neck) anteroposterior and lateral view radiographs may be obtained, if patient is relatively stable.
7. If history is suggestive of inhalation of foreign body followed by respiratory distress in a previously asymptomatic child, bronoscopic removal of foreign body may be required under anesthesia. In a child with history of foreign body obstruction, PALS (Pediatric advanced life support) protocol comprising of back blows, chest thrusts and Heimlich's maneuver should be followed.

**Indices used to assess Lung as an oxygenator** are (Flow chart 7.1):

1.  $\text{PaO}_2$
2.  $\text{SaO}_2$
3.  $\text{Qs}/\text{Qt}$
4.  $\text{PA}-\text{PaO}_2$
5.  $\text{PaO}_2/\text{FiO}_2$

**$\text{PaO}_2$ :** Normal value in newborn infant at sea level 40-70 mm Hg, then increase till adult values of 90-120 mm Hg.

**Hypoxemia**— $\text{PaO}_2$  lower than the acceptable range for age.

In general for a child hypoxemia is if  $\text{PaO}_2$  is <60 mm Hg

**Hypoxia**—inadequate tissue oxygenation

**$\text{SaO}_2$ :** Aim to maintain saturation of oxygen  $\geq 92\%$

**$\text{Qs}/\text{Qt}$ :** Normally shunt fraction < 10% of total cardiac output.

In case of respiratory failure shunt fraction is >15%

**$\text{PA}-\text{PaO}_2$ :** Normally, < 20 mm Hg in child and < 50 mm Hg in newborn

In respiratory failure difference is >300 torr with  $\text{FiO}_2$  of 100%

**$\text{PaO}_2/\text{FiO}_2$ :** Normal ratio is > 400 mm Hg breathing room air at sea level

Ratio < 300—Acute lung injury

Ratio < 200—ARDS

### Indications for Admission to the PICU

In general, all patients too unstable to be managed in ward should be admitted to the PICU. These include:

1. Severe respiratory distress, tachypnea and retractions.
2. Oxygen requirement on the rise > 50 percent to maintain hemoglobin saturations above 90 percent.
3. Desaturation below 90 percent on highest flow of oxygen.
4. Lethargic child.
5. Arterial blood gas showing hypoxemia, hypercarbia or metabolic acidosis.

### Indications of Mechanical Ventilation

The indications are mainly clinical. Although blood gas is important for decision, it is not absolutely necessary. The usual indications include:

1.  $\text{PaO}_2 < 55$  mm Hg or  $\text{PaCO}_2 > 60$  mm Hg despite 100 percent oxygen therapy.
2. Deteriorating respiratory status despite oxygen and nebulization therapy.
3. Anxious, sweaty lethargic child with deteriorating mental status.
4. Respiratory arrest (must be avoided at all cost).

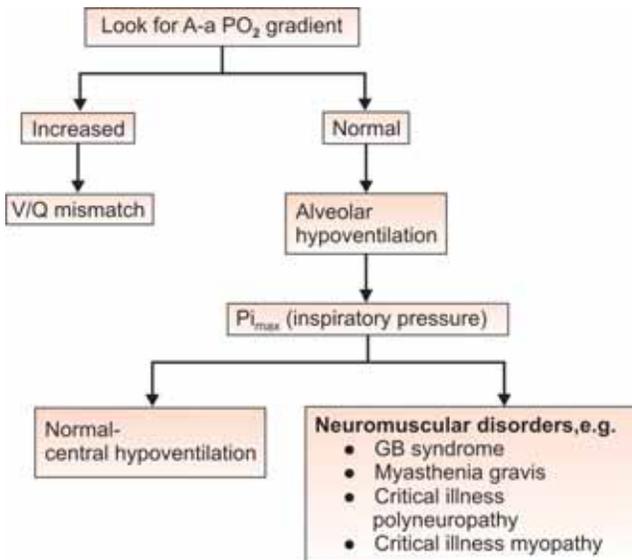
### Emergency Management

Emergency management of few important clinical problems is discussed below:

#### Upper Airway Obstruction

Nasal<sup>1,2</sup> and pharyngeal causes such as choanal stenosis or atresia will cause cyanosis at rest. The

Flow chart 7.1: Evaluation for hypoxemia



common symptom of upper airway obstruction is stridor.

In *infancy* important causes of stridor include laryngomalacia, vocal cord paralysis,<sup>3</sup> laryngeal web, vascular ring, tracheal stenosis, airway hemangiomas, hypocalcemia, and hypoparathyroidism.

In *older child*, common infectious causes causing upper airway obstruction (signs and symptoms of hoarseness, drooling, and swallowing difficulty, stridor with or without respiratory distress) include laryngotracheobronchitis, epiglottitis, diphtheria, tonsillitis/peritonsillar abscess, retropharyngeal abscess, bacterial tracheitis, and tracheobronchomalacia.

Other causes of upper airway obstruction should be looked into such as airway foreign bodies, airway tumors, post-intubation stridor and subglottic stenosis.

The emergency department investigations and management comprise.

1. Oxygen for all patients and no sedation.
2. To assess: Is airway maintained and stable?

***If the airway is stable:***

- Maintain position of comfort.
- Do not force to examine the airway.
- Do not lay the child forcefully.
- Accompany the child for portable soft tissue anteroposterior and lateral neck X-rays.

***If the airway is unstable:***

- Secure airway first in the best possible location in controlled environment, i.e. operation theater or the PICU with availability of emergency tracheostomy.

***Once the airway has been secured:***

- Give intravenous antibiotics and steroids as indicated.
- Ceftriaxone/Cefuroxime for tracheitis, peritonsillar abscess and epiglottitis.
- Adrenaline nebulization and intravenous methylprednisone/dexamethasone for laryngotracheobronchitis and hypertrophic tonsils in infectious mononucleosis. For angioedema, subcutaneous adrenaline and intravenous dexamethasone is indicated.
- After initial stabilization transfer to PICU.

**Acute Respiratory Distress Syndrome/ Pneumonia**

Acute respiratory distress syndrome (ARDS) and pneumonia are predominantly alveolar disease with respiratory distress with or without fever affecting oxygenation as well as ventilation.<sup>4</sup>

Emergency department management includes quick history and rapid cardiopulmonary assessment.<sup>5</sup> The following steps should be taken in the emergency department:

1. Place pulse oximeter and begin oxygen therapy.
2. Consider endotracheal intubation and initiation of mechanical ventilation if indicated by clinical deterioration (or arterial blood gases).<sup>6</sup>
3. Portable chest X-ray is done to confirm alveolar disease (diffuse infiltrates/consolidation usually with normal size heart).
4. Complete blood count, blood culture, coagulation profile, electrolytes, urea creatinine, and liver functions are obtained.
5. Intravenous line is secured, if not successful then introsseous access is obtained.
6. Fluid bolus is administered if patient is in shock as indicated by poor capillary refill and other parameters.
7. Intravenous antibiotics are administered.
8. If hypotension and poor perfusion is seen despite fluid therapy consider dopamine at 10 microgram/kg/min and central venous pressure (CVP) monitoring.
9. Initiate transfer/arrange transport to the nearest pediatric intensive care unit by discussing with the pediatric intensivist.

**Status Asthmaticus (Detailed Management is Discussed Elsewhere)**

- High flow oxygen
- Steroids-Intravenous(IV) hydrocortisone or IV methylprednisolone
  - Inhaled Beta Agonist-Salbutamol of choice, no added benefit of
  - Levosalbutamol clinically (though causes less tachycardia compared to salbutamol)
  - IV and subcutaneous beta agonist-Terbutaline
  - Methylxanthines-Theophylline (to be used when no response to steroids, inhaled and IV beta agonist)
  - Anticholinergic-Inhaled ipratropium bromide
  - Magnesium sulphate
  - Heliox (If available).

**Indication of Intubation**

- Cardiorespiratory arrest
- Refractory hypoxemia
- Significant respiratory acidosis unresponsive to pharmacotherapy
- Rapid deterioration in mental status.

### Tension Pneumothorax

This is a medical emergency and should be promptly recognized and treated. Severe respiratory distress with shock occurs due to decreased intrathoracic venous return caused by tamponade effect of air leak from lungs under pressure compressing the heart. These result in acute fall in cardiac output as indicated by hypoxemia; poor perfusion, and hypotension. If left untreated it can result in cardiopulmonary arrest. Clinically one finds absent or low breaths sounds on the affected side as well as muffled heart sounds and shifted apical impulse. Chest X-ray shows mediastinal shift as well as compression with free air in the pleural cavity depressing the dome of diaphragm. Chest X-ray may take time so one should not wait for chest X-ray, before intervention.

Chest needling on the suspected side with 16 to 18 gauge intravenous cannula or scalp vein needle may be attempted in 2nd intercostal space anteriorly, in midclavicular line to relieve tension pneumothorax.

However, once the chest X-ray is obtained the patient will require tube thoracostomy on the affected side.

### Neuromuscular Disorders

The commonly seen disorders are briefly discussed below:

#### *Central Hypoventilation Syndrome*

Central hypoventilation may be congenital or acquired. Congenital form (ondines curse) typically presents as cyanosis at birth readily responsive to mechanical ventilation (but not to oxygen therapy alone) with normal chest radiographs but repeated weaning failures. In less severe cases, abnormalities in respiration during sleep such as periodic breathing, apnea or acute life-threatening episodes are reported. This must be differentiated from reversible systemic processes such as sepsis, hypothermia, electrolyte abnormalities, hypocalcemia and seizures, CNS infections, intracranial hemorrhage, and acute hydrocephalus. It also needs to be distinguished from obstructive sleep apnea (OSA) due to hypertrophied tonsils, and adenoids, macroglossia (Down's syndrome), micrognathia (Pierre Robin syndrome) other oral or nasal congenital anomalies, temporomandibular ankylosis, vascular ring and vocal cord paralysis, and post cleft palate surgical repair.

*Therapy* is immediate ventilatory support, if in acute respiratory failure. Doxapram (a central respiratory stimulant) theophylline, caffeine have been tried to get a better apnea free respiratory effort.

*Tracheostomy with home mechanical ventilatory assistance* during sleep is commonly required. Recently, non-invasive methods such as use of nasal mask continuous positive airway pressure (nasal CPAP) or non-invasive positive pressure ventilation (NIPPV) have been shown to be very effective and need for tracheostomy can be averted.

#### *Guillain-Barré Syndrome (Acute Postinfectious Polyneuritis)*

This condition commonly presents as a post-viral immune mediated paralysis affecting skeletal muscles as well as autonomic nervous system leading to profound muscle weakness, ascending in nature with paresthesias.

Diaphragmatic and intercostal muscle weakness leads to neuromuscular respiratory failure requiring mechanical ventilation in 20 percent of affected children. Therefore, frequent assessment of respiratory reserve is necessary. Concern for respiratory failure if forced vital capacity (FVC) falls below 15 to 20 ml/kg, maximum negative inspiratory pressure less than 20 to 30 cm H<sub>2</sub>O and pCO<sub>2</sub> > 50 mm Hg.

Cranial nerve palsy and or cerebellar ataxia may be first presenting feature. More than 10 percent patients present with upper extremity weakness. CSF protein level is usually elevated > 45 mg/100 ml in absence of pleocytosis (cytoalbuminoid dissociation).

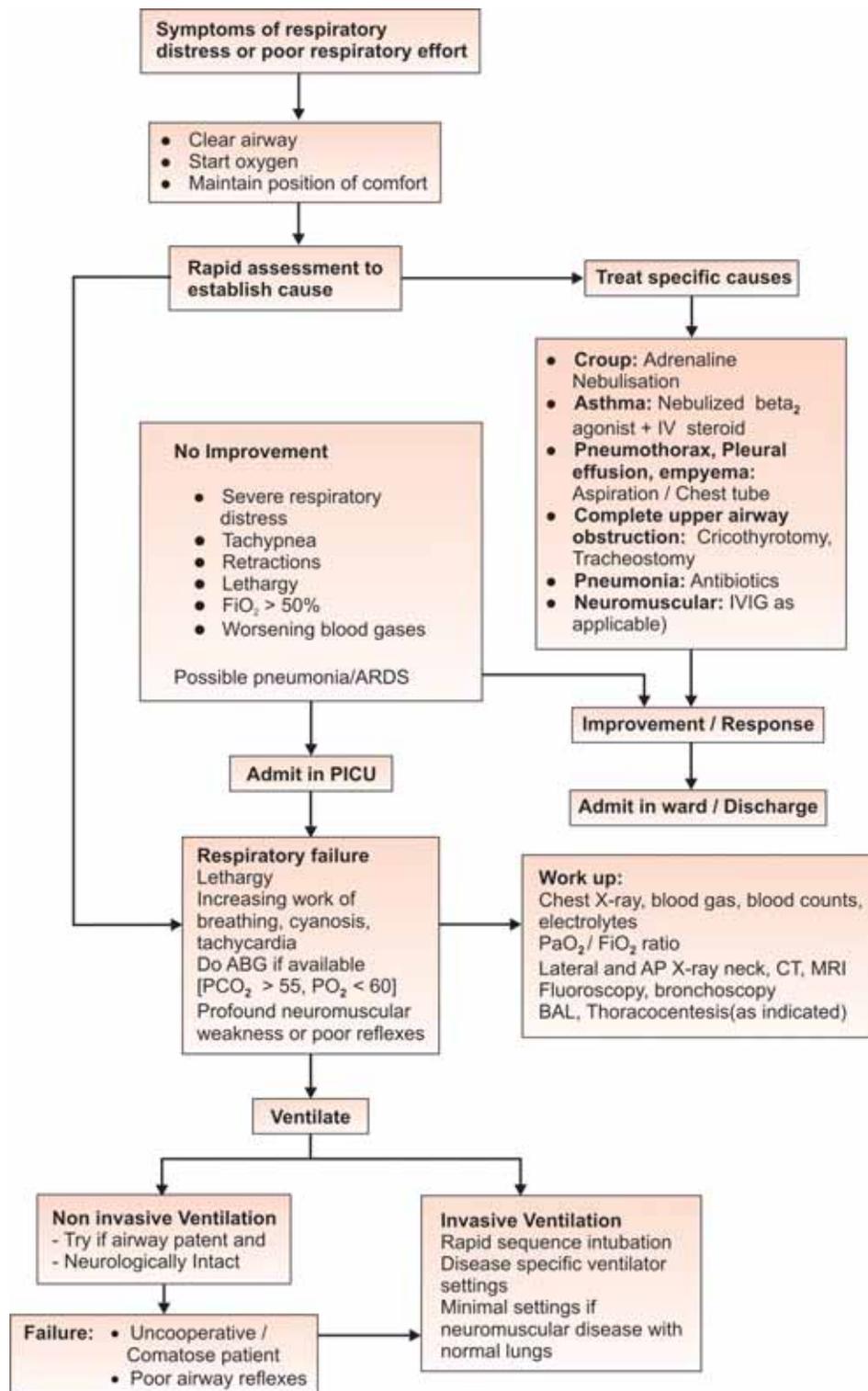
Electromyograph (EMG) shows evidence of lower motor neuron disease and nerve conduction velocity is delayed.

Bladder and bowel dysfunction is common with hypertension due to effect on autonomic nervous system. Sinus tachycardia, bradycardia, ST and T wave abnormalities and postural hypotension may be seen.

Early plasmapheresis for removing autoimmune factors within 7 days of onset of disease has been found to be beneficial. Gamma globulin therapy has demonstrated to be more effective when compared to plasmapheresis.<sup>7,8</sup> However, the mainstay of treatment remains supportive.

Prognosis is usually good with recovery in three to four weeks. However, muscle power and neurological recovery may be incomplete and may be prolonged in a few cases.

Flow chart 7.2: Management algorithm of respiratory failure



### *Unilateral Phrenic Nerve Paralysis*

This condition results from birth trauma to phrenic nerve and usually presents with respiratory distress in infancy. Fluoroscopy of the diaphragmatic motion is diagnostic. Diaphragm moves upward with inspiration. Usually adequate gas exchange can be maintained with CPAP alone or institution of mechanical ventilation; however, long-term management will require surgical plication of affected diaphragm.

Other important causes of phrenic nerve injury include direct phrenic nerve injury during open heart surgery and aortopulmonary shunt procedures. Half the cases occur during closed heart surgery such as during pulmonary artery banding and patent ductus arteriosus ligation.

These patients are usually detected when the subject fails to wean from the mechanical ventilation. Transcutaneous phrenic nerve stimulation can be applied in cervical region and if response is seen, a plication surgery of diaphragm may be avoidable, especially in older child.

### *Poliomyelitis*

Poliomyelitis represents an acute viral infection of the central nervous system that results in widespread muscle paralysis due to involvement of anterior horn cells and secondary respiratory failure.

Minor febrile illness, URI or gastroenteritis begins lasting for one to two days. In less than a week later severe muscle pain, fever, irritability, paresthesias, muscle fasciculation and diminished deep tendon reflexes in affected muscles are seen. In some cases it rapidly progresses to total paralysis. CSF shows mild pleocytosis with polymorphs in early course and mononuclear cells in later phase. Causative virus can be isolated from fecal and oropharyngeal specimens. Serological confirmation is made by identifying specific antibodies to poliovirus.

Bulbar palsy can result in loss of airway control due to pharyngeal muscle paralysis and can lead to airway obstruction and aspiration of pharyngeal secretions.

Endotracheal intubation, mechanical ventilation and chest physiotherapy remain the key treatment modalities.

Tracheostomy is often required. Intensive care unit survival is good. However, the pediatric mortality can exceed 30 percent if good ICU facilities are not available. Chronic respiratory insufficiency can result

from vocal cord paralysis, scoliosis, secondary respiratory restriction and central hypoventilation.

### *Spinal Cord Trauma*

High cervical injuries (C3 and C5) result in loss of diaphragmatic, intercostal and abdominal muscle function. Accessory muscles in neck and shoulder remain intact. Intubation and ventilation are invariably required. As pointed out earlier, other accompanying chest and lung injuries contribute to severity of respiratory failure.<sup>9</sup> Tracheostomy and long-term mechanical ventilation is usually required. In patients with intact nerve conduction phrenic nerve radiofrequency electrophrenic pacing has been tried.

### KEY POINTS TO PONDER

Approach and management of acute respiratory failure is summarized in Flow chart 7.2. Early recognition and urgent institution of treatment is of paramount importance in children. This is due to low respiratory reserve and propensity to bradycardia in pediatric age group and cardiac arrest is usually secondary to hypoxemia as well as due to increased vagal tone. Airway control and oxygen should be used as a first measure. Indications of instituting mechanical ventilation are clinical and not entirely dependent on blood gases, as blood gases may be normal in early respiratory failure. Noninvasive ventilation should be tried first if available (except in uncooperative comatose patient or a patient with poor airway reflexes as well as in patient with ARDS). Prolonged ventilation in neuromuscular disorders may require tracheostomy. If detected early acute respiratory failure is a treatable condition with mortality and morbidity related to primary cause and secondary complications as a result of prolonged mechanical ventilation in the pediatric ICU.

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The term *anaphylaxis* introduced by Portier and Richet in 1902 literally means "against life". Anaphylaxis is an acute, potentially fatal allergic reaction. It is a clinical syndrome with a wide spectrum of signs and symptoms reflecting involvement of multiple organ systems, primarily the skin, gastrointestinal tract, cardiovascular and respiratory systems with fatal consequences if not treated promptly. Anaphylaxis is a syndrome with a multiplicity of inciting etiological agents and a variety of pathogenetic mechanisms.

The first cases in humans were seen in the preantibiotic era after injection of horse serum antitoxin used mainly for the treatment of diphtheria or tetanus.

### Epidemiology

The exact incidence of anaphylaxis in children is unknown. Analysis of data in adults estimates 1;10,000 penicillin administration results in anaphylaxis.<sup>1</sup> With as many as 500 deaths annually. In the hospital, 1 in every 2700 patient will experience drug-induced anaphylaxis.<sup>2</sup> Penicillins and cephalosporins are the most commonly involved in anaphylaxis. Other common causative agents are listed in Table 8.1.

The cumulative lifetime incidence of all types of anaphylaxis has been estimated at nearly 1 percent. The risk of anaphylaxis increases with the length and frequency of exposure to a specific antigen; repeated,

interrupted courses make one most susceptible. The parenteral route rather than the oral route of drug administration is associated with an increased likelihood of developing a reaction.

Atopy increases the risk of anaphylaxis with foods, latex, and radiocontrast media but not with medications. Predictably, severe reactions to food occur in patients who are highly allergic, and the presence of asthma appears to be a risk factor for more severe outcomes.

### Pathophysiology

The clinical manifestations of anaphylaxis represent the physiologic effects of potent cell mediators released by activated mast cells and basophilic cells. The effects include vasodilatation, increased vascular permeability, and bronchial smooth muscle constriction. The classic anaphylaxis is IgE dependent<sup>3</sup> and is triggered by exposure to an allergen in a sensitized individual (Table 8.2). Mast cells and basophils are widely distributed in the body. On first exposure, antigen specific IgE antibodies are formed which circulate briefly in the peripheral blood before getting attached to various IgE receptors on the surface of cells. This attachment of antigen specific IgE on the surface of mast cells and basophils makes an individual "sensitized". On subsequent exposure to the antigen, activation of these cells takes place (Flow chart 8.1). This leads to various intracellular events which results

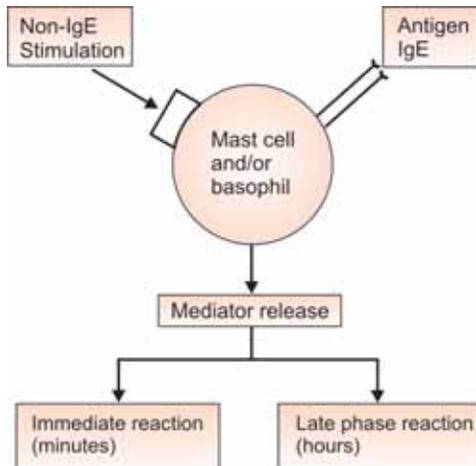
**Table 8.1: Agents causing anaphylaxis**

Ingestants	Food, milk products, coloring agents
Sting bites	Bees, wasps
Pharmaceuticals	Antibiotics, NSAIDs neuromuscular blockers, other drugs, contrast medium
Blood and blood products	
Environmental and physical factors	Pollens, dust, heat and cold
Foreign proteins	Enzymes and vaccines
Rubber/latex	

**Table 8.2: Pathophysiologic mechanisms of anaphylaxis**

IgE dependent	Classic anaphylaxis
IgE independent	Opiates, muscle relaxants, radiocontrast medium, antibiotics, chemotherapeutic agents and plasma expanders.
Immune complex mediated	Blood and blood products, immunoglobulins.
Arachidonic acid metabolism	Aspirin and NSAIDs

**Flow chart 8.1:** Activation of mast cells/basophils leading to anaphylaxis



in the release of various preformed (histamine, tryptase) or newly formed (leukotrienes) mediators.<sup>4</sup> These mediators act locally at the site of release or circulate to distant sites.

### Clinical Features

The clinical presentation of anaphylaxis represents the biologic effects of various cell mediators on various end organs. Skin, gastrointestinal tract, respiratory and cardiovascular systems are the most commonly involved organs. These systems can be affected singularly or in combination, resulting in a wide variety of signs and symptoms.

Ingestion or injection of an antigen is the usual mode of exposure, but it can also occur by absorption or inhalation. Typically, the reaction starts within minutes after exposure and usually reaches its maximum within 15 to 30 minutes. Initial symptoms include flushing, erythema, pruritis (hands, feet, groin and palate), cramping abdominal pain and light headedness. These symptoms are followed by the more objective symptoms involving the four most commonly affected organ systems<sup>5</sup> (Table 8.3).

Involvements of the cardiovascular and respiratory systems are the most serious and often fatal if not treated promptly. The anaphylactic shock is characterized by four types of shock. Capillary fluid leak leads to hypovolemia, vasodilation contributes to distributive shock, and cardiogenic shock is caused by reduced contractility and inappropriate bradycardia due to neurocardiogenic reflex. Pulmonary vasospasm also may introduce an obstructive component by reducing

**Table 8.3: Clinical features of anaphylaxis**

*Cutaneous:* Urticaria and angioedema (90%)

*Gastrointestinal:* Nausea, vomiting, abdominal cramps, diarrhea (25-30%)

*Respiratory:*

*Upper:* Hoarseness, dysphonia, feeling of a “lump” (fullness) in the throat. This may progress to laryngeal edema, stridor and upper airway obstruction (> 25%)

*Lower:* Wheezing, dyspnea (55-60%)

*Cardiovascular:* Hypotension, shock, cardiovascular collapse and arrhythmias (30-35%)

*General:* Sneezing, rhinorrhea, itch and watery eyes, diaphoresis, fecal or urinary incontinence, and nasal and palatal pruritis

left ventricular filling. These multiple effects reducing the ability of the body compensate, probably explain the rapid onset of severe hypotension and unconsciousness that is characteristic of anaphylaxis.<sup>6</sup> An interesting feature of anaphylaxis is that recurrences tend to be similar in terms of target organs involvement.<sup>7</sup> Although mild symptoms may abate without therapy over a period of hours (e.g. urticaria), life-threatening symptoms need to be aggressively treated. Mortality may be early within minutes or late after days or weeks because of organ damage at the time of acute insult.<sup>8</sup>

Anaphylactic reactions usually resolve within hours of their onset (Isolated *immediate reactions*). In 5-20 percent of reactions, a *biphasic pattern* is observed. This is characterized by an initial onset of symptoms with partial or complete resolution of these symptoms but reappears hours later, mimicking the initial response. *Protracted reactions* are characterized by refractory symptoms not responding to any therapy for hours or days. Biphasic and protracted reactions are seen after exposure to antibiotics, other biological materials including vaccines and radiocontrast media and to certain food articles.

### Differential Diagnosis

Its abrupt onset and dramatic physiological and temporal features association with exposed antigen characterize the diagnosis of anaphylaxis. However, in the absence of external features of urticaria and angioedema, one must consider other causes of sudden collapse, including foreign body, seizures, dysarrhythmias vasovagal collapse, hereditary angioedema, serum sickness, hyperventilation syndrome and cold urticaria.

### Monitoring and Laboratory Tests

Most anaphylactic reactions resolve within an hour but all patients who have experienced this dramatic event should be observed for 8-12 hours in view of the late phase reactions, especially in those patients who have had an oral ingestion of the antigen or when the onset of anaphylaxis is more than 1 hour after exposure.

In case the patient has had respiratory or cardiovascular instability, pediatric intensive services are needed for further treatment and monitoring, which may include both non-invasive and invasive methods.

Anaphylaxis is a clinical diagnosis and no laboratory test can aid its diagnosis. Tryptase is an inactive metabolite, released from the intracellular cell granules during anaphylaxis. The best time to estimate it is up to 6 hours after exposure to the offending agent and at the onset of anaphylaxis (Table 8.4).

### Treatment

The successful treatment of anaphylaxis depends on both the prompt recognition and aggressive intervention. The treatment is aimed at reversing and preventing the subsequent propagation of the biological effects of mediators. The extent of intervention depends on the severity of the clinical manifestations.

Basic life support measures take priority over any pharmacological intervention. The initial step in the management is rapid assessment of the cardiorespiratory status and state of consciousness. In a patient with respiratory compromise, establishing a patent airway with adequate oxygenation and ventilation are the first priorities. Due to laryngeal edema, intubation with a smaller size endotracheal tube is desirable. If endotracheal intubation fails, emergent or surgical cricothyroidotomy may be required. Early treatment

with injectable or aerosolized epinephrine may reduce or abort the laryngeal edema.

The drugs commonly used for the treatment of anaphylaxis are given in Table 8.5.

#### *Sympathomimetics: Epinephrine*

The drug of choice for the acute management of anaphylaxis is epinephrine. Due to an increase in the systemic vascular resistance ( $\alpha$ -agonist effects), hypotension is reversed and urticaria and angioedema are reduced. The  $\beta$ -agonist properties lead to bronchodilation and positive inotropic and chronotropic effects. Moreover, stimulation of  $\beta$  receptors on the surface of mast cells increases cAMP formation, which attenuates mediator release from these cells.

Subcutaneous or intramuscular routes of administration are suitable for most reactions, except in the presence of hypotension or if the patient is unconscious, when the intravenous route should be used. A continuous infusion of epinephrine may be needed when hypotension does not respond to 3 doses given at intervals of 15 to 20 minutes. Other inotropes may be needed at this stage like norepinephrine and dopamine. Patients on  $\beta$  blockers may need higher doses of epinephrine and if they do not respond well to sympathomimetics, glucagon administration can be tried.<sup>9</sup> Estimation of serum electrolytes and acid-base status is required in patients not responding to inotropes. It is important to keep a close watch on the side effects of epinephrine like arrhythmias, hypertension and myocardial infarction.<sup>10</sup>

#### *Intravenous Fluids*

Placement of a large-bore peripheral venous or central line is essential for successful fluid therapy. Intraosseous route should be used early till arrangements

**Table 8.4: Laboratory tests to be considered in establishing the differential diagnosis of anaphylaxis and anaphylactoid events**

Test	Comments
Serum Tryptase	Level peak 1-2 hours after onset of reaction and persist for 6 hours
Plasma histamine	Levels rise 5-10 min after onset and decline within 60 min Little helpful as diagnostic test
24-h urinary histamine	Persist in urine for up to 24 hour after onset of symptoms Metabolite (methyhistamine)
Plasma-free metanephrine and urinary vanillylmandelic acid	Rule out paradoxical pheochromocytoma
Serum serotonin and urinary 5-hydroxyindole acetic acid	Carcinoid syndrome
Serum vasointestinal polypeptides: Pancreastatin, vasointestinal polypeptide Hormone, substance P, neurokinin	Gastrointestinal tumor or medullary carcinoma of thyroid

**Table 8.5: Pharmacotherapy of anaphylaxis**

<i>Drug of choice</i>	<i>Dosage and schedule</i>
<b>Essential Drugs</b>	
<i>Volume expander</i>	
Crystalloids	
Normal saline, Ringer lactate	20 mL/kg boluses. Repeat 3 times or more with hemodynamic monitoring
Colloids	
Hydroxyethyl <i>Epinephrine (1:1000)</i>	0.01 mg/kg dose (0.01 ml/kg of epinephrine 1:1000) SC/IV/IM q 15-20 min × 3 (maximum adult dose 0.3-0.5 ml per dose); 0.1-1.0 µg/kg/min by continuous infusion Epinephrine nebulization (3-5 ml of 1:1000)
<i>Hydrocortisone</i>	5 mg/kg/dose IV q 6 hrly
<i>Methylprednisolone</i>	2 mg/kg load IV followed by 1 mg/kg/dose q 6 hrly
<i>Prednisolone</i>	1-2 mg/kg/day orally q 6-8 hrly
<i>Diphenhydramine</i>	5 mg/kg/day IV/IM/PO divided q 6-8 hrly (maximum 300 mg/day)
<b>Other Drugs</b>	
<i>Norepinephrine</i>	0.05-01 µg/kg/min by continuous infusion
<i>Dopamine</i>	0-20 µg/kg/min by continuous IV infusion
<i>Salbutamol</i>	0.15 mg/kg nebulized q 10-30 min prn until patients is stable, then q 4-6 hrly prn (maximum 10 mg)
<i>Terbutaline</i>	0.1-0.3 mg/kg nebulized q 30 min prn × 2, then q 2-4 hrly (maximum 10 mg)
<i>Aminophylline</i>	4-6 mg/kg loading dose followed by continuous IV infusion of 0.5-1.0 mg/kg/hr
<i>Ranitidine</i>	0.75-1.5 mg/kg/dose IV/IM q 6-8 hrly; 2 mg/kg/dose PO q 8 hrly (maximum daily dose 400 mg)
<i>Glucagon</i>	1-5 mg by slow IV infusion
<i>Atropine</i>	0.02 mg/kg; minimum 0.1 mg, maximum 0.6 mg
<i>Ipratropium bromide</i>	250 µg per nebulization

of central line insertion are made and attempts to insert peripheral IV line have failed. Often large volumes of fluid are needed to restore relative hypotension produced by vasodilatation and increased permeability. Isotonic crystalloids like normal saline and Ringer's lactate are the fluid of choice. Consider early use of colloids like 5 percent albumin if large volumes of crystalloids are needed. The volume and rate of rehydration should be guided by hemodynamic measurements and physiological response.<sup>11</sup>

#### *Antihistamines*

Both H-1 and H-2 antihistamines may be helpful for some of the clinical manifestations of anaphylaxis to counter the mediator effects. The usual H-1 antihistamine used is diphenhydramine and H-2 antihistamines are cimetidine and ranitidine. Because of their interference with hepatic blood flow, resulting in decreased drug metabolism, H-2 antihistamines should be used with caution in patients on β blockers.

#### *Corticosteroids*

High-dose corticosteroids have traditionally been used as an important adjunct to the treatment of anaphylaxis

because of their ability to enhance tissue responsiveness to β-agonist, attenuate mediator formation, prevent neutrophil aggregation and decrease edema formation by tightening of the epithelial junctions.<sup>11</sup> Commonly used steroids include: Hydrocortisone,

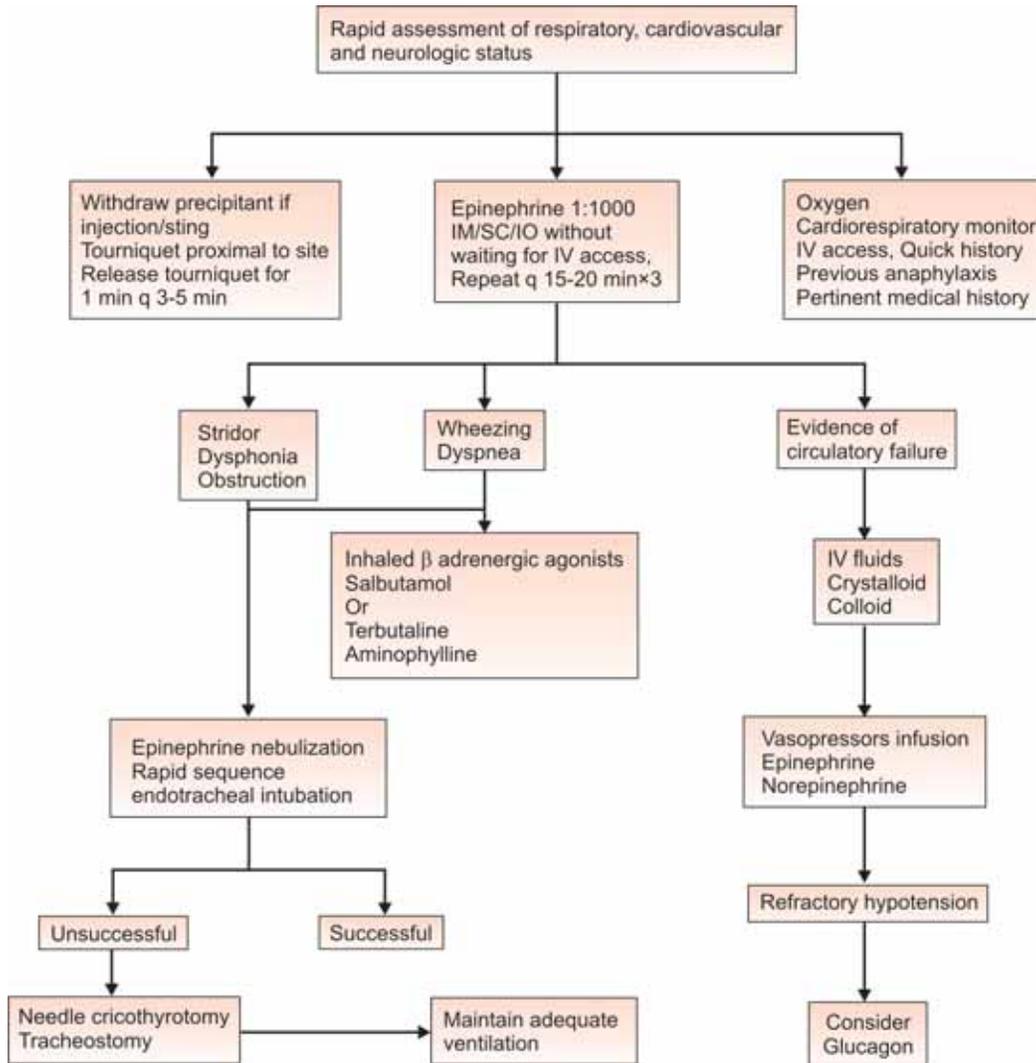
**Table 8.6: Measures to reduce the incidence of anaphylaxis and related deaths**

#### **General measures**

Thorough history for drug allergy  
Avoid drugs with immunologic or biochemical cross-reactivity with known offending agent  
Use oral drugs rather than parenterally when possible  
Check all drugs for proper labeling  
Keep patient in office for 20-30 min after injections  
Measures for patients at risk  
Patient to wear warning identification  
Teach self injection of epinephrine  
Discontinue β-blocking agents, ACE-inhibitors, MAO inhibitors, tricyclic antidepressants  
Use preventive techniques like pretreatment, provocative challenge and desensitization

ACE = Angiotensin converting enzyme, MAO = Monoamine oxidase

Flow chart 8.2: The management of anaphylaxis



prednisolone and methyl-prednisolone. A suggested protocol for the management of a patient with anaphylaxis is depicted in Flow chart 8.2.

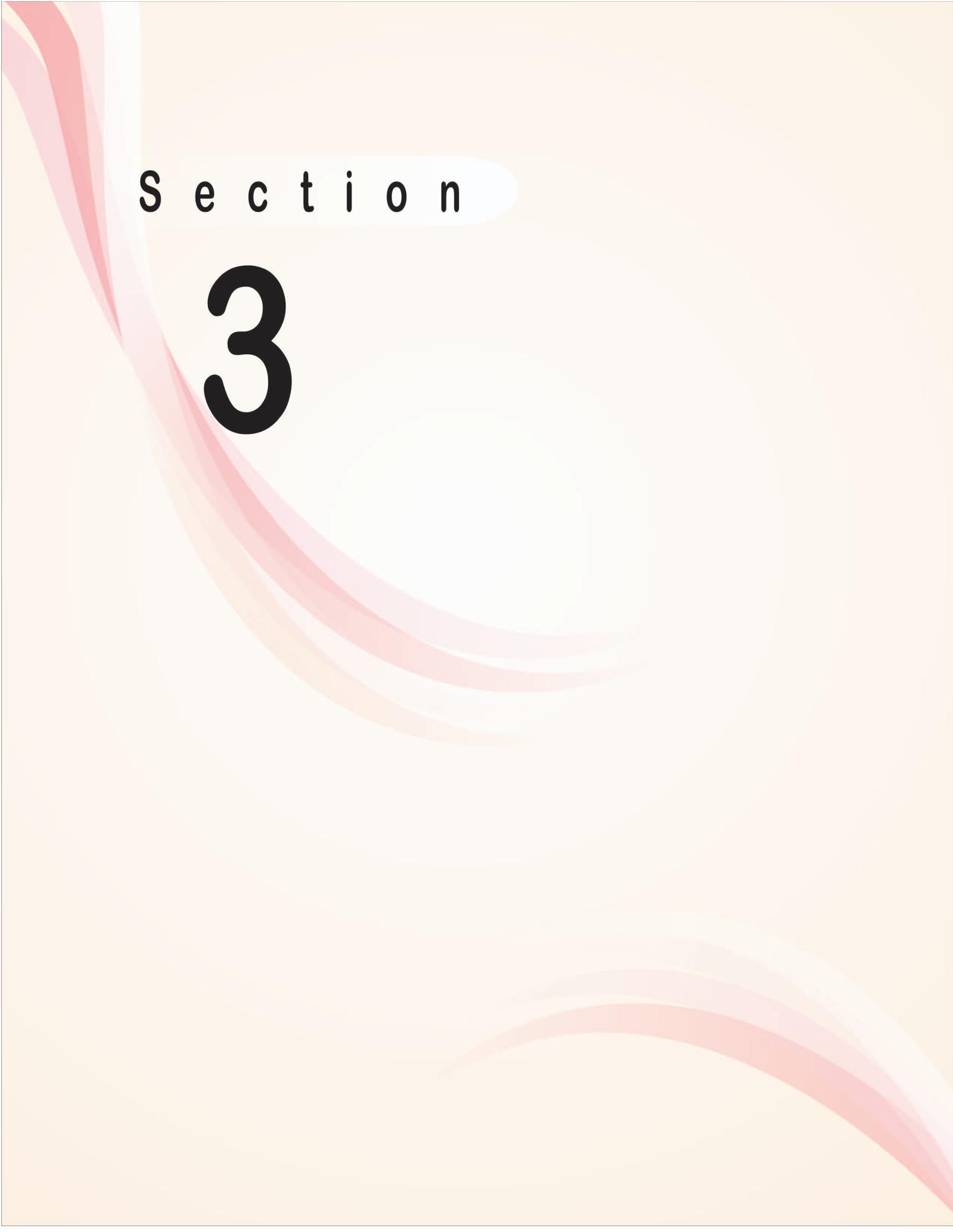
### Prevention

Avoiding anaphylaxis is ultimately the best treatment. Identification of the causative factor is the first step towards preventing a recurrence. Patient education is crucial so that susceptible are aware of where they may encounter the antigen, the type of presenting symptoms and the importance of prompt therapy with self-injectable epinephrine or antihistamines (Table 8.6).

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S e c t i o n

3



Acute exacerbations of asthma are acute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness or a combination of these symptoms. An acute severe exacerbation of asthma that does not respond to conventional therapy is called Status asthmaticus.

Acute exacerbations of asthma are an important cause of morbidity, school absenteeism and frequent visits to the clinic or hospital. There is enough data globally to prove that the prevalence and severity of asthma is increasing.<sup>1-4</sup> There has been an increase in mortality as well, particularly in younger age groups.<sup>5-8</sup> Patients with acute exacerbation who have had near fatal asthma requiring intubation and mechanical ventilation in past, recent hospitalization or recently stopped oral steroids, are at higher risk of death and require closure attention.

This chapter will deal only with management of acute severe asthma. A stepwise approach is necessary for appropriate management. The steps in management are:

1. Assessment of severity and identification of life-threatening attack.
2. Initiation of therapy.
3. Assessment of response to initial therapy.
4. Modification of or addition to therapy and referral.

### STEP 1: INITIAL ASSESSMENT OF SEVERITY

#### Identification of Life-threatening Attack

Initial assessment is necessary to rapidly determine the degree of airway obstruction and hypoxia. One can immediately identify severe or life-threatening cases and give these patients vigorous therapy even before undertaking a detailed assessment (Table 9.1). The features of a life-threatening attack of asthma are: (i) Cyanosis, silent chest or feeble respiratory efforts; (ii) Fatigue or exhaustion; (iii) Agitation or reduced level of consciousness.

Any child with features suggestive of a life-threatening attack should ideally be treated in a hospital

where intensive care facilities are available. However, the child should receive oxygen, bronchodilator and a dose of steroids before making arrangements for transfer to a tertiary level health facility. Oxygen and inhalation therapy (MDI with Spacer) should be continued while the child is being transferred.

#### Detailed Clinical Assessment

Once an appropriate level of management has been instituted in a sick child, a detailed assessment is done based on history, physical examination and objective measurement of degree of airway obstruction and hypoxia.

#### History

Once an appropriate level of management has been instituted in a sick child, a detailed history should be taken with emphasis on certain points. It is necessary to know the duration of worsening and any specific allergen or irritant which could have triggered the attack, any history of previous hospitalizations, frequent emergency visits, chronic corticosteroids use or recent withdrawal from systemic steroids and history of previous admissions to an intensive care unit or intubation. These factors, if present, indicate an increased risk of the attack becoming very severe and such children should be intensively monitored.

#### Physical Examination

The initial examination should rapidly determine the severity of airflow obstruction, degree of hypoxia, and identify complications. Categorization of an acute exacerbation of asthma into mild, moderate or severe can be done based on physical examination and objective parameters as shown in Table 9.1. In any child with severe degree of respiratory distress, presence of alteration of sensorium confusion, and cyanosis will suggest respiratory failure. Examination needs to be repeated after each step of treatment to assess the response.

**Table 9.1: Estimation of severity of acute exacerbation of asthma**

<i>Symptom/sign</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Respiratory rate	Normal	Increased	Increased
Alertness	Normal	Normal	May be decreased
Dyspnea	Absent or mild; speaks in complete sentences	Moderate; speaks in phrases or partial sentences	Severe; speaks only in single words or short phrases
Pulsus paradoxus	<10 mm Hg	10-20 mm Hg	20-40 mm Hg
Accessory muscle use	No or mild intercostal retractions	Moderate intercostal retractions with tracheosternal retractions, use of sternocleidomastoid muscle	Severe intercostal and tracheosternal retractions with nasal flaring
Color	Pink	Pale	Ashen gray or cyanotic
Auscultation	End expiratory Wheeze only	Wheeze during entire expiration and inspiration	Breath sounds becoming almost inaudible
Oxygen saturation	> 95%	90-95%	< 90%
PaCO <sub>2</sub>	< 35 mm Hg	< 40 mm Hg	> 40 mm Hg
PEFR	70-90% of predicted or personal best	50-70% of predicted or personal best	< 50% of predicted or personal best

PEFR: Peak expiratory flow rate.

### Objective Assessment

Many patients may not perceive any distress even when they have moderate degree of airway obstruction. More importantly, even when symptoms and physical signs are minimal, the patient may have considerable level of airflow obstruction. An objective measurement of lung function thus becomes necessary. The two methods of objective measurement of lung function that can be used are (i) Measurement of air flow obstruction by peak expiratory flow rate (PEFR) or forced expiratory volume in the first second (FEV<sub>1</sub>), and (ii) Arterial blood gas analysis (ABG) or pulse oximetry. However, PEFR and spirometry are effort dependent and may not be possible to perform in an acute severe exacerbation even in an older child.

PEFR can be measured using a simple peak flow meter. A child is made to use the peak flow meter in a standing position, three times and the best of the three values is taken as the child's PEFR during the acute attack. This is compared with child's personal best or predicted PEFR.

### Chest Radiograph and Other Laboratory Studies

Laboratory studies are generally not indicated in a routine acute exacerbation. However, if the child is

unusually ill or there is a doubt of an infection, blood samples can be taken for (i) White blood cell count for detecting polymorphonuclear leukocytosis and bandemia which suggests bacterial infection, (ii) Serum electrolytes since both beta-2 agonists and corticosteroids may cause hypokalemia, and (iii) Serum theophylline levels (if facilities are available). If the child is already on theophylline, these levels may be necessary before institution of further systemic drug therapy as it has a very low safety margin.

A chest radiograph is indicated only when the diagnosis is doubtful or there is a suspicion of a foreign body. It is also useful in a child with high grade fever, localized crepitations, decreased breath sounds and any other finding suggestive of infection or complications like pneumothorax, atelectasis and pneumomediastinum.

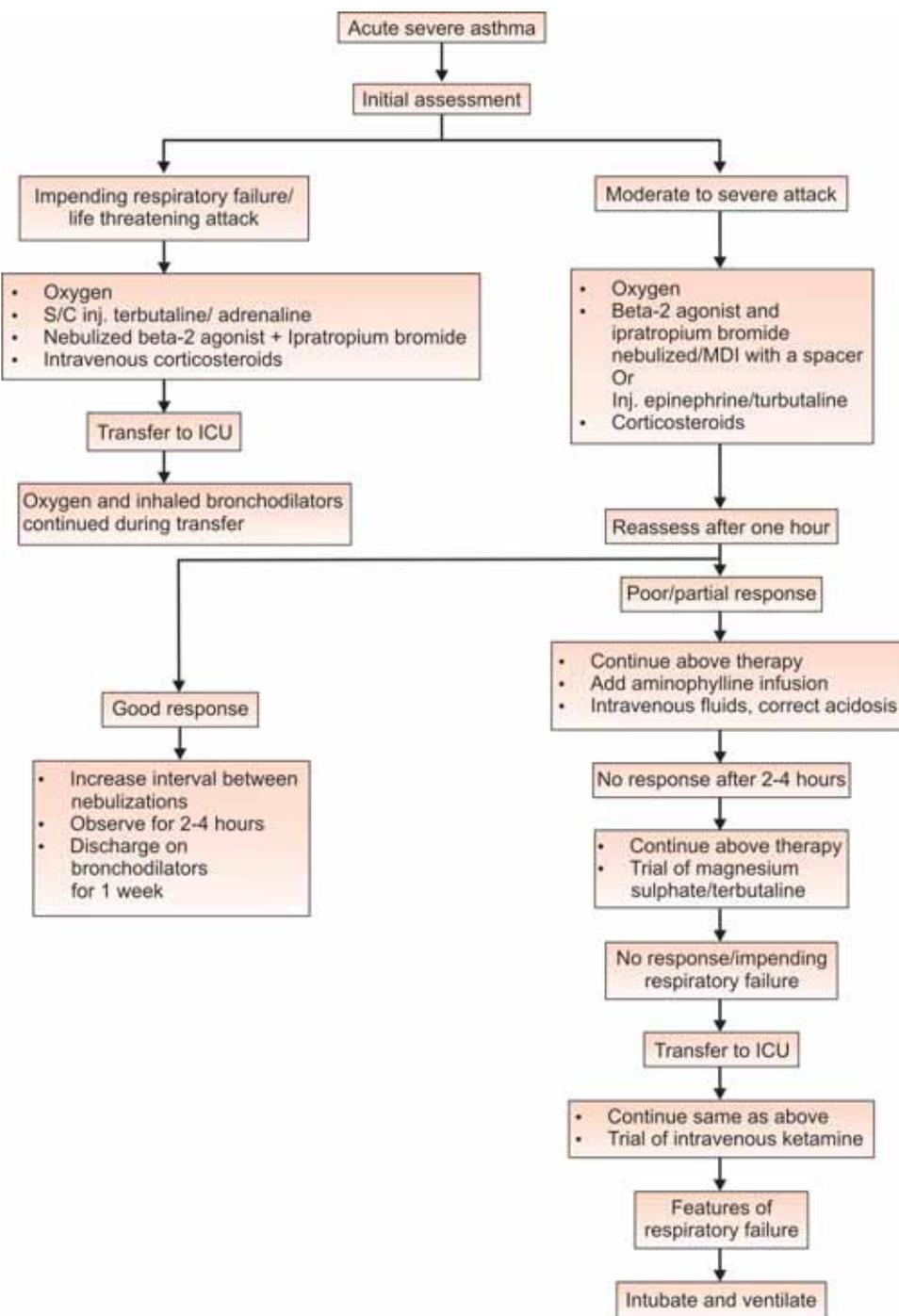
## STEP 2: INITIATION OF THERAPY

### Principles of Therapy

The following are the broad objectives:

- The goal is to rapidly reverse the acute air flow obstruction with consequent relief of respiratory distress. This is achieved by repeated use of inhaled beta-2 agonists (Flow chart 9.1).
- Hypoxia is treated by proper oxygenation of all acutely sick children.

Flow chart 9.1: Management of acute severe asthma



- Corticosteroids are added early in an acute attack if the response to inhaled bronchodilators is not satisfactory.
- Repeated clinical and objective assessment is done to evaluate the response to the above, add other drugs (Table 9.2) if necessary and also to detect impending respiratory failure at the earliest.

### Initial Therapy

#### Oxygen

All patients of acute severe asthma have some degree of hypoxia. Oxygen at the rate of 3-6 liters/minute should be started. The flow should be enough to maintain oxygen saturation above 92 percent.

Table 9.2: Drug dosages in children with acute attack of bronchial asthma

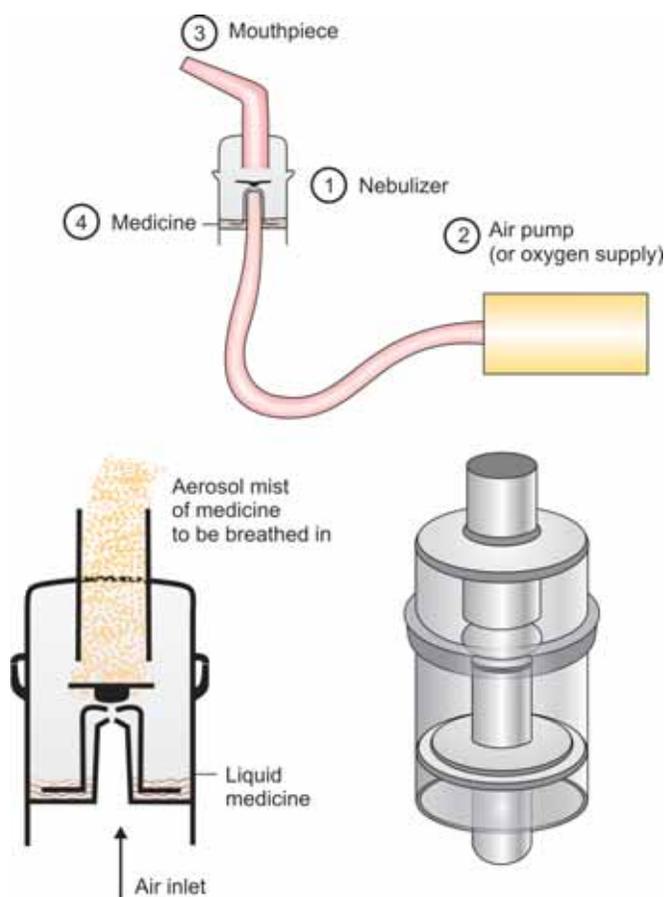
Drug	Available form	Dosage
<b>Inhaled beta-2 agonist</b>		
Salbutamol		
<i>Metered dose inhaler</i>	100 µg/puff	2 inhalations every 5 min for a total of 10-20 puffs, with 0.1-0.15 mg/kg dose up to 5 mg every 20 min for 1-2 h (minimum dose 1.25 mg/dose) or 0.1-0.5 mg/kg/h by continuous nebulization (maximum 15 mg/hour) or 3.4 ±2.2 mg/kg/h in ventilated patients
<i>Nebulizer solution</i>	0.5% (5 mg/ml)	
Terbutaline		
<i>Metered dose inhaler</i>	250 µg/puff	2 inhalations every 5 min for a total of 10-20 puffs < 20 kg 2.5 mg > 20 kg 5 mg
<i>Nebulizer solution</i>	10 mg/ml	
<b>Systemic beta-2 agonists</b>		
Epinephrine HCl	1:1000 sol (1 mg/ml)	0.01 mg/kg up to 0.3 mg subcutaneously every 20 min for 3 doses
Terbutaline	0.05% (0.5 mg/ml) solution for injection in 0.9% saline	Subcutaneous 0.005 mg/kg up to 0.3 mg every 2-6 hours as needed. Intravenous bolus of 10 µg/kg over 30 minutes followed by intravenous infusion at the rate of 0.1 µg/kg/ min. Increase as necessary by 0.1 µg/kg/min every 30 min. Maximum dose is 4 µg/kg/min
<b>Inhaled anticholinergics</b>		
Ipratropium bromide		
<i>Metered dose inhaler</i>	20 µg/puff	2 inhalations every 5 min for a total of 10-20 puffs 1 ml diluted in 3 ml normal saline every 20 minutes for 1-2 hours. This may be mixed with salbutamol nebulizer solution or alternated with salbutamol
<i>Nebulizer solution</i>	250 µg/ml	
<b>Aminophylline</b>	80% anhydrous theophylline (250 mg/10 ml inj.)	Give a loading dose of 5-6 mg/kg and maintain at 0.9/mg/kg/h. If patient is already receiving theophylline, avoid bolus dose
<b>Prednisolone</b>	5,10,20 mg tabs	1-2 mg/kg/dose every 6 hour for 24 hour, then 1-2 mg/ kg/day in divided doses every 8-12 hour for 5-7 days
<b>Hydrocortisone</b>	50 mg/ml inj	10 mg/kg intravenous bolus followed by 2.5-5.0 mg/kg q 6 hour
<b>Methylprednisolone</b>	40 mg/ml inj	4 mg/kg intravenous single dose
<b>Magnesium sulphate</b>	50% soln. for inj (500 mg/ml)	30-70 mg/kg in 30 ml N/5 saline intravenous infusion over 30 minutes

### Beta-2 Agonists

The currently recommended standard bronchodilator therapy is, repeated inhalations of beta-2 agonist aerosol. Salbutamol nebulizer solution (5 mg/ml) in the dose of 0.1-0.15 mg/kg diluted in 3 ml of normal saline is administered over a period of 10-15 min (Figs 9.1 and 9.2). It is preferable to use central oxygen supply at the rate of 6-7 L/min to run the nebulizer, at least initially, to avoid hypoxia. The dose can be repeated every 20 min for three times and the child reassessed after that. The rationale behind giving repeated doses of inhaled bronchodilators is that the bronchodilatation that follows the initial dose allows more distal

deposition of drug particles during further dosing. This results in dilatation of smaller airways and the short dosing interval prevents any deterioration of clinical status in the intervening period.<sup>9</sup> Recent studies, however, suggest that continuous nebulization may be more effective than intermittent nebulization.<sup>10-13</sup> This method of therapy can continue for a prolonged period without having to set up nebulization at regular intervals.

Also patient are more likely to get acclimatized to continuous nebulization and therefore maintain a more constant breathing pattern. This would result in subsequent reduction of inspiratory flow and more peripheral deposition of inhaled bronchodilator



**Fig. 9.1:** Nebulization of salbutamol with air pump/oxygen. Flow of air or oxygen should be 6-7 L/min. The drug is put in the chamber with 2-3 ml of normal saline and the device switched on or attached to central oxygen supply. The nebulized drug is delivered to the patient in the form of mist, through a mouth piece or a mask, in 10-15 minutes

aerosol.<sup>13</sup> Recommended doses are 0.1-0.5 mg/kg/h via a delivery system comprising preferably of a constant infusion pump and central oxygen supply. Higher doses of  $3.4 \pm 2.2$  mg/kg/h have been used in ventilated patients.<sup>12,14</sup> This set up is difficult to maintain, since it requires power and oxygen supply for a prolonged period. However, the superior efficacy of continuous nebulization over intermittent nebulization has not yet been unequivocally proven.

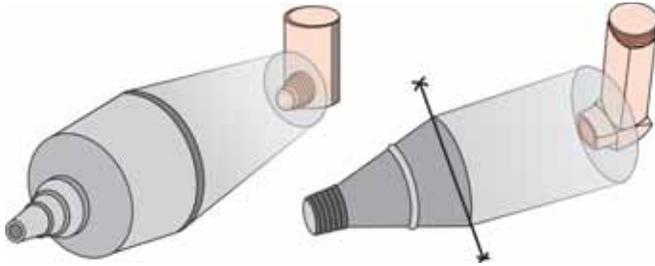
Alternatively, metered dose inhaler (MDI) can be used with a spacer device to give repeated inhalations of beta-2 agonist. It is considered equivalent or better<sup>15,16</sup> than nebulizer driven by compressed air. It does not cause oxygen desaturation unlike the former. The duration of therapy is less than a minute as compared to 15 minutes with a nebulizer. Use of MDI reduces the cost of therapy, is easily performed, and



**Fig. 9.2:** The mouthpiece and mask for use with the nebulizer

does not require power supply. One to two puffs every 5-10 min can be used for 10-20 times. One can use a commercially available large volume (750 ml) spacer device. However, if this is not available, any plastic bottle of about one liter capacity cut at the bottom for introduction of the mouth-piece of inhaler can also be used. The mouth of the bottle can be cut and widened appropriately to cover the mouth and nose of the child like a mask (Fig. 9.3).

In some children with severe bronchospasm, an initial dose of epinephrine may be helpful prior to initiating inhalational treatment.<sup>17</sup> Oxygen desaturation seen with nebulization therapy is not seen with this form of therapy. On the contrary transient increases in  $paO_2$  has been noticed by some workers.<sup>18,19</sup> Injectable terbutaline may also be used in place of epinephrine. Use of epinephrine is limited by its shorter duration of action, cardiac side effects and it cannot be repeated more than 2-3 times. Terbutaline has a longer duration of action and a repeat dose may not be required for 2-6 hours.



**Fig. 9.3:** MDI with a large volume spacer commercial or home made. On pressing the cannister, drug is released into the chamber and the child takes 5-7 gentle breaths from the mouth piece of spacer. Bottle can be cut here (cut edges covered with tape) and used like a mask with spacer

### Anticholinergics

Some studies have shown that concomitant use of inhaled anticholinergics and a selective beta-2 agonist produces significantly greater improvement in lung function than beta-2 agonist alone.<sup>20,21</sup> Only ipratropium bromide is used in view of negligible side effects.<sup>22</sup> Transient anisocoria and angle closure glaucoma have been noticed in adults.<sup>23,24</sup> As it has few systemic adverse effects, its use is advocated for patients with life-threatening features or those who do not respond to initial high dose inhaled beta-2 agonists.<sup>25,26</sup>

Parasympathetic fibers are present in larger airways, in contrast to beta adrenergic receptors which are located in more peripheral airways. Ipratropium may also have a generalized action throughout the lung.<sup>27</sup> It being an acetylcholine antagonist while salbutamol is a beta-2 agonist, both acting at different sites in the lung and via different pharmacologic mechanisms, provides the basis for using these drugs together. There are, however, some studies which have shown no benefits of using anticholinergic drugs.<sup>28,29</sup>

In a recent meta-analysis of 13 studies, adding multiple doses of anticholinergic to beta-2 agonist was found to be safe and improved lung functions to avoid hospital admission in 1 of 12 such treated patients. Available evidence supports its use only in severe asthma.<sup>30</sup>

An optimal dose of 250 µg contained in 1.0 ml of the respirator solution, may be mixed with salbutamol solution and both given together at an interval of 20 minutes with the nebulizer.<sup>31</sup> It may also be given alternating with the dose of nebulized salbutamol. Dosing frequency may be reduced as the patient improves.

In patients who suffer from tachycardia or marked tremors in response to standard dose of beta-2 agonists

and in younger age group (3-30 months) ipratropium may be more effective than salbutamol.<sup>32,33</sup>

### Corticosteroids

Since inflammation is an important component of airway obstruction in an acute attack of asthma, there is no doubt that the use of steroids in an acute exacerbation is useful in resolving the obstruction.<sup>34,35</sup> But it is somewhat difficult to decide precisely when steroids should be administered. It has been proved both in adults and children<sup>36,37</sup> that steroids given for a short duration of 3-7 days, improve the resolution and reduce the chances of an early relapse.

It is evident that the timing of initiation of steroid therapy plays a major role in the subsequent outcome of the attack. Studies have shown that the efficacy of steroid therapy is maximal when they are started soon after the patient presents in the emergency room.<sup>38-41</sup> In contrast, benefits were minimal when steroids were initiated 24-48 hours after observation.<sup>42,43</sup> A single dose of intramuscular methylprednisolone in a dose of 4 mg/kg, when given as an early adjunct to the beta 2-adrenergic therapy has been reported to reduce the hospitalization rates.<sup>44</sup> In following situations, steroids should be started as soon as patient presents in the emergency.

- i. A child with a very severe attack of asthma.
- ii. Previous history of life-threatening attack or severe attacks not responding to bronchodilators.
- iii. If the child is on oral steroids or high doses of inhaled steroids for prophylaxis. An oral dose of 1-2 mg/kg of prednisolone may be as effective as an equivalent dose of hydrocortisone given intravenously, because the time for onset of action is the same. The total duration of therapy can be 3-7 days depending upon the response. However, children who have already been on long-term oral steroids would require a longer course with tapering of doses over 5-10 days.

### Role of Inhaled Steroid in Acute Severe Asthma

A number of studies have been carried out to assess the efficacy of inhaled steroids in acute exacerbation of asthma. Inhaled dexamethasone was the first to be compared with oral prednisolone in management of acute severe asthma. This study<sup>45</sup> suggested that inhaled steroids were quicker acting than oral. This was followed by number of studies comparing budesonide with oral prednisolone.<sup>46,47</sup> These also suggested that inhaled steroids were effective in acute severe attack. However, there were doubts that high

dose used could lead to systemic effect after local absorption. A controlled trial with high dose of Fluticasone, another inhaled steroid but with little local absorption did not find inhaled steroids effective,<sup>48</sup> instead there were few patients in the study group who showed worsening of lung functions. A recent meta-analysis of controlled trials with inhaled steroids suggested that there is no clear evidence till now that inhaled steroids are better than systemic steroids.<sup>49</sup>

### STEP 3: ASSESSMENT OF RESPONSE TO INITIAL THERAPY

Close monitoring for any signs of improvement or deterioration is important. The patient should be assessed after initial therapy of 2-3 doses of bronchodilator along with oxygen over a period of one hour. The plan for further management will depend on whether the response to initial therapy has been good, partial or poor.

#### Good Response

The subject with good response to initial therapy will become free of wheeze and have no breathlessness. Heart rate and respiratory rate will decrease. Auscultation of chest will show minimal or no rhonchi and PEFR or FEV1 will improve to more than 70 percent of the predicted or personal best. Such a child can be observed in the emergency room for 2-4 hours and if remains stable, can be discharged on bronchodilators (inhaled or oral) for a period of 5-7 days. The parents should be advised to come for follow-up and all other necessary instructions should be given for prophylaxis.

#### Partial Response

A child may show some response after bronchodilators but may still have breathlessness and wheezing. Physical examination will reveal persistence of rhonchi. Heart rate and respiratory rate will be above the physiologic norms. Pulsus paradoxus of 10 to 15 mm Hg and oxygen saturation of 91 to 95 percent may be observed. PEFR will be between 40 to 70 percent of the predicted normal. Treatment of a child with partial response is discussed later.

#### Poor Response

If there is no subjective or objective improvement after initial therapy, it indicates a poor response. This child will continue to have severe respiratory distress and wheeze. Physical examination will reveal severe airway obstruction as indicated by significant pulsus

paradoxus ( $\geq 15$  mm Hg), use of accessory muscles and extensive rhonchi. Oxygen saturation of  $\leq 90$  percent and PEFR  $< 40$  percent of predicted normal may be observed.

### STEP 4: MODIFICATION OF THERAPY FOR PATIENTS WITH PARTIAL AND POOR RESPONSE TO INITIAL THERAPY

#### Continue Oxygen and Bronchodilator Therapy

If the response to the initial therapy is not good, oxygen and beta-2 agonist inhalation should be continued. The frequency of inhalation should be decided according to the severity of respiratory distress. Children who do not have severe respiratory distress and have shown partial response may only require 2-4 hourly inhalation while children with severe distress should be given more frequent inhalations. Inhalation as frequently as every 20 min, or even continuous, can be given without side effects for the next two hours and child reassessed. If ipratropium is not used at the onset, it is added at the end of first hour as described earlier. MDI with a spacer can also be used frequently as an effective alternate device. It should also be ascertained whether the nebulizer and MDI are being used correctly (Tables 9.3 and 9.4).

#### Continue Corticosteroids

Corticosteroids should be continued as 0.25-0.5 mg/kg/dose of prednisolone or 2.5-5.0 mg/kg/dose of hydrocortisone every 6 hourly.

#### Intravenous Fluids and Correction of Acidosis

Children admitted with an acute severe attack of asthma often have mild to moderate dehydration. Dehydration may produce more viscous mucus, leading to bronchiolar plugging.<sup>50</sup> Humidification of inspired air and correction of dehydration, therefore, are always indicated. However, at the same time, inappropriate antidiuretic hormone secretion has been reported in some cases of bronchial asthma. Hence fluid therapy should be individualized to keep the child in normal hydration.

Hypokalemia has been reported with frequent beta adrenergic and corticosteroid therapy.<sup>51</sup> It should be corrected when present. Metabolic acidosis that occurs during an acute attack may decrease the responsiveness of bronchi to bronchodilators. It has been recommended that if pH is less than 7.3 or base deficit is greater than 5 mEq, intravenous correction with

**Table 9.3: Correct use of a nebulizer**

1. It is preferable to use central oxygen supply source or oxygen from a cylinder at a rate of 6-8 liters/min to nebulize the drug during an acute attack. However, if oxygen is not available, compressed air can be used. Face mask or mouth device is used depending upon the age and cooperation of the child.
2. The drug volume should be at least 3 ml. If residual volume (volume after nebulization is over) is more than 1 ml, a larger amount of drug volume should be prepared. Three doses of the drug should be nebulized after every 20 minutes during first hour of therapy.
3. Patient should be instructed to inhale from his mouth. Although it may be difficult to control breathing pattern during an acute attack but deep and slow breathing is advocated.
4. Drug should be nebulized over a period of 8-10 minutes. If the procedure is taking longer than 10 minutes, either the chamber is malfunctioning or supply of compressed air/oxygen is defective.
5. A good mist formation suggests that the procedure of nebulization is satisfactory.

**Cleaning the Nebulizer**

It is preferable to use either disposable or separate nebulizer chamber for each patient. However, if that is not possible, cleaning the nebulizer and tubings thoroughly in between patients is mandatory. A light detergent can be used followed by plain water to wash the equipment. One percent vinegar solution can be used for overnight immersion to disinfect the nebulizer and tubings. After sterilization and before next use, the nebulizer should be run dry for a few minutes

sodium bicarbonate is indicated, initially using half the calculated dose and then repeating the ABG.

**Monitoring**

If the child is very sick and is deteriorating, he may require continuous monitoring. Repeated assessments are necessary, at least at hourly intervals, in less sick children. PEFR or FEV<sub>1</sub>, wherever possible, and ABG should be assessed for an objective evaluation especially in very sick and young children.

**Addition of Other Drugs**

If the patient has improved with continuation of the above therapy for about two hours, he can be observed for few hours and then discharged with proper advice. In case there is no improvement, treatment is intensified with addition of other drugs and the child is transferred to a place where intensive care facilities are available.

**Role of Aminophylline**

The role of aminophylline in an acute attack of bronchial asthma is still controversial. There is no doubt that methylxanthines have bronchodilator activity but it is uncertain whether this adds to the bronchodilator effect achieved by beta-2 agonists and corticosteroids.

In a meta-analysis of 13 controlled trials of intravenous aminophylline in acute asthma, no benefit of routine addition of aminophylline to inhaled beta-2 adrenergic and corticosteroids was documented. It has been proved in adult studies that aminophylline does not have additional bronchodilator effect.<sup>52-54</sup> In addition methylxanthines have a very low therapeutic index and side effects can be numerous and serious.

However, in a recent double blind placebo-controlled trial on hospitalized children, a clear benefit of aminophylline was demonstrated.<sup>55</sup> Two recent prospective, randomized controlled trial in children<sup>56,57</sup>

**Table 9.4: Correct use of MDI with a spacer**

1. MDI alone is not advocated in children because of poor hand-lung coordination. A spacer device is a must while using MDI in children.
2. Drug is held in suspension after actuation for a period of at least 10 seconds in the holding chamber.
3. A slow deep breathing through mouth is advised after actuation of MDI and provides better delivery of drug in the lungs.
4. Breath-holding after a deep slow breath is not advocated, particularly during an acute attack because it may be very uncomfortable or impossible. Continuous slow and deep breathing is recommended.
5. Two puffs should be used every 5 minutes during first hour of therapy. In between puffs child should receive oxygen therapy.
6. While using a commercially available spacer, it must be ensured that the patient is able to operate the valve with each inspiration. The click of the valve should be audible with each breath.
7. A small volume (250 ml) spacer for younger children and a large volume spacer can be used for all age groups.
8. Indigenously fabricated spacer is as good as a commercial device in treating an acute attack. Absence of valve intact makes it easier to use in younger and sicker children.
9. MDI with a spacer is as good as a nebulizer. However, 4-6 doses of MDI are equivalent to one dose administered through a nebulizer.
10. The spacer should be washed with a detergent every week and air dried.

have shown clear benefit of intravenous aminophylline in preventing respiratory failure in severe acute attack of asthma. None of the cases in these two studies required intubation after introduction of theophylline while 13 and 7 percent among the controls in these two studies were intubated. It is believed that aminophylline may act by mechanisms other than bronchodilation as well, such as stimulation of the respiratory drive, reduction in respiratory muscle fatigability and enhancement of mucociliary clearance.<sup>57</sup>

A bolus dose depending upon previous treatment with methylxanthines is given followed by infusion of maintenance dose. The dose of theophylline is reduced in fever by 50 percent<sup>52</sup> and by 25-30 percent when concomitantly used with drugs like erythromycin, aminoquinolones, cimetidine and related drugs. The dose may have to be increased in children getting drugs like rifampicin, phenytoin and phenobarbitone. If facilities are available, drug levels are mandatory to ensure its safety and efficacy.

As soon as the patient shows response, aminophylline infusion may be substituted by injectable deriphylline (6 hourly bolus) or even oral theophylline, if the patient is able to take orally.

### Intravenous Terbutaline

In children, with low inspiratory rates where nebulization of beta-2 agonists has failed, intravenous terbutaline, has been tried.<sup>58,59</sup> Therapy is started with an initial bolus of 10 µg/kg over 30 minutes, followed by an infusion at the rate of 0.1 µg/kg/min which may be increased by 0.1 µg/kg/min every 30 minutes, up to a maximum of 4 µg/kg/min<sup>60</sup> or until there is a fall in PaCO<sub>2</sub>, with clinical improvement. Dose of terbutaline should be reduced by half, if theophylline is used concomitantly.<sup>61</sup> Significant adverse effects noted with intravenous terbutaline are tachycardia, arrhythmias, hypertension, myocardial ischemia, hyperglycemia, hypokalemia, rhabdomyolysis, lactic acidosis and hypophosphatemia.<sup>62</sup>

### Magnesium Sulphate

Some patients with acute severe asthma, treated with intensive initial nebulization therapy with beta-2 agonists and corticosteroids may not improve and progress to respiratory failure. One drug which may be worth trying in these refractory patients, to avert mechanical ventilation, is magnesium sulphate. *There is now evidence that magnesium sulphate can be given in children who failed to respond to initial treatment particularly if FEV1 fails to rise above 60% at the end of 1st hour.* A double blind placebo controlled trial suggests

that early institution of intravenous magnesium sulphate along with conventional therapy may result in relief of airflow obstruction.<sup>63</sup> It acts by counteracting calcium mediated smooth muscle contraction, through its influence on calcium homeostasis,<sup>64</sup> inhibition of acetylcholine release<sup>65</sup> at the neuromuscular junction, inhibition of histamine release,<sup>66</sup> direct inhibition of smooth muscle contraction and sedation.<sup>67</sup> The recommended dose for infusion is 30-70 mg/kg over 20-30 minutes.<sup>68</sup> It is available as a 50 percent solution, 0.2 ml/kg of which can be given as an infusion in 30 ml N/5 normal saline in 5 percent dextrose over 30 minutes.<sup>69</sup> *There is also evidence that nebulized salbutamol administered in isotonic magnesium sulphate provides greater benefit than if it is delivered in normal saline.* Serum levels greater than 4 mg/dl are necessary for bronchodilation. Onset of action occurs within a few minutes of intravenous infusion and lasts for 2 hours.<sup>70,71</sup> Side effects include transient sensation of facial warmth, flushing, malaise and hypotension. At serum levels greater than 12.5 mg/dl, side effects like areflexia, respiratory depression and arrhythmia may be noted, but this requires administration of doses greater than 150 mg/kg.<sup>69-71</sup> Thus, it may be used as an adjunct to beta-2 agonist therapy, through its exact place in treatment of acute asthma remains to be determined. Two recent meta-analysis<sup>72,73</sup> of controlled trials on efficacy of magnesium sulfate in acute severe asthma suggest that it is safe and beneficial when conventional therapy with beta-2 agonist and steroids has failed. One of the studies<sup>72</sup> suggests that practice guidelines need to be changed to reflect these result. The current evidence favors use of magnesium sulfate over intravenous terbutaline in a patient who has failed to respond to initial therapy.

### Role of Antibiotics

Respiratory tract infections that trigger exacerbations of asthma are usually viral. Bacteria and mycoplasma may be infrequently associated. Role of antibiotics, hence, is limited to; (i) Patients who are running high grade fever, look sick, and toxic; (ii) There is polymorphonuclear leukocytosis; (iii) Sputum is purulent with presence of polymorphs and not eosinophils; and (iv) Chest radiograph shows a consolidation. In all other cases, even if steroids are used, there is no need to add antibiotics.

### Role of Antihistaminics, Mucolytics, Cough Syrups and Sedatives

Older antihistaminics possess relatively weak antihistaminic action and cause more sedation. In contrast,

newer non-sedating, more potent H-1 receptor antagonists appear to achieve more effective histamine blockade. Astemizole inhibits broncho-constriction in early asthmatic attack. Recent studies have demonstrated significant reduction in severity of symptoms and bronchodilation, with concomitant use of these drugs.<sup>74</sup> Azelastine, another new antihistaminic, has been shown to partially inhibit bronchoconstriction in allergen-induced late reaction of atopic asthma, possibly by suppressing the release of additional inflammatory mediators.<sup>75,76</sup> At present, therefore, there is no general contraindication to the use of newer antihistaminics in asthmatic patients; in fact they may be useful adjunct to asthma therapy. In some patients they may make the secretions viscid thus adversely affecting expectoration.

There is no evidence that addition of mucolytics and cough syrups, are in any way helpful to the patient with acute asthma. Sedation may be harmful in patients who are anxious and irritable because of hypoxia, and should be avoided. Instead measures to treat hypoxia should be made effective. Occasionally younger infants may cry excessively due to reasons other than hypoxia, like hunger and unknown surroundings. This may increase the oxygen demand and also make management more difficult. The best way is to treat these children in the lap of mother. Rarely, sedation may be required and chloral hydrate or triclofos are safe drugs for this purpose.

### Intensive Care Management

#### *Indications for Transfer to an Intensive Care Unit*

The patient is observed on above therapy for next few hours and is monitored frequently. The decision to transfer to intensive care unit (ICU) will depend upon the status of the child at the time of presentation and response to therapy. Any child with signs of life-threatening attack, should be immediately transferred to ICU. If the child has been receiving therapy and has shown poor response after being observed for a few hours or develops clinical signs of impending respiratory failure like persistent hypoxemia, exhaustion or change in the level of sensorium, he should be immediately transferred to ICU. Continuous monitoring with the help of pulse oximetry or repeated ABG analysis are mandatory since most of these patients may not be in a position to perform PEFR.

#### *Continuation of Therapy in ICU*

The focus of care continues to be close observation and delivery of frequent nebulized beta-2 agonists,

combines with corticosteroids and possibly aminophylline. As mentioned earlier, a trial of intravenous terbutaline and magnesium sulphate is desirable in a child who has not responded to above therapy due to low inspiratory flow rates.

#### *Intubation and Controlled Ventilation*

Despite maximal pharmacologic therapy, some children do not respond favorably and require intubation and mechanical ventilation. The decision to ventilate is usually reserved as a last option.

Indications for mechanical ventilation<sup>62</sup> include:

1. Failure of maximal pharmacologic therapy.
2. Cyanosis and hypoxemia ( $\text{paO}_2$  less than 60 mm Hg).
3.  $\text{PaCO}_2$  greater than 50 mm Hg and rising by more than 5 mm Hg/hour.
4. Minimal chest movements.
5. Minimal air exchange.
6. Severe chest retractions.
7. Deterioration in mental status, lethargy or agitation.
8. Recumbent and diaphoretic patient.
9. Pneumothorax or pneumomediastinum.
10. Respiratory or cardiac arrest.

ABG values alone are not indicative of the need for mechanical ventilation and should be interpreted in context of the clinical picture. Frequently, more than one of these indications are present before the decision to ventilate is made. However, it must be stressed that in spite of being aware of the morbidity that ventilation entails, it is better to intubate a child electively rather than to wait for cardiorespiratory arrest to occur.

The patient should be stabilized using 100 percent oxygen administered with a bag and mask. Oral and airway secretions should be cleared and stomach decompressed using nasogastric tube, to diminish risk of aspiration. Premedication with intravenous atropine and topical anesthesia to hypopharynx and larynx, helps to decrease bronchospasm and laryngospasm, which may be produced as a result of upper airway manipulation. An ideal sedative that may be used for intubation is intravenous ketamine in a dose of 1-3 mg/kg. The largest recommended endotracheal tube should be used. Muscle relaxation eliminates ventilator-patient asynchrony and improves chest wall compliance. It reduces  $\text{PaCO}_2$  for any given level of minute ventilation. Additionally, this gives the patient with respiratory muscle fatigue, a period of desperately needed physical rest. Vecuronium bromide, with an intermediate duration of action and without any cardiovascular or autonomic side effects, in a dose of 0.2-0.3 mg/kg may be used. Succinylcholine may be

used too, but it has a short duration of action. A volume cycled ventilator is recommended with low respiratory rate (8-12 per min) and long expiratory time (I:E ratio of 1:4 or 1:3) to prevent hyperinflation. Airway obstruction in itself causes intrinsic PEEP, therefore end expiratory pressure (PEEP) should be minimal. Tidal volume of 10-12 ml/kg and peak airway pressure less than 40-50 cm of water should be maintained. High inspiratory flow rates should be kept to improve gas exchange. This can usually be achieved with heavy sedation or use of muscle relaxants. Throughout ventilation, beta-2 agonists are nebulized into the inspiratory circuit of ventilator.

In the ventilated patients, therapeutic bronchoscopy with lavage after administration of saline, sodabarb and acetylcysteine<sup>77,78</sup> has been used in very ill patients with persistent mucus plugging, to prevent atelectasis and nosocomial pneumonia.

#### *Role of Droperidol*

Dyspnea promotes anxiety, which may impair ventilation and interfere with efficacy of aerosol therapy. Therefore, in pediatric ICU set up, one may use safe sedatives with bronchodilator properties. Droperidol which has both of these properties may be used in asthmatics on assisted ventilation. It antagonizes bronchoconstriction mediated by alpha-adrenergic receptors in peripheral airways. Recommended dose is 0.22 mg/kg and its main side effect is hypotension.<sup>79</sup>

#### *Role of Ketamine*

This drug is a disassociative anesthetic with excellent sedative and analgesic properties. It relaxes smooth muscle directly, increases chest wall compliance and also decreases bronchospasm in ventilated asthmatic children. It is given in a loading dose of 0.5-1.0 mg/kg, followed by an infusion of 1.0-2.5 mg/kg/hour in ventilated children.<sup>79</sup> The common side effects include arrhythmias, increased secretions and laryngospasm. It has been used in sub-anesthetic doses in non-ventilated adults in ICU set up in the bolus dose of 0.75 mg/kg over 10 minutes, followed by an infusion at a rate of 0.15 mg/kg/hour.<sup>80</sup> Thus intravenous ketamine can be used to relieve acute intractable bronchospasm, provided expert anesthetic help is available at hand.

#### *Extracorporeal Membrane Oxygenation (ECMO)*

The use of extracorporeal membrane oxygenation as a therapeutic option in resistant severe asthma for carbon dioxide removal, has been reported.<sup>81,82</sup> Whether this has any definitive role or not is still unclear.

#### *Heliox*

Helium-oxygen mixture has been used to reduce air viscosity and treat upper airway obstruction. Though there are no published controlled trials, some workers have reported a return of normal blood gases following this treatment, in patients with alveolar hypoventilation due to severe acute asthma.<sup>83</sup>

#### *Inhaled Anesthetic Agents*

In patients who fail to improve with mechanical ventilation, with beta-2 agonists continuously delivered through ventilator tubing a trial of inhaled anesthetic gases may be given. Use of halothane 1.0-1.5 percent,<sup>84,85</sup> isoflurane 1 percent<sup>86</sup> and ether have been seen to produce significant improvement within 1 hour. Inhalation may be discontinued within 12 hours, though some patients require extended therapy. The exact mechanism of action of anesthetic agents is unclear. They may relax airway smooth muscle directly,<sup>87</sup> inhibit the release of bronchoactive mediators, or inhibit vagal induced bronchospasm. It is suggested that halothane has an action similar to beta-2 agonists.<sup>88</sup> Administration of anesthetic agents can be done by fitting a standard ventilator with an anesthetic gas vaporizer.

The resolution of bronchospasm in ventilated asthmatic patient will become evident when PaCO<sub>2</sub> values fall, while the same or lower peak airway pressure is being used. Once the PaCO<sub>2</sub> is less than 45 mm Hg, the peak airway pressure is less than 35 cm water and there is mild or no bronchospasm on auscultation, the muscle paralysis can be stopped. As soon as respiratory muscle function returns to normal, the patient can be placed on spontaneous ventilation. If the child can maintain a PaCO<sub>2</sub> of less than 45 mm Hg without assisted ventilation, extubation may be safely done.

#### **Management During Recovery Phase**

The frequency of inhalation should be reduced gradually, and oral drugs should be instituted in place of parenteral medications. The patient can be discharged once symptoms have cleared and lung functions stabilized (PEFR >75% predicted). Bronchodilator therapy consists of oral or inhaled beta-2 agonist depending upon the age of the child and affordability, and a long acting theophylline. The instructions to the parents and the child regarding the importance of correct timing of the drugs and proper inhalation techniques are of utmost importance. The child should

be under follow-up to detect any early relapse and monitor the medication techniques. The parents must be told to monitor the child's symptoms and wherever possible, objective measurements like PEFR should be recorded to detect any worsening.

### Prevention of Future Attacks

The following points must be observed to prevent exacerbations of asthma.<sup>89</sup>

1. Written instructions should be provided to parents of children regarding the administration of drugs during acute asthma episode. Parents should also be taught how to recognize deteriorating control, both clinically and by measurement of PEFR in older children.
2. Parents should know when to seek medical help and where, and supervise the children regularly.
3. Prophylactic therapy should be planned depending upon the age and affordability. A child who has suffered from a very severe attack will generally require inhaled steroids. Oral cromoglycate for prophylaxis has given variable results. Oral montelukast sodium and zafirlukast are now available and hold great promise for prophylaxis.
4. Simple methods of delivery like MDI with spacer (home made or commercial) and rotacap inhalers should be easily available with the patients.
5. There should be written protocols giving clear guidelines of management for acute asthma, in the hospitals.
6. The frequency and severity of exacerbation may be reduced by avoidance of household allergens like carpet dust, house mites, cockroaches, pet animals, synthetic edible colors and food preservatives (soft drinks, chiclets, sauce, canned foods, etc). There is some evidence that negative ion generators purifies the air we breathe but they are expensive.
7. Children with asthma should avoid smoky, stuffy, overcrowded and polluted places. Insect sprays, strong perfumes and mosquito repellents should not be used as far as possible.
8. Breathing exercises and yoga are useful to improve the vital capacity of the lungs. The physical activity should be limited to the tolerance level of the child.
9. Skin testing is unreliable for identification of allergens in children and is not justified routinely.

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Stridor is defined as an abnormal respiratory sound which is produced by critical narrowing of the extrathoracic airways.<sup>1</sup> It is more or less a musical inspiratory sound, which due to its origin from narrowed central airways always connotes a serious and potentially life-threatening affliction leading to respiratory compromise needing immediate management. The narrowing can be in the pharynx, trachea or one of the major bronchi.

### PATHOPHYSIOLOGY

The middle airway and the upper part of the lower airway in children specially infants is barely adequate to sustain normal ventilation of the lungs. There are a number of critical points at which even mild intrusion results in severe compromise. The airway resistance rises exponentially to the decrease in airway radius at the level of the larynx. The junction of posterior tongue with pharynx in the supraglottic region, and the glottis and subglottic area are particularly exposed to the risk of airway narrowing. Supraglottic obstruction produces inspiratory stridor, associated hoarseness and less severe dyspnea and cough. Tracheal obstruction leads to biphasic or expiratory sounds and more marked dyspnea and a brassy cough. The stridor in croup is usually inspiratory, while that due to a bronchial foreign body is either expiratory or biphasic.

Table 10.1 enumerates the common causes of stridor in children and the important among these are described in some detail below:

### Infectious Disorders

**Laryngotracheitis** is a viral infection of the larynx and subglottic region. The commonest etiologic organism is parainfluenza virus (PIV) type I (accounting for 48% cases) with PIV type III, respiratory syncytial virus and PIV type II being next in order.<sup>2</sup> The disease has an insidious onset and often follows an upper respiratory infection. The child presents with hoarseness of voice, stridor and a peculiar brassy cough. Laryngotracheitis

Table 10.1: Common cause of stridor

<i>Infectious</i>
Laryngotracheitis
Acute epiglottitis
Bacterial tracheitis
Retropharyngeal abscess
<i>Congenital</i>
Laryngomalacia
Vocal cord paralysis
Congenital subglottic stenosis
Vascular ring
Congenital saccular cyst
<i>Acquired causes</i>
Post-tracheostomy
Laryngeal granuloma
Foreign body aspiration
<i>Neoplasms</i>
Laryngeal papilloma
Subglottic hemangioma
<i>Allergic</i>
Acute angioneurotic edema
Allergic reaction, e.g., peanuts

is characterized by inflammatory edema and narrowing in the subglottic larynx, trachea and main stem bronchi. The region of the cricoid is the narrowest part of the extrathoracic airway in young children.<sup>3</sup> Progressive narrowing of the airway at this level produces stridor while the increased resistance to airflow causes turbulence and gives a high pitched sound to the cough in croup.

Most cases are mild and self limiting and respond to humidification of the inspired air. A few, however, require intensive care. The Downe's scoring system (Table 10.2) is a useful guideline towards management.<sup>4</sup>

**Epiglottitis** is an acute fulminant bacterial inflammation of the supraglottic structures, i.e. epiglottis, arytenoids, aryepiglottic folds and uvula. The causative organism is *Haemophilus influenzae* type B (Hib).<sup>5</sup> This condition has been reported from India due to causes

Table 10.2: Downe's score for signs of upper airway obstruction

	Score		
	0	1	2
1. Stridor	None	Inspiratory	Inspiratory + Expiratory
2. Cough	None	Hoarse cry	Barking
3. Retraction + nasal flaring	None	Flaring + Supra-sternal retraction	Flaring + Suprasternal, subcostal, intercostal retraction
4. Cyanosis	None	In air	In 40 percent oxygen
5. Inspiratory breath sounds	Normal	Harsh with wheezing and/or rhonchi	delayed

Adapted from Downe's *et al.*

Score— Up to 4 : Observation

4-6 : Referral to a center with facilities for intubation and tracheostomy.

> 6 : Immediate insertion of an artificial airway.

unknown even before the introduction of Hib vaccination. Child looks toxic and has significant respiratory distress. In order to maintain patency of the airway, he/she tends to assume a protective posture with flexion at the waist, chin thrust forward and tripod placement of the supporting upper extremities.<sup>3,6</sup> The brassy cough, so prominent in laryngotracheitis, is absent and the stridor is characteristically low pitched.<sup>6</sup> Due to the rapidly progressive nature of the disease, which often results in airway obstruction, a quick diagnosis and prompt intervention are mandatory.

In epiglottitis, sometimes the arytenoids may become rapidly swollen producing a sudden and almost complete supraglottic obstruction. The reduced airflow produces muffled and low-pitched stridor at the vocal cords. Dysphonia, at times aphonia, characterizes this condition and is a manifestation of the diminished airflow.<sup>3</sup> It has also been suggested that as the epiglottis and aryepiglottic folds become edematous, they also become rigid, preventing complete obstruction of the airways. One can, therefore, safely employ bag and mask (or mouth-to-mouth) ventilation, should severe airway obstruction occur before, an artificial airway can be secured.<sup>7-9</sup> It may, however, be noted that though in epiglottitis it is the supraglottic larynx which is primarily involved, the infection can spread to the paraglottic space as well, thereby adding to the airway compromise.<sup>10</sup> This condition has significant morbidity and mortality.<sup>11</sup>

**Diphtheria** is usually seen in unimmunized or incompletely immunized children and is still a major cause of mortality. Although seen uncommonly now, it is a cause of fatal croup. There may be membrane

formation in the pharynx and sometimes, in and around the larynx which leads to stridor. It rarely causes tracheitis without marked supraglottic involvement. The child looks ill and the toxicity is often out of proportion to the fever. The diphtheritic membrane may give rise to sudden, complete obstruction if it gets dislodged from the surface. Tracheostomy must, therefore, be done at the earliest signs of airway compromise.

**Spasmodic croup** is a sudden attack of stridor occurring usually during the night and is often recurrent in nature, not preceded by any upper respiratory infection. The exact cause is not known but both allergic and viral causes have been hypothesized.<sup>12</sup> It often responds dramatically to humidification of inspired air and reassurance. These patients may show good response to corticosteroids<sup>13</sup> and even bronchodilators.<sup>14</sup> On follow-up as many as 20% are reported to develop bronchial asthma.<sup>15</sup> The exact pathophysiology of spasmodic croup is not completely understood though a viral infection and allergic reaction are both implicated in the production of intermittent and recurrent obstructive symptoms. Virus specific IgE has been demonstrated in many patients.

**Bacterial tracheitis** is caused primarily by *Staphylococcus aureus*<sup>15</sup> and is characterized by severe airway obstruction, high fever, toxicity and subglottic narrowing. Direct laryngoscopy reveals pus flowing out of the glottic opening. The thick inspissated secretions in the infraglottic region may cast a soft tissue shadow, which often changes appearance, in subsequent radiographic examinations.<sup>16,17</sup> The obstruction in bacterial tracheitis is due to the thick pus and inflammatory edema in the infraglottic region producing airway compromise.<sup>17,18</sup>

## Congenital Disorders

**Laryngomalacia** is the most common cause of stridor presenting at or near birth. Symptoms are typically aggravated with crying. Examination reveals partial collapse of a flaccid supraglottic airway with inspiration. The condition is generally benign, self-limited and is not associated with severe respiratory distress. Severe cases may require laser epiglottoplasty if the distress prevents adequate feeding.<sup>19</sup>

**Vocal cord paralysis** occurs following injury to the vagus or recurrent laryngeal nerves. *Bilateral vocal cord paralysis* usually presents with marked stridor and cyanosis. It is generally due to vagus nerve stretching from aggressive traction during delivery, Arnold-Chiari malformation, hydrocephalus, intracranial hemorrhage, or hypoxia. *Unilateral vocal cord paralysis*, in contrast, usually presents with hoarseness rather than with the stridor, and is more frequently due to peripheral nerve injury. Accidental injury during patent ductus arteriosus ligation is frequent cause of unilateral paralysis in infants. Tracheostomy is required to secure the airway in bilateral paralysis, though generally not in unilateral paralysis unless there is excessive aspiration.

**Congenital subglottic stenosis** may present as recurrent episodes of stridor within the first 6 months of life and may be mislabeled as “croup”. Even slight edema in congenitally narrowed cricoid region can cause significant obstruction. Acute exacerbations are treated medically, while surgery can correct the stenotic segment. Tracheostomy is frequently needed for airway security.

**Vascular ring** is an anomaly of the great vessels that causes extrinsic compression of both the trachea and the esophagus. The child with vascular ring anomaly usually presents with dysphagia as well as stridor. Other anomalies of the innominate or pulmonary arteries can present with stridor alone. The degree of stridor may vary with the physiologic state of the cardiopulmonary vasculature, i.e. patency of the ductus. Treatment for vascular anomalies is surgical.

**Congenital saccular cyst** of the larynx is an unusual lesion that commonly presents with varying degrees of respiratory obstruction in infants and young children. The cyst is typically mucus-filled and is treated surgically by deroofting or marsupialization, although concomitant tracheostomy may be needed in some cases. *Laryngeal web*, a persistent membrane across the glottis at birth, also varies in the severity of

obstruction, and may require dilatation, surgical division, or occasionally tracheostomy.

## Acquired Causes

**Iatrogenic** causes include long-term intubation which may lead to *acquired laryngotracheal stenosis*, the most common cause of chronic stridor in children. Treatment varies by the severity of the lesion. Minor stenoses may be observed, while more severe stenoses may be treated by a variety of surgical methods including widening of the stenotic subglottis or trachea, cartilage grafting, and tracheostomy. *Laryngeal granuloma* also results from prolonged intubation, and often may be removed endoscopically.

**Accidental foreign body** aspiration should always be considered as a potential cause of stridor and airway obstruction in children. Foreign bodies aspirated in children most commonly are food articles (nuts and seeds), coins, beads, whistles attached to squeaky toys, pen caps, etc.<sup>20</sup> Young age is the greatest risk factor for injury or death from a foreign body in the aerodigestive tract. Conforming objects such as balloons pose the greatest risk of death due to choking, followed by round non-food objects such as balls or marbles. After securing the airway, treatment consists of endoscopic visualization and removal by an experienced surgeon.

## Neoplastic Disorders

**Subglottic hemangioma** is a vascular malformation that usually presents in the first few months of infancy. Patients with subglottic hemangioma usually present with progressive stridor and respiratory difficulty. Half of the children have some type of skin lesions which involute by age 5-9 years without aggressive surgical intervention. Steroids and alpha interferon administration are also options for large obstructing lesions. Tracheostomy or surgical debulking may be necessary in some cases.<sup>21</sup>

**Recurrent respiratory papilloma** is the most common benign tumor of the larynx and presents with symptoms related to gradual airway obstruction. Endoscopy reveals single or multiple irregular, wart-like glottic masses in the larynx or pharynx. The condition is believed to be caused by human papillomavirus types 6 and 11, which also cause genital condyloma in adults. Transmission is believed to be from infected mother to fetus. Treatment is with CO<sub>2</sub> laser ablation, though alpha-interferon and indole-3-carbinol also have proven value. The clinical course is highly unpredictable, and death may occur in

some children due to distal tracheobronchial spread and lung cavitation.

### Allergic Disorders

Acute angioneurotic edema or allergic reaction can present at any age and with rapid onset of dysphagia, stridor and possible cutaneous allergic signs such as urticarial rash. Children might have history of allergy or previous attack. In a study, 110 children were studied 9 years after each had been in hospital for croup.<sup>22</sup> Fifty-seven of them had recurrent episodes of croup, and 33 were defined as allergic. The association between allergy and recurrent croup was highly significant. Airways hyper-reactivity was found in 23 of them, and was associated with allergy and recurrent croup. The group of children with a history of recurrent croup could be distinguished from the group with one or two episodes by male predominance, onset of the disease at a younger age, familial predisposition, a significantly greater association with allergy and airways hyper-reactivity, slightly lower expiratory flow rates in pulmonary function tests, and a tendency towards the subsequent development of asthma.

### ASSESSMENT OF A CHILD WITH STRIDOR

Appropriate assessment is necessary. Children with acute stridor need emergency management and care. Most of the time the diagnosis can be made on history and typical clinical features. The severity of stridor can be graded on the basis of Downe's score or Croup score (Tables 10.2 and 10.3<sup>23</sup>). Although such scores are useful for research studies, none has been shown to enhance routine clinical care. Certain important facts, however, must be borne in mind. If epiglottitis is suspected, all efforts should be made to keep the child quiet, provide him oxygen. One should insist on keeping the child in mother's lap. All casual throat examinations are strictly forbidden. An artificial airway

must be expeditiously secured and only after this has been done intravenous fluids should be started and venepunctures made for bacteriologic and other investigations. Not doing so may precipitate complete obstruction in an already compromised airway. Similarly, in diphtheritic pharyngitis, repeated casual throat examination should be avoided as this may dislodge the membrane and produce complete obstruction and death. Cardiorespiratory monitoring, including continuous pulse oximetry, is indicated in children with severe croup but it is not necessary in mild cases. Also, children without severe croup could occasionally have low oxygen saturation, presumably as a result of intrapulmonary involvement of their viral infection; thus, ongoing assessment of overall clinical status is important.

### Radioimaging

The role of radiology in the assessment of acute stridor is limited. Radiographs are not indicated if there is a clinical picture of epiglottitis or bacterial tracheitis. In children in whom the diagnosis is uncertain, however an anteroposterior and lateral soft-tissue neck radiograph can be helpful in supporting an alternate diagnosis. However certain characteristic radiologic features have, however, been described on lateral radiographs of the neck.<sup>24</sup> In epiglottitis, a rounded thickening of the epiglottic shadow having the configuration of an adult thumb, gives rise to the so called 'thumb' sign.<sup>25,26</sup> Similarly children with upper airway obstruction without epiglottic involvement have normal epiglottic shadow with the configuration of an adult's little finger (little finger sign). The symmetrical narrowing of the subglottic air shadow in laryngotracheitis on anteroposterior projection is better known as the "church steeple" sign.<sup>27</sup> These views are, however, neither always necessary nor helpful. Interpretation of the radiologic signs is often rendered difficult if films are not taken in appropriate phases of inspiration and

**Table 10.3: Westley croup score**

Score	Stridor	Retraction	Air entry	Cyanosis	Level of consciousness
0	None or only when agitated	None	Normal	None	Normal
1	Audible with stethoscope at rest	Mild	Mild decrease		
2	Audible without stethoscope at rest	Moderate	Marked decrease		
3		Severe			
4				With agitation	
5				At rest	Depressed

**Total score:** Less than 4: mild; 4-6: moderate; 7 or more: severe

expiration. Stankiewicz et al, in a review of the role of radiology in croup came to the conclusion that the lateral X-ray of neck and chest may be unreliable and inaccurate and that a good clinical judgment be utilized when interpreting the radiographs.<sup>28</sup>

It must be kept in mind that a meticulously performed pharyngoscopy is much more informative than the radiology.<sup>27-30</sup> Needless to say, the X-ray should be obtained at the bedside with the child in mother's lap; sending the child unaccompanied to the radiology department can be very risky.

Children with stridor of chronic nature can be evaluated in a systematic way. They are generally well compensated for hypoxia but at times may have pulmonary hypertension. Recently, availability of high KV films has helped delineate the airway anatomy specially in children with tracheal or bronchial lesions. It has also become possible to perform virtual bronchoscopy with the help of spiral CT.

### Endoscopy

Fiberoptic laryngoscopy and bronchoscopy are extremely useful in evaluation of a child with chronic stridor although these can be performed in acute cases as well. Fiberoptic endoscopy permits an atraumatic evaluation for laryngomalacia, vocal cord paralyses, tracheal stenosis or a web. Endoscopy also allows therapeutic interventions with the help of laser.

## TREATMENT

### Oxygen

Oxygen is administered by a simple mask with the baby in the mother's lap. Utmost care should be taken not to irritate the child or initiate crying. All attempts must be made to keep the child quiet. Should complete airway obstruction occur at home, bag mask (or mouth-to-mouth) ventilation and external cardiac massage must be instituted without delay. This procedure is mostly successful even in epiglottitis. Cardiopulmonary resuscitation should be followed by either nasotracheal intubation or a tracheostomy. At the periphery, where facilities for either procedure may not be readily available, recourse may be taken to a large intravenous catheter inserted through the cricothyroid membrane. This can act as an efficient airway in all babies for a short period of time.

### Airway Management

If there is a suspicion of epiglottitis, direct pharyngoscopy should be performed by an experienced

pediatric anesthesiologist in the operation theater,<sup>31</sup> preferably in the presence of a skilled surgeon. Some authors, however, prefer pharyngoscopy examination in the pediatric intensive care unit by a pediatric anesthesiologist, using IV anesthetic agents and muscle relaxants.<sup>32</sup> In either case, five minutes of mask pre-oxygenation with 100 percent oxygen, with the child in the mother's lap is essential.<sup>7</sup> Facilities for nasotracheal intubation, tracheostomy and mechanical ventilation should be at hand.

All the patients with epiglottitis must have an artificial airway. Most patients with laryngotracheitis, on the other hand, can be managed conservatively with humidification and nebulized epinephrine. Diphtheria requires a tracheostomy at the earliest signs of upper airway obstruction while in bacterial tracheitis it is mandatory.

### *Nasotracheal Intubation (NTI) versus Tracheostomy*

Short-term NTI is now the preferred mode of airway management in epiglottitis and laryngotracheitis.<sup>31-34</sup> Not only is the duration of tracheal intubation shorter than with tracheostomy, but the length of hospital stay and cost of hospitalization are markedly decreased. Smaller than age predicted endotracheal tubes,<sup>31</sup> short intubation time and ensuring a tracheal air-leak at 20-25 cm water external airway pressure<sup>34</sup> reduce the complications of the procedure.

Nasotracheal intubation must only be performed by highly skilled and experienced personnel. It should ideally be done under general anesthesia but intubation of conscious subjects can often be accomplished after topical spray of 10 percent xylocaine to the nasal mucosa. Five minutes of mask preoxygenation with 100 percent oxygen is an essential prerequisite.<sup>3</sup> In difficult cases fiberoptic broncholaroscopy may be necessary to permit glottic cannulation. It may again be stressed that if experienced medical personnel are not available or if skilled nursing care is lacking a tracheostomy (or even a cricothyrotomy) may be life saving in case of epiglottitis.<sup>35</sup>

### *Duration of Intubation and Timing of Extubation*

The length of intubation and criteria used for extubation are controversial.<sup>36-39</sup> Some authors extubate these children when the fever resolves and the toxicity diminishes,<sup>39</sup> and there is improvement in the general condition as judged by decrease in the severity of stridor, retractions, cyanosis and pulse rate. On the other hand, others opine that the child should be kept intubated till there is a documented reduction in

epiglottic size by direct laryngoscopy.<sup>33</sup> The mean intubation time is 41 hours if the former criteria are used as compared to 33-35 hours reported by those using direct laryngoscopy.<sup>39</sup>

Corticosteroids, single dose dexamethasone, 1 mg/kg body weight, is used in some centers before extubation which may help in preventing post-extubation stridor.

### Humidification

Treatment of croup with humidified air is not effective, despite its long history of use. Humidification of air is neither completely benign nor does it improve respiratory distress. In a systematic review of three randomized controlled trials of humidified air treatment in emergency settings in 135 children with mild to moderate croup concluded that there is no difference in croup score after such treatment.<sup>40</sup> Humidification is achieved by mist vaporization, nebulization or steam inhalation. Apart from difficulties in administration of humidified air, hot humidified air can cause scald injuries; mist tents can disperse fungus and moulds into the environment unless they are properly cleaned and most importantly mist tents are cold and wet and separate the child from the parent, which usually causes them to be agitated and worsen their symptoms.

### Heliox

Helium is an inert low-density gas with no inherent pharmacological or biological effects. Administration of helium-oxygen mixture (heliox) to children with severe respiratory distress can reduce their degree of distress since the lower density helium gas (*vs* nitrogen) decreases airflow turbulence through a narrow airway. Heliox was compared with racemic epinephrine in a prospective randomized controlled trial of 29 children with moderate-to-severe croup who had received treatment with humidified oxygen and intramuscular dexamethasone. Clinical outcomes included a clinical croup score, oxygen saturation, and heart and respiratory rates. Both heliox and racemic epinephrine were associated with similar improvements in croup score over time. Findings of a second prospective, randomized, double-blind controlled trial in 15 children with mild croup presenting to an emergency department indicated a trend towards greater improvement in a clinical croup score in the heliox group versus the oxygen-enriched air group, although the scores did not differ significantly. However, since heliox has yet to be shown to offer greater improvements than standard

treatments and can be difficult to use in unskilled hands, there is insufficient reason to recommend its general use in children with severe croup. Furthermore, there are practical limitations to heliox use, including limited fractional concentration of inspired oxygen in a child with significant hypoxia.<sup>40</sup>

### Intravenous Fluids

Once an adequate airway has been secured and the patient oxygenated, intravenous fluids are started. Extra fluids may have to be given if dehydration is present which may result due to respiratory water loss. It may be mentioned that rarely pulmonary edema may complicate an extrathoracic airway obstruction as in croup. It results from alveolar hypoxia, increased capillary transmural pressures and increased pulmonary vascular resistance. In such cases fluid restriction and diuretics may become necessary.<sup>41,42</sup>

### Nebulized Epinephrine

Racemic epinephrine is an aerosolized vasoconstrictor and consists of equal amounts of levo and dextro-rotatory isomers of epinephrine (2.25% solution diluted 1:8 with water in doses of 2-4 ml over 15 minutes). It effectively decreases subglottic edema and is, therefore, of use in laryngotracheitis and spasmodic croup.<sup>43</sup> Its action is short lasting and initially the treatment may need to be repeated at frequent intervals. Its use has virtually reduced the need for tracheostomy in laryngotracheitis to zero. Side effects are minimal and unlike epinephrine, it does not produce rebound vasodilation or troublesome systemic effects.<sup>44</sup> It can be administered either by intermittent positive pressure breathing (IPPB) or by nebulization.

It should be noted, however, that nebulized epinephrine itself is a safe and effective alternative to racemic epinephrine.<sup>45,46</sup> Usually 4-5 ml of 1:1000 solution (available in India as injection adrenaline) is nebulized over 5-10 minutes; this dose may need to be repeated.<sup>46</sup>

### Corticosteroids

Corticosteroids have a long history of use in children with croup; evidence for their effectiveness for treatment of croup is now clear. Children with severe croup and impending respiratory failure who are treated with corticosteroids have about five fold reduction in the rate of intubation; if they are intubated, they remain ventilated for about a third less time and have a seven fold lower risk for reintubation than patients not treated with these drugs. In moderate-to-severe croup patients

who are treated with corticosteroids, an average 12 h reduction in the length of stay in the emergency department or hospital, a 10% reduction in the absolute proportion treated with nebulized epinephrine, and a 50% reduction for both the number of return visits and admissions for treatment.<sup>40</sup>

Tibbals et al<sup>47</sup> have published a prospective randomized double-blind comparison of prednisolone and placebo in 70 children intubated for severe airway obstruction caused by croup. Prednisolone (1 mg/kg) was given every 12 hours by nasogastric tube until 24 hours after extubation. Steroids not only reduced the duration of intubation but also decreased the need for reintubation.

#### Route of Administration—Oral, IM, Inhaled

The best route of administration of corticosteroids in children with croup has been investigated extensively. The oral or intramuscular route is either equivalent or superior to inhalation. The addition of inhaled budesonide to oral dexamethasone in children admitted with croup did not confer any additional advantage.<sup>40</sup> Comparator studies on the use of oral steroids in the treatment of croup show the superiority of dexamethasone in reducing rates of return for medical care.

Other practical issues should also be considered. For instance, for a child with persistent vomiting, the inhaled or intramuscular route for drug delivery might be preferable. In cases of severe respiratory distress, oral administration could be more difficult for the child to tolerate than an intramuscular dose. In a child with hypoxia, decreased gut and local tissue perfusion can

impair absorption *via* the oral or intramuscular route, respectively. In these cases, the inhaled route should be considered and would also allow for administration of oxygen or racemic epinephrine concurrently.

#### Dose

The conventional dose of dexamethasone is 0.60 mg/kg. One would expect the epinephrine to control edema until dexamethasone takes effect as laryngotracheitis can be expected to run its course for a couple of days. One dose of dexamethasone is usually sufficient.

Specific treatment of conditions leading to stridor in children are given in Table 10.4.

#### Antimicrobials

The use of antimicrobials in croup should be restricted to the situations shown in Table 10.5.

#### Antitussives, Decongestants and $\beta_2$ -agonists

No physiologically rational basis exists for use of antitussives or decongestants, and they should not be administered to children with croup. Similarly, in view of the pathophysiology of croup as an upper airway disease, there is no clear reason to use short-acting  $\beta_2$ -agonists for treatment of the disease.<sup>40</sup>

#### PROGNOSIS

Laryngotracheitis usually causes mild croup and carries an excellent prognosis. Stridor due to epiglottitis is often severe and, untreated, has a mortality up to

**Table 10.4: Specific treatment of conditions leading to stridor**

	<i>Laryngotracheitis</i>	<i>Epiglottitis</i>	<i>Diphtheria</i>	<i>Spasmodic croup</i>	<i>Bacterial tracheitis</i>
1. Oxygen	Essential	Essential	Essential	Essential	Essential
2. Airway	No intervention in most, nasotracheal intubation in severe cases	Nasotracheal intubation	Tracheostomy	None	Tracheostomy
3. Intravenous fluids	Not necessary in most	Essential	Essential	Not essential	Essential
4. Racemic epinephrine	Beneficial	Ineffective	Ineffective	Beneficial	Ineffective
5. Dexamethasone	May be beneficial	Not beneficial	Beneficial in myocarditis	Not beneficial	Not beneficial
6. Antimicrobials	No	Yes (ampicillin + chloramphenicol)	Yes (penicillin)	No	Yes (cloxacillin + gentamicin)

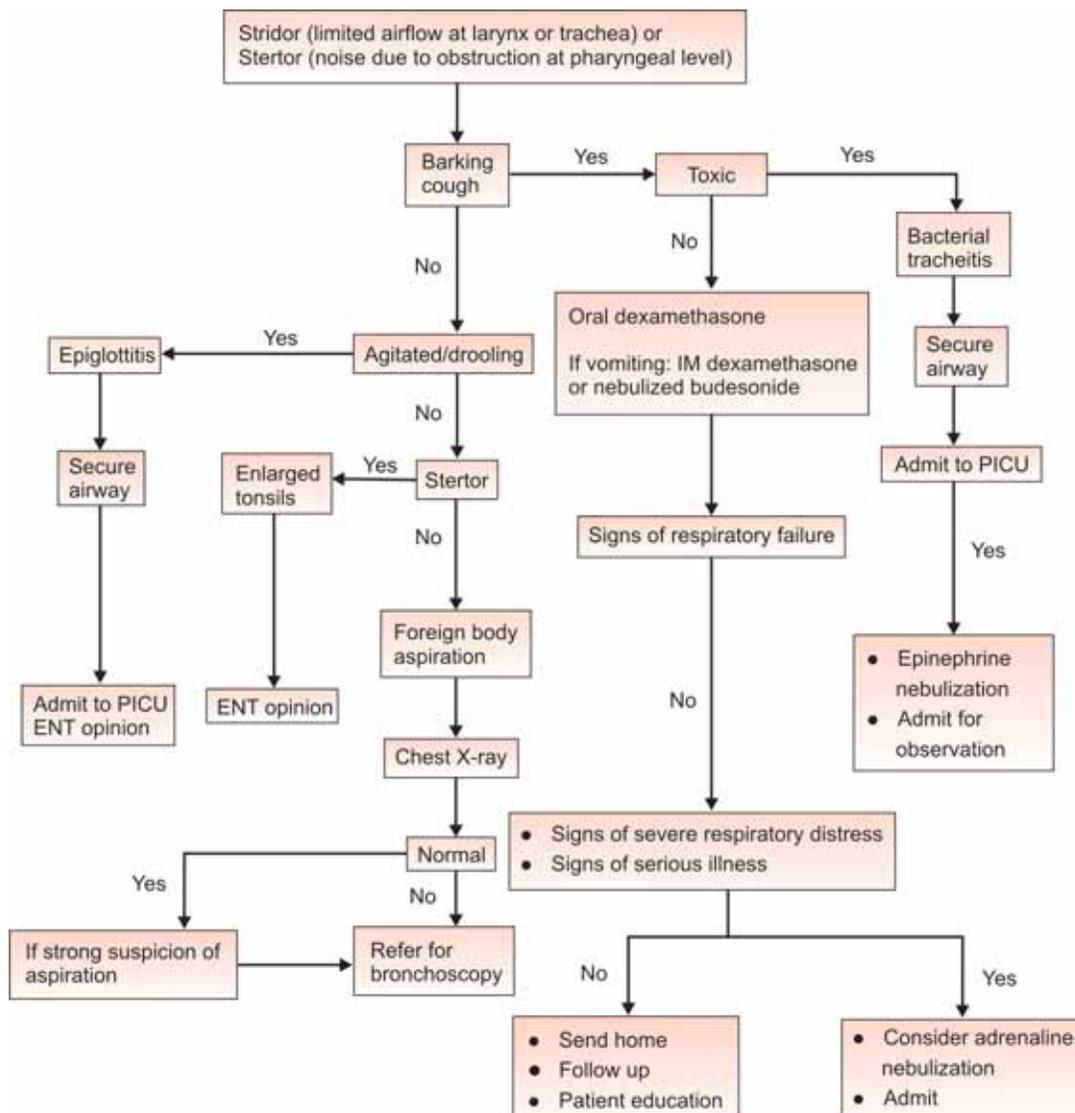
Adapted from Diaz<sup>3</sup>

**Table 10.5: Use of antimicrobials in infectious croup**

Indication	Drugs	Dose per 24 hr	Duration of therapy
1. Epiglottitis			
<i>Therapeutic</i>	Ampicillin + Chloramphenicol	200 mg/kg IV; 6 hr doses 100 mg/kg IV; 6 hr doses	7-10 days
<i>Prophylactic</i> (households and day care center contacts)	Rifampicin	20 mg/kg OD orally (max 600 mg)	4 days
2. Diphtheria	Crystalline penicillin + ADS*	1,00,000 units/kg IV; 6 hr doses	7-10 days
3. Bacterial tracheitis	Cloxacillin + Gentamicin	200 mg/kg IV; 6 hr doses 7.5 mg/kg IV; 8-12 hr doses	10-14 days

\*ADS: Antidiphtheric serum (80000-120000 units IV)

**Flow chart 10.1: Management of stridor**



25 percent. If, however, the diagnosis is made and the treatment initiated before the patient is moribund, most patients recover. In contrast to an aggressive approach to epiglottitis in young children, in older children a conservative line of management is recommended. Though still mainly a pediatric emergency, an increasing incidence of epiglottitis is being reported among adults.<sup>48</sup>

Spasmodic croup is usually self limiting but the patient may have recurrent episodes. Diphtheria is preventable with adequate immunization. It is a grave illness but many patients can be salvaged with efficient airway management and prompt administration of anti-diphtheritic serum. The high mortality in bacterial tracheitis is partly due to the fact that the illness is often diagnosed late. If an adequate airway can be secured and the correct antimicrobials given, the prognosis would definitely improve.

The outcome in severe croup depends essentially on the promptness with which a correct diagnosis is made as also on the knowledge and experience of the attending physicians. Availability of appropriate equipment is an essential prerequisite. An algorithm for evaluation and management of stridor is shown in Flow chart 10.1.

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# Lower Respiratory Tract Infection

Acute respiratory infections (ARI) comprise a wide spectrum of infections ranging from common cold to severe infection like pneumonia. Although majority of ARI episodes are self limiting, pneumonia is a serious life-threatening illness accounting for 80-90 percent of acute lower respiratory infections and approximately 30 percent of all childhood fatalities.<sup>1</sup>

Infections above glottis are grouped as acute upper respiratory tract infection (AURTI) which includes common cold, pharyngitis, otitis media and sinusitis and below glottis as acute lower respiratory tract infection (ALRTI) which includes epiglottitis, laryngitis, tracheobronchitis, bronchiolitis and pneumonia.

Young children experience an average of 6-8 respiratory illnesses per year in urban setup and slightly lower in rural areas.<sup>2</sup>

Viruses are the most common cause of acute upper respiratory infection throughout the world. The variant of corona virus (associated with severe acute respiratory syndrome) and human metapneumovirus, (new respiratory pathogen) have stressed the continuing importance of viral respiratory infections over the whole age spectrum.

## ACUTE LOWER RESPIRATORY TRACT INFECTION

Acute lower respiratory tract infections (ALRTI) range from acute bronchitis to pneumonia. Unlike AURI which are a major cause for childhood morbidity, ALRTI are the major cause of childhood deaths. Among ALRTI, pneumonia is a serious disease which should be recognized and treated immediately otherwise it may prove to be fatal.

According to WHO, in children under 5 years old, pneumonia was the leading cause of childhood mortality in the world.<sup>3</sup> It is estimated that 95% of such infections occur in developing countries.

## Evaluation of ALRTI

In children, acute respiratory infection and its complications require careful evaluation and close

monitoring. Cough, wheezing, rales, tachypnea, and dyspnea were considered to be signs of lower respiratory tract infection. Character of the cough may help to localize the site of infection. Paroxysmal cough of pertussis, dry spotty nocturnal cough of asthma, throat clearing cough of postnasal drip, brassy or metallic cough of tracheitis, barking cough of glottic pathology, dysphonic or bovine cough of vocal cord paralysis, needs special mention.

Clinical features like the sensorium of the child, respiratory rate, chest retractions, and respiratory sounds like stridor, wheezing and grunting should be evaluated.

It is important to realize that increased respiratory rate can occur even in non-respiratory conditions like metabolic acidosis and diabetic ketoacidosis. To differentiate respiratory from non-respiratory conditions, increased work of breathing like chest retraction is helpful; which is marked in respiratory disease, minimal in cardiac disease and absent in other conditions. In addition to tachypnea and chest indrawing, the presence of stridor (upper airway obstruction, e.g. croup), wheeze (small airway obstruction, e.g. asthma) and grunt (parenchymal lesion, e.g. pneumonia) will help to localise the site of disease. At times snoring which originates from the flutter of the tissues of the oropharynx should be differentiated from other noisy breathing. By careful interpretation of clinical signs, anatomical diagnosis is possible in vast majority of infants presenting with respiratory disorders.

## Types of Lower Respiratory Tract Infection

Lower respiratory tract infection includes tracheitis, bronchitis, bronchiolitis and pneumonia. Among these pneumonia, laryngotracheobronchitis (croup) and bronchiolitis are important clinical conditions. Considering its severity laryngotracheobronchitis is invariably included under lower respiratory tract infection.

### LARYNGOTRACHEOBRONCHITIS (CROUP)

The term croup refers to a clinical syndrome characterized by barking cough (particularly after coughing and crying), inspiratory stridor and hoarseness of voice. Most cases of croup are of viral etiology and sixty five percent of viral croup is caused by one of the three types of parainfluenzae virus. Since the viral infection involves the larynx, trachea and bronchi the viral croup is commonly referred as acute laryngotracheobronchitis and the term croup usually refers to the viral croup.

Clinical examination is the most important aspect that helps in both the diagnosis and in the assessment of severity of disease. As viral croup is the commonest cause of upper airway obstruction, attempts to identify the other causes in the emergency room may unnecessarily delay treatment.

#### Assessment

Viral croup occurs between the ages of 3 months and 5 years but croup of bacterial cause usually occurs in older children (3-7 years). Children with croup present with viral prodrome along with hoarseness of voice, barking cough, inspiratory stridor, and respiratory distress. Children with progressive stridor, severe retractions, hypoxia, cyanosis, depressed sensorium need hospitalization. The management protocol differs depends upon the severity of croup (Table 11.1).

#### Management

Child should be kept as calm and quiet as possible, preferably in the mother's lap (in her own posture) to avoid crying as it may aggravate the obstruction and work of breathing.

Attempts to examine the throat or laryngoscopic examination may precipitate laryngeal spasm and cardiorespiratory arrest so such things should be avoided. The role of warm mist, steam, and cold steam from nebulizer is limited.

Many children with mild croup may improve without treatment however parents should be

explained about natural course of the disease. Some with mild croup may require steroids. Nebulized budesonide (2 mg/dose) or dexamethasone (0.15 to 0.3 mg/kg) or even oral prednisolone (1 to 2 mg/dose) may be used as all are equally effective. Glucocorticoids hasten the improvement of clinical symptoms and reduce the duration of hospitalization.

In children presenting with moderate to severe croup, humidified oxygen through comfortable device should be administered to maintain  $\text{SaO}_2 >92\%$ . Nasal cannula with oxygen flow rate up to 5 liters per minute or simple face mask with 4–10 liters per minute may maintain adequate saturation.

In severe croup, nebulized adrenaline (0.5 ml/kg of 1:1000 dilutions to maximum of 5 ml) may be repeated once in 4 hours in addition to the above treatment. In patients with croup, adrenaline provides a significant benefit because of its ability to reduce bronchial and tracheal secretions and mucosal edema (Table 11.2).

Though spasmodic croup is well defined entity (develops suddenly without much of a viral prodrome and resolves quickly), differentiating it from viral croup is difficult in the first attack and mostly it may be a retrospective diagnosis. Extrathoracic foreign body, bacterial tracheitis, retropharyngeal abscess, epiglottitis (bacterial croup) and diphtheria are other conditions which may present with acute upper airway obstruction.

### BRONCHIOLITIS

Bronchiolitis is a viral disease of the lower respiratory tract characterized by inflammatory obstruction of smaller airways. It predominantly occurs around age of 6 months; however, it may occur any time between 3 months to 2 years. Common viruses implicated with bronchiolitis are respiratory syncytial virus (>50%), parainfluenzae type II, adenovirus, and corona virus.

Viral invasion leads to edema, accumulation of mucus and cellular debris leading to bronchiolar obstruction, which results in hypoxemia and progressive air hunger due to impairment of normal gas exchange.

Table 11.1: Grading severity of croup

	Mild	Moderate	Severe
General appearance	Feeds well; Interested in surroundings	Fussy, comforted	Restless; sensorium may be altered
Stridor	Stridor while coughing and crying; no stridor at rest	Stridor at rest, worsening with agitation	Stridor at rest, worsening with agitation
Respiratory distress	No distress	Tachypnea, tachycardia and chest retractions	Marked tachycardia with chest retractions
Oxygenation	>92% in room air	>92% in room air	<92% in room air; cyanosis.

**Table 11.2: Management of croup**

Drug	Mild	Moderate	Severe
Steroids (Oral or nebulized or IM)	May require	Yes	Yes
Nebulized adrenaline	No	May be given if deterioration noted during observation	Repeated doses may be required
Oxygen	No	No	Required to keep SaO <sub>2</sub> >92%

Clinical manifestations start with symptoms of upper respiratory catarrh with cough, sneezing and nasal discharge with gradual increase in respiratory distress. Apneic spells can occur in young infants. Symptoms are disproportionate to auscultatory findings. Progressive dyspnea is the hallmark of the disease with expiratory wheeze.

Bronchiolitis is a clinical disease and investigations add little. When symptoms are atypical, investigations may be done. Skiagram chest reveals hyperinflation of lungs with bow sign at times (enlarged thymus along with right border of the heart), peribronchial thickening, and patchy atelectasis. RSV antigen can be demonstrated from the naso-pharyngeal secretions by rapid fluorescent antibody testing or enzyme immunoassay test.

The clinical presentation of bronchiolitis is so typical that there are hardly very few differential diagnosis. Rarely first attack of asthma may confuse, where positive family history, and prompt response to nebulized bronchodilator may be useful. Other differential diagnosis includes bronchopneumonia, congestive heart failure and congenital airway anomalies.

### Treatment

From therapeutic point of view, based on respiratory distress, feeding ability and oxygen saturation, bronchiolitis can be graded into mild (minimal respiratory distress, normal intake, no signs of hypoxemia), moderate (respiratory distress, difficult to feed, saturation <92%) and severe (severe distress, apneic spells, saturation <92%).

Incessant crying may be a sign of hypoxemia and sedation should be avoided. Since hypoxemia is an underlying factor, administration of humidified oxygen 3 to 6 liters/minute by a cannula kept a little away from the face is the treatment of choice which immediately reduces the respiratory distress. Oxygen saturation should be maintained above 92%. Severe respiratory distress may lead the child to refuse normal intake and

the child should be on maintenance intravenous fluids. Fever control, nasal clearing with saline drops, and frequent small feeding may be useful in majority of infants with mild or moderate bronchiolitis.

A trial of therapy with nebulized salbutamol may be useful when there is a strong family history of atopy and may be repeated if there is a good response. Nebulized epinephrine (0.1 ml/kg per dose of 1:1000) can be used as rescue medicine before hospitalization. Corticosteroids are not beneficial. Antibiotics may be added when there is strong suspicion of superadded pneumonia evidenced by constitutional symptoms, blood count and skiagram chest.

Young infants with risk factors like prematurity, congenital heart disease, and bronchopulmonary dysplasia are prone to develop bronchiolitis. Monoclonal antibodies to respiratory syncytial virus (palivizumab) are found to be useful prophylactically for high-risk groups.

### PNEUMONIA

Pneumonia denotes inflammation of the lung parenchyma characterized by consolidation or lung infiltrates usually due to microorganisms and at times due to non-infectious causes (lipid).

### Lung Defence Mechanism

The defence mechanism of the respiratory system include mechanical (coughing, sneezing, mucociliary escalator), the innate immunity (complement cascade, adhesion proteins, antimicrobial peptides like lysozyme, lactoferrins, and defensins, alveolar macrophages, neutrophils), and adaptive immunity (T cell-mediated and B cell-mediated immune response) which constantly work to keep the airway sterile despite the constant threat by microorganisms. However, if the dose, virulence and the size of inoculum increase or when the resistance and immunological response of the body go down, the attempts of defence mechanism fail resulting in establishment of lung infection.

### Community Acquired Pneumonia

Community acquired pneumonia (CAP) is an acute infection of the pulmonary parenchyma in a previously healthy child, acquired outside of a hospital setting (the patient should not have been hospitalized within 14 days prior to the onset of symptoms). Hospital acquired pneumonia denotes that occurs 48 hours or more after admission. In this chapter CAP will be discussed.

### Microbial Pathogens

Microbial pathogens may enter the pulmonary system by anyone of following ways:

- (a) Aspiration after colonization of oropharyngeal secretions (virulent organisms—*S. pneumoniae* and Hib nontypable)
- (b) Droplet inhalation (*Legionella*, *Mycoplasma*, *Chlamydia*, and most viral infections and
- (c) Hematogenous—*Staphylococcus* (pulmonary circulation act as filter for venous blood).

### Risk Factors

Regardless of cause, risk factors for pneumonia include crowding in household, low socioeconomic status, low parental educational status, lower respiratory tract infection, and young maternal age, exposure to tobacco smoke, outdoor air pollution and overcrowding in child care facilities. Other important factors identified in developing countries are lack of breast milk and malnutrition.

### Clinical Evaluation

Detailed history and thorough clinical examination should be done including other system involvement and nutritional status. Depending upon the severity, pneumonia presents with varied clinical presentations like cough, fever, tachypnea, chest pain, chest retraction (intercostal, subcostal, sternal, suprasternal) flaring of alae nasi, grunt, head bobbing, rales, and decreased breath sounds. Signs of severe illness like cyanosis, grunting respiration, dehydration should be assessed in addition to vital signs and saturation.<sup>4,5</sup>

The World Health Organization's age-specific criteria for tachypnea are the most widely used to diagnose pneumonia and also in assessing the severity of pneumonia. It recommends using "fast breathing" (tachypnea) to diagnose pneumonia at the community level.

Fast breathing denotes the underlying pneumonia. Since respiratory rate differs in different ages, the

**Table 11.3: WHO diagnosis of pneumonia**

Age	Respiratory rate (breaths per minute)
< 2 months	60 or more
2 months up to 12 months	50 or more
12 months up to 5 years	40 or more

definition of fast breathing also changes with age. A clinician must use this merely as a beginning step and advised to use all clinical skills for making a final diagnosis (Table 11.3).

Tachypnea with chest retraction (definite inward motion of the lower chest wall during inspiration) denotes *severe pneumonia*. Tachypnea with chest retraction (accessory muscles working) with altered sensorium, or cyanosis, or difficulty in feeding, or poor perfusion, denotes *very severe pneumonia*.

### Investigations

Investigations play limited role in the diagnosis of CAP. All patients do not require a chest radiograph particularly if on domiciliary treatment. A X-ray cannot differentiate reliably between bacterial and viral infections. However, if clinical features are atypical or complications suspected, a radiograph should be taken.

Though it is ideal to identify the causative microbial pathogens before starting therapy, it is practically not feasible because of contamination from upper respiratory tract flora and time required for bacteriologic culture. Younger children (<6 yr) do not expectorate and microbiology plays a little role because of many compounding factors like prior antibiotics, contamination, and colonization.

Acute phase reactants like white cell counts and C-reactive protein do not help in the diagnosis but may be useful to monitor the response. Pulse oximetry is a useful tool for assessing the severity.

### Pathogens

The child's age is the single most important consideration in determining the most prevalent pathogen for evaluation of CAP (Table 11.4).<sup>6</sup> *Streptococcus pneumoniae* is the most common bacterial pathogen at all ages. Viruses are the most frequent cause of pneumonia in preschool children.

### Treatment

Treatment decisions are based on the child's age and clinical and epidemiologic factors. Before instituting

**Table 11.4: Pathogens causing community acquired pneumonia**

Age	Organisms presumed	Comment
Below 3 months	Gram negative group B streptococci, <i>S. pyogenes</i> , <i>Chlamydia</i>	In young neonates organisms from maternal flora to be considered
3 months to 5 years	<i>S. pneumoniae</i> , <i>H. influenza</i> , viruses <i>S. pyogenes</i> , Staphylococci, <i>Mycoplasma</i>	<i>S. pneumoniae</i> and viruses are the most common causes in infants three weeks to three months of age.
Above 5 years	<i>S. pneumoniae</i> , <i>Chlamydia</i> , viruses Staphylococci, <i>Mycoplasma</i> <i>S. pyogenes</i> , <i>H. influenzae</i>	<i>Mycoplasma pneumoniae</i> and <i>Chlamydia pneumoniae</i> are important etiologic agents in children older than five years and in adolescents.

therapy detailed history and thorough clinical examination should be done. Differentiating viral infection from bacterial infection is difficult. Considering the serious nature of the disease, children need to be started with empirical antimicrobial treatment immediately.

Children with CAP who are debilitated and acutely ill, especially neonates, children with severe protein energy malnutrition, with other system involvement and with severe respiratory distress should be hospitalized and treated with appropriate antibiotics based on their age. Infection with *S. aureus* should be considered if the child is sick or progression of the disease is fast along with skin lesions and in post measles state.

Infants below 3 months of age usually have severe pneumonia and must be hospitalized. Children above 3 months can be treated as outpatients (Tables 11.5 and 11.6).<sup>7</sup>

Oral route of drug administration is enough in mild respiratory infections. Intravenous route is preferred in newborn and infants, in children with shock or suffering from bleeding, diathesis and severe pneumonia.

**Table 11.5: Outpatient treatment of community acquired pneumonia**

Age	First line	Second line
3 months to 5 yr	Amoxicillin	Coamoxiclav
Above 5 yr	Amoxicillin	Coamoxiclav, macrolide

Majority of children show signs of improvement 5- 7 days after starting appropriate antibiotics. Some complicated, severe infections require prolonged antibiotic therapy. Staphylococcal infection (e.g. empyema, pyopneumothorax) require at least 3 to 4 weeks of therapy.

### Complications and Prognosis

Complete resolution after treatment should be expected in the vast majority of cases. In debilitated children, bacterial invasion of the lung tissue can cause complications like pleural effusion, empyema and lung abscess.

**Table 11.6: Inpatient treatment of community acquired pneumonia**

Age	First line	Second line
<3 months	Cefotaxime, Ceftriaxone	Add aminoglycoside
3 months-5 yr	Ampicillin with chloramphenicol	Cefotaxime, Ceftriaxone
>5 yr	Ampicillin, Coamoxiclav Add macrolide if suspected mycoplasma infection	Cefotaxime, Ceftriaxone, add macrolide
<i>S. aureus</i> infection	Coamoxiclav, Ceftriaxone Add cloxacillin	Ceftriaxone with vancomycin or teicoplanin

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## INTRODUCTION

Heart failure is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues, or does so only at elevated filling pressures.<sup>1,2</sup> The current American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines defines heart failure as a 'complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.'<sup>3</sup> Heart failure can have multiple manifestations which determine the terminology used as well as the intended management. New onset severe heart failure, acute heart failure, and decompensated chronic heart failure can all have an emergency presentation, signifying the relative fast development of symptoms rather than severity per se. Our current understanding of heart failure is that of not just a case of cardiac dysfunction but that of a multiorgan syndrome which explains the myriad pathophysiological and clinical features that accompany it.

The pathophysiology and etiologies for heart failure in children are very different from those in adults. Common causes of adult heart failure including ischemia, hypertension and valvular inflammation are less common in children. Infants and children develop heart failure more commonly due to volume overload secondary to shunt lesions, and obstructive lesions of the heart. Less common causes include homeostatic abnormalities and cardiomyocyte dysfunction secondary to myocarditis/cardiomyopathies. Palliated congenital heart disease (CHD) leading to heart failure is increasingly being recognized.

With the aim of keeping this chapter focused on clinical aspects and management of heart failure, the pathophysiology of heart failure shall not be discussed in detail. Briefly, the manifestations of heart failure arise due to mismatch of the circulatory load and the ability

of heart, or its components, to pump it in an adequate fashion. These can be accompanied or followed by compensatory changes in the regional perfusions and renal, muscular and endocrine physiology (notable among changes in virtually every organ). The outcome of this, manifesting as symptoms, is excess extracellular volume in lungs and periphery (over a longer duration) and decreased perfusion of vital organs like kidneys and brain as well as the muscles. The time course of development of these changes is variable (and different in younger children); hence the presentation especially during an emergency may vary.

## CAUSES OF HEART FAILURE IN INFANTS AND CHILDREN

The prominent causes of heart failure or ventricular dysfunction in children are provided in Table 12.1. Table 12.2 enumerates the likely causes of heart failure by age at presentation. This is important, as the symptoms and signs of heart failure can be confusing or fairly non-specific in children. It is notable that all these causes can present initially in an emergency as acute heart failure, while volume overload lesions, rheumatic heart disease, and myocyte dysfunction (intrinsic or post-operative) can also have a chronic course with recurrent decompensation. In general, the younger the age, more likely is an acute presentation of heart failure.

Heart failure presenting on the first day of life is commonly due to metabolic abnormalities. Structural diseases that cause heart failure in neonates usually do not manifest on the first day of life. The cardiac causes of heart failure on day one of life are same as those for heart failure in fetus, like Ebstein anomaly, supraventricular tachycardia, complete heart block, etc.

About 90% of all cases of heart failure in children occur before the end of first year of life with CHD as the dominant cause. In the first week of life, obstructive and duct-dependent lesions can present with acute heart failure or circulatory shock. Development of heart

**Table 12.1: Causes of heart failure in children by underlying pathology**

Cause	Comment
Volume overload (relative or absolute)	CHD with increased pulmonary blood flow (VSD, PDA, AVSD, TGA, Truncus, TAPVC) (1)
Obstructive lesions/atretic valves or great vessels	AV fistula or malformations, anemia, thyrotoxicosis (3) AS, PS, MV atresia or stenosis, coarctation of aorta, aortic interruption (2)
Regurgitant lesions (MR/TR)	Congenital (e.g. as part of AVSD, Ebstein anomaly), acquired (e.g. RF/RHD), post-operative (1)
<i>Myocyte dysfunction</i>	
Primary	Inborn errors of metabolism, muscular dystrophy, DCM, drug-induced, hemoglobinopathies (3)
Inflammatory	Myocarditis, HIV (1)
Hemodynamic	Obstructive or regurgitant lesions, hypertension (2)
Abnormal rate/rhythm	Tachycardiomyopathy, bradycardia, AV dyssynchrony (3)
Abnormal morphology	Single ventricle physiology (2)
Ischemic	ALCAPA, CAD (including premature IHD) (3)
Post-operative	Post-bypass, SV surgeries, post-TGA repair (2)
Abnormal homeostasis	Hypothermia, hypoxia, hypocalcemia, hypoglycemia, sepsis (3) [Peculiar to neonatal period]

1: common    2: uncommon    3: rare (may be common in specific age group/settings)

**Table 12.2: Common causes of heart failure by age at presentation**

<b>Day 1 of life/fetal</b>		<b>1 to 2 months</b>	
Asphyxia	Metabolic	VSD	PDA
Systemic AV fistula	Arrhythmias	AVSD	Aorto-pulmonary window
Myocarditis	Ebstein anomaly	Transposition and malposition complexes	Unobstructed TAPVC
		ALCAPA	
<b>1st week of life (after day 1)</b>		<b>2 to 6 months</b>	
Critical AS/PS	Obstructed TAPVC	Causes at 1-2 months	
HLHS	Coarctation	Coarctation	
Adrenal insufficiency	Hypertension	Aortic stenosis	
TGA with IVS			
<b>2nd week of life</b>		<b>Older children</b>	
Large VSD	Large PDA	CHD with complications	
AV septal defect	Persistent truncus arteriosus	Rheumatic heart disease	
		Cardiomyopathies	
		Palliated CHD/postoperative	
		Corrected transposition great arteries (TGA)	
Unobstructed TAPVC		PS, TR	
		Tachycardiomyopathy	

3

failure due to left-to right shunts usually follows the fall in pulmonary vascular resistance at 4-6 weeks, though large VSD, PDA, AVSD and aortopulmonary window can cause heart failure by the second week

of life, especially if associated with coarctation of the aorta. Isolated ASD are mostly asymptomatic in children and if an infant is diagnosed to have ASD and is in failure, the likely diagnosis is TAPVC.

The myocardium per se is normal in most CHD and the heart failure, if not presenting in the first year, is unlikely to develop for the next 10 years unless complicated by infective endocarditis, anemia, infections or arrhythmias. Thus older children (usually beyond two years) are likely to have other causes for heart failure like acute rheumatic fever with carditis, decompensated chronic rheumatic heart disease, myocarditis, cardiomyopathies and palliated CHD (post Senning operation for transposition of great arteries or Fontan group of surgeries for univentricular hearts).

### EPIDEMIOLOGY OF HEART FAILURE

In Germany, a hospital based study at University Children's Hospital at Essen studied the epidemiology of heart failure between 1989 and 1998.<sup>4</sup> Heart failure occurred in 40% of all admissions for CHD and one-third of all admissions for all heart disease (congenital and acquired, n=1755); if post-operative congestive heart failure was excluded, heart failure accounted for a quarter of all CHD admissions. Incidence of heart failure was 289/1000 heart disease patients and 20.1/1000 of all pediatric admissions. In 70%, it occurred in the first year of life. Overall mortality in children with heart failure was 14%, more than double when compared to mortality in all heart disease patients. One large database from US found out that the heart failure in children (<18 years of age) was complicated by more frequent procedures, longer stay, but similar mortality as adults (7.5%).<sup>5</sup> The cause was predominantly congenital heart disease in infants (<1 year of age) at 83% while it was present in only 34% in children older than 1 year of age.

In developed countries, the annual incidence of CHD is about 8 per 1000 (0.8%) of live births, of which one-third to on-half are severe enough to warrant attention. Of these, about half result in heart failure, often as an emergency; thus, due to CHD, the incidence of heart failure is about 0.1-0.2% of all live births.<sup>6</sup>

Ninety percent of all cardiomyopathies in children are of the dilated variety, others being hypertrophic and restrictive type. The reported population incidence of idiopathic dilated cardiomyopathy (DCM) in children is 0.6/100,000 children<sup>7</sup> with recent studies showing 5 year rates of death or transplantation of 46%.<sup>8</sup> More than 50% present within the first year of life. Children with myocarditis as a cause of DCM have a favorable prognosis, with 50-80% showing resolution within 2 years of presentation. The population based studies on childhood cardiomyopathies systematically excluded cardiomyopathies secondary to cancer drug therapy. At least in the past, anthracycline toxicity has

accounted for 50% of admissions due to congestive cardiomyopathy in Boston Children's Hospital.<sup>6</sup>

Prevalence of heart failure in palliated or operated CHD cases is unknown. It has been estimated that 10-20% of operated cases with Mustard/Senning surgery for transposition of vessels and those with Fontan-type of operation have symptoms of heart failure and a significant proportion develop recurrent decompensation.

Rheumatic fever/rheumatic heart disease is an important cause of heart failure in children in developing countries like India. While the incidence and prevalence of RF/RHD are well documented, there are no data on presentation with heart failure in this group, though a significant majority of acute rheumatic carditis and established juvenile mitral stenosis will present with acute heart failure.

### CLINICAL FEATURES

The clinical features of heart failure in children vary according to the cause and the age of the child. The presentation of heart failure in fetus is that of hydrops fetalis and fetal wastage, while in newborns acute heart failure can often have prominent non-cardiac findings.

An important point to remember is that raised jugular venous pressure, peripheral edema, effusions and chest crepitations (commonly used to diagnose heart failure in adults) are not seen in neonates and are unlikely in young children as signs of acute or decompensated heart failure. Chest crepitations in fact suggest the possibility of underlying chest infection, which so often accompanies heart failure in children especially in high pulmonary flow situations.

Common clinical features of heart failure in children are given in Table 12.3. Certain features deserve mention:

- The clinical features of heart failure in a newborn can be fairly non-specific; sometimes the clinical picture resembles that of septicemia. Thus a high index of suspicion is required.
- Cardiogenic shock as a presentation is more likely in neonates with left ventricular outflow tract obstruction like hypoplastic left heart, interrupted aortic arch, severe coarctation of aorta and critical aortic stenosis.
- Unequal upper and lower limb pulses, peripheral bruits or raised/asymmetric blood pressure indicating aortic obstruction (including non-specific aortoarteritis, Takayasu arteritis) should always be looked for in a child with unexplained heart failure at any age.
- An interrupted aortic arch or coarctation of aorta in neonates can have normal femoral pulsations in

**Table 12.3: Clinical features of heart failure by age and associated findings**

<i>Newborn/Neonates</i>		
Tachypnea Hepatomegaly Feeding difficulties	Tachycardia Cardiomegaly Excessive sweating	Bounding pulses in AV malformations, PDA
Subcostal recession	Cyanosis and wheeze	Asymmetric upper and lower limb blood pressure in aortic arch anomalies Central cyanosis in TGA, TAPVC, Truncus, TA with no PS Differential cyanosis in PPHN and R-L shunt through patent ductus Wide split second sound with cyanosis in TAPVC, Ebstein's and AVSD Multiple heart sounds in Ebstein's anomaly Ejection systolic murmur in AS/PS Syndromic anomalies (Down's, Noonan syndromes)
Shock	Third heart sound	HLHS, Coarctation of aorta, Interrupted aortic arch, critical AS, tachyarrhythmias, myocarditis
<i>Infants</i>		
Poor feeding Excessive sweating Slow weight gain	Lethargy Tachypnea, tachycardia Hepatomegaly Third heart sound	Precordial bulge, signs of pulmonary artery hypertension and less impressive systolic murmurs suggest larger L-R shunts  Cyanosis in TAPVC, TGA with VSD, AVSD, Truncus Findings of CHF and cyanosis in suspected ASD suggest TAPVC Later onset of heart failure in infancy can be due to certain forms of TAPVC and ALCAPA
<i>Older children</i>		
Poor weight gain Cardiomegaly Peripheral edema Fatigue Raised JVP	Effort intolerance, orthopnea Gallop rhythm, murmurs Basilar crepitations Hepatomegaly	Diastolic murmur in a child with known VSD suggests associated AR Pericardial rub in appropriate settings suggests acute RF Hypertension and unequal pulses or bruits suggest Takayasu arteritis

presence of patent ductus arteriosus (PDA); when the ductus closes, these babies may present with acute shock.

- Coarctation of the aorta usually does not cause heart failure after one year of age, when sufficient collaterals have developed.
- Central cyanosis, even if mild, associated with heart failure and soft or no murmurs in a newborn, should always be taken seriously (seen in transposition of great arteries, pulmonary atresia, obstructed total anomalous pulmonary venous connection, etc.).
- An ASD or VSD does not cause heart failure in first 2 weeks of life; their presence with heart failure

should prompt evaluation for associated TAPVC or coarctation of aorta respectively.

- A premature newborn with significant respiratory distress and a systolic murmur should be evaluated for patent ductus arteriosus causing heart failure.
- Heart rates above 220/min are unusual in a neonate even with heart failure and should always be investigated to rule out tachyarrhythmias as a cause of heart failure.
- Several children with CHD or cardiomyopathies have associated chromosomal anomalies or extra-cardiac manifestations which provide clues for diagnosis.
- Older children with TOF physiology can have heart failure due to complicated course (anemia, infective

endocarditis, bicuspid aortic valve with aortic regurgitation) or overshunting from aorto-pulmonary shunts.

Unlike adults, children (especially neonates) presenting in emergency with heart failure often have specific causes that need immediate diagnosis and specific treatments beyond those for relief of symptoms and volume overload. Thus prompt management can often have salutary impact on amelioration of heart failure in children.

### INVESTIGATIONS

The cornerstones for rapid clinical diagnosis of heart failure in children are chest radiograph and an electrocardiogram, once immediate therapy including resuscitation, if required, has been administered. Prompt evaluation of arterial blood gases, oxygen saturation, metabolites, plasma glucose and temperature are as important in newborns, who often have non-cardiac causes for heart failure.

**Chest radiograph.** This should be done in all patients with suspected heart failure; an echocardiogram is not a substitute for radiograph. It enables diagnosis of cardiomegaly, quantification of pulmonary blood flow, presence of associated chest infection, pleural effusion etc., as well as being pathognomonic in certain disease states. A cardiothoracic ratio of  $>60\%$  in neonates and  $>55\%$  in older children suggest cardiomegaly though expiratory films should be interpreted with caution. A large thymus can also give false impression of cardiomegaly in neonates and infants (Fig. 12.1). Cardiomegaly with increased pulmonary blood flow (pulmonary plethora), prominent main and branch pulmonary arteries, left atrial enlargement, etc. are signs of significantly increased pulmonary blood flow (a finding not appreciable on echocardiogram!) which could cause heart failure (Fig. 12.2). Typical radiographs strongly suggestive of certain diagnosis include those with transposition of great arteries (egg-on-side, Fig. 12.3), obstructed TAPVC (snowstorm appearance, Fig. 12.4), unobstructed TAPVC (figure of 8 appearance in older children, Fig. 12.5), Truncus arteriosus (waterfall appearance of hila, Fig. 12.6), Ebstein anomaly (globular cardiomegaly with decreased pulmonary flow), constrictive pericarditis (calcification in RV/AV groove), juvenile mitral stenosis (left atrial appendage enlargement), etc. It must be remembered however that such typical X-rays are seen in a minority of cases.

**Electrocardiogram.** An electrocardiogram is very useful in heart failure for elucidation of cardiac diagnosis. It



Fig. 12.1: X-ray chest of a normal neonate with a large thymus

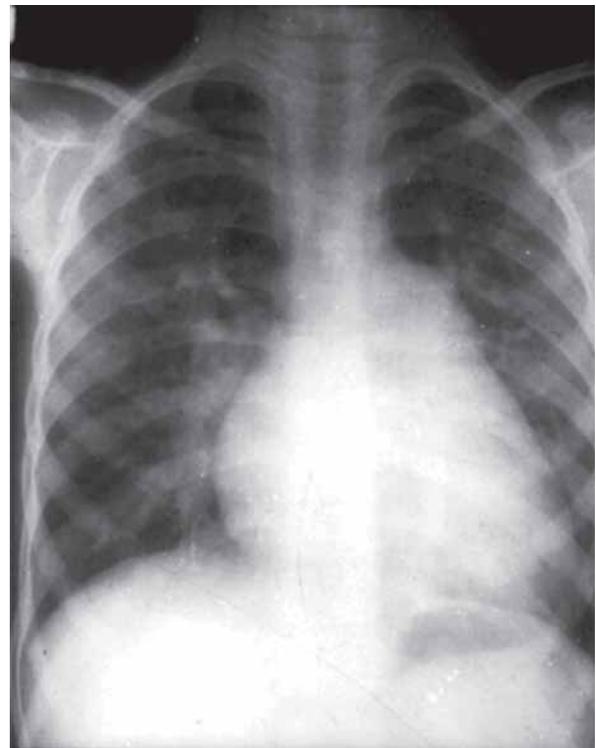


Fig. 12.2: Chest radiograph showing cardiomegaly, prominent pulmonary artery segment and increased pulmonary blood flow in a case of large VSD

shows biventricular hypertrophy with volume overload of the left ventricle in the most common cause of heart failure in the infant, i.e. a large VSD. Tachycardiomyopathy, a potentially reversible cause of heart



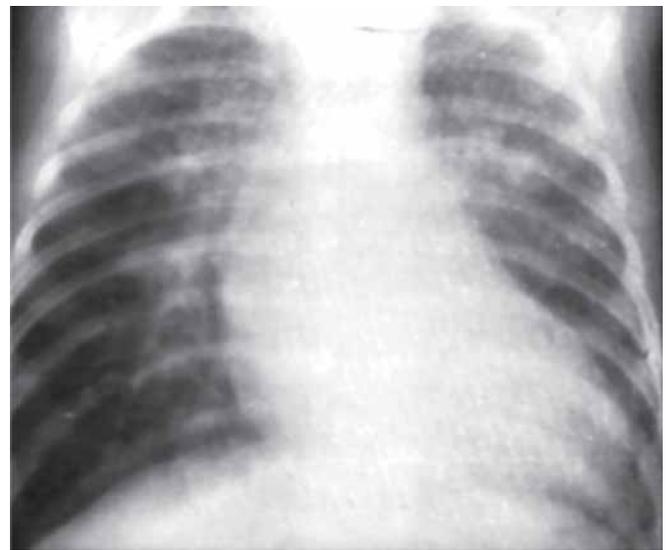
**Fig. 12.3:** Chest radiograph of a newborn with transposition of great arteries (egg-on-side)



**Fig. 12.5:** Chest radiograph in an older child with unobstructed TAPVC showing the typical 'figure of 8' appearance of the mediastinum

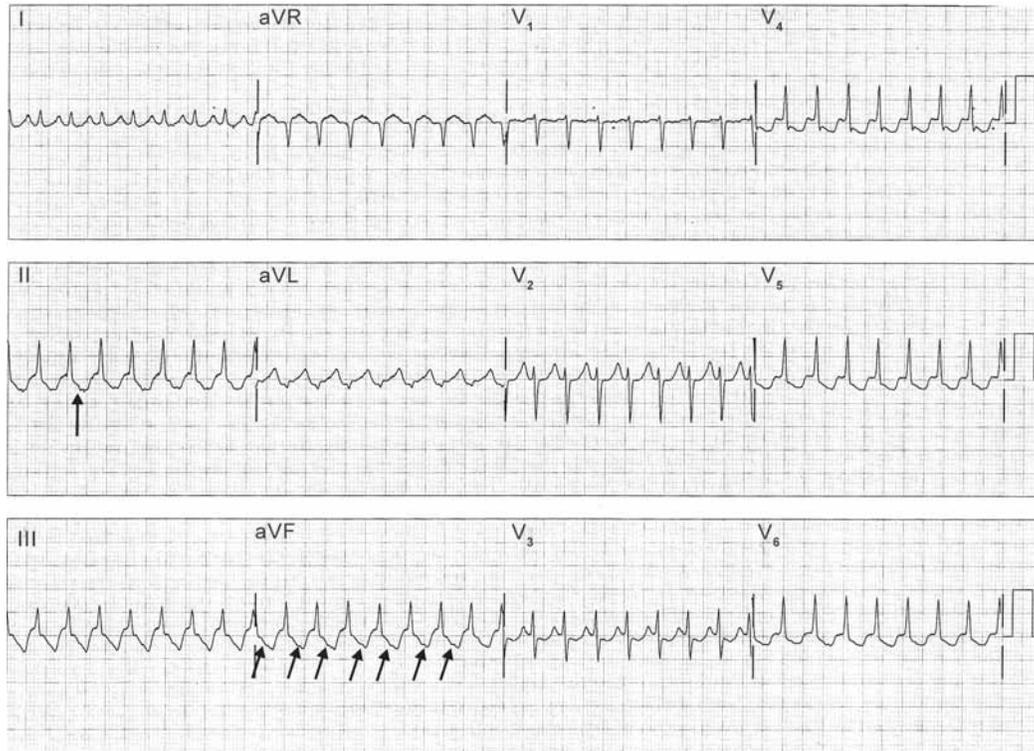


**Fig. 12.4:** Chest radiograph of a newborn with obstructed TAPVC showing the 'snow-storm' appearance



**Fig. 12.6:** Chest radiograph in an infant with persistent truncus arteriosus

failure, due to incessant supraventricular tachycardias (like ectopic atrial tachycardia) can only be picked up by ECG (Fig. 12.7). Similarly, bradyarrhythmias due to congenital complete heart block are detected on ECG (Fig. 12.8). Certain patterns on ECG are virtually diagnostic of specific cardiac pathologies. Thus,



**Fig. 12.7:** Electrocardiogram of a child presenting with heart failure due to atrioventricular re-entrant tachycardia at the rate of 200 beats per minute. Arrows point to P waves. Note that RP interval is shorter than PR interval

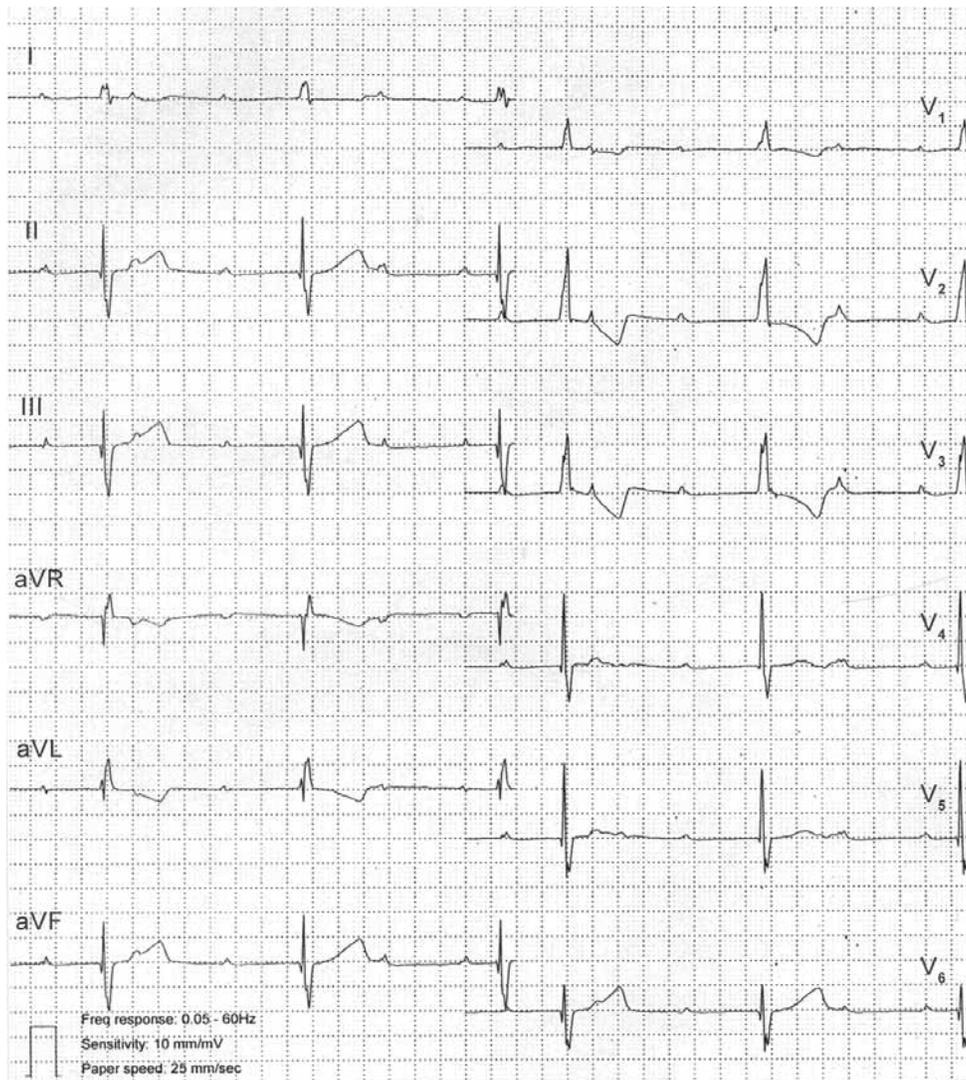
ALCAPA can present with pathognomonic pathologic q waves in anterolateral leads (Fig. 12.9). A superior or northwest axis with biventricular hypertrophy suggests atrioventricular septal defect as a cause of heart failure (Fig. 12.10). In a neonate with unexplained heart failure, a prolonged QTc interval with terminal T wave inversion are suggestive of hypocalcemia as the cause of left ventricular dysfunction (Fig. 12.11).

**Echocardiogram:** An echocardiogram is invaluable in the diagnosis of heart failure. It confirms the presence of structural heart disease and great vessel anomalies and aids in the acute and long term management strategy. While an echocardiogram is essential for diagnosis of heart disease in heart failure, it should always be interpreted in an integrated fashion with clinical, radiographic and ECG findings. Owing to its dependence on operator skills and inherent problems of imaging small children, an echo can miss findings such as TAPVC and aortic arch anomalies and thus cannot be relied upon as the only screening tool. However, an echocardiogram by a skilled physician is adequate for diagnosis and initial management of practically all diseases causing heart failure.

### Other Investigations

**B-type natriuretic peptide (BNP):** BNP, a cardiac natriuretic hormone secreted in escalating fashion in ventricular dysfunction and progressive heart failure, is increasingly used in acute settings for differentiation of heart failure from pulmonary causes of respiratory distress. While its utility in adults is established, its value in children is still investigational. Plasma BNP elevation is a reliable test however for recognizing ventricular dysfunction in children with a variety of CHD.<sup>9</sup>

**Hemoglobin** is important in diagnosis of heart failure in children; while protracted values around 5 g/dl can cause heart failure even with a normal heart, hemoglobin of 7-8 g/dl can cause decompensation in cases with underlying heart disease. **Electrolytes** like serum calcium, phosphorus and blood glucose should be routinely measured in all children with heart failure, especially neonates, where these abnormalities are an uncommon but reversible cause of ventricular dysfunction. Similarly, screening for hypoxia and sepsis also constitute evaluation of heart failure in a newborn. Work-up for ascertainment of etiology of myocarditis and cardiomyopathy is exhaustive and detailed



**Fig. 12.8:** Holter trace of an infant with bradycardia (ventricular rate of 40 beats per minute) due to congenital complete heart block. Note that there is no relationship between P waves and QRS complexes

elsewhere.<sup>10</sup> *ASO* (anti-streptolysin O) and *CRP* (C-reactive protein) are invaluable in work up for diagnosis of suspected primary attack of rheumatic fever or its recurrence in cases with rheumatic heart disease.

### Staging the Severity of Heart Failure

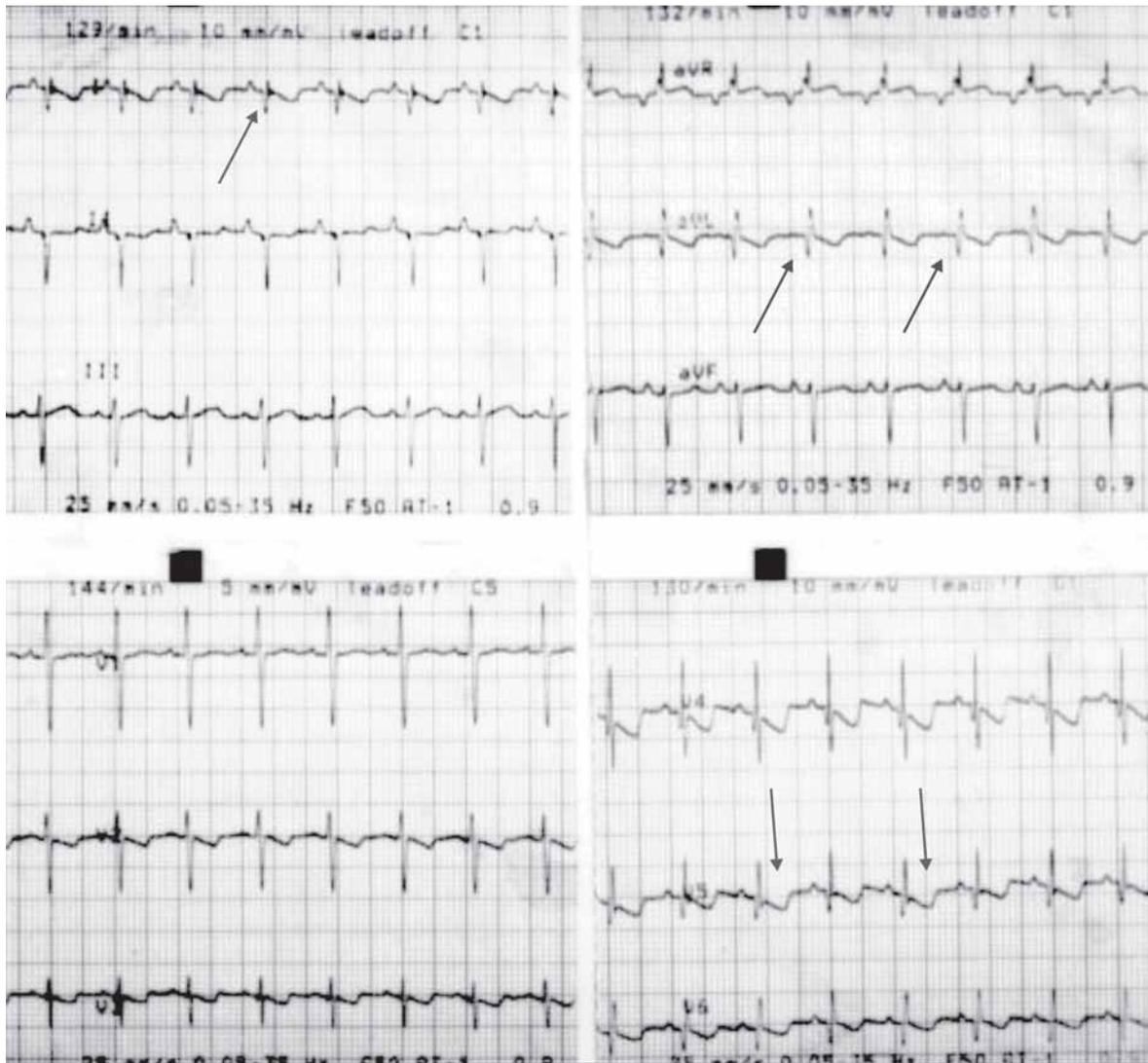
While several systems exist for grading severity of heart failure in adults, including universally known New York Heart Association Class, it is difficult to grade heart failure or apply these classifications in children especially infants. A common system followed

is that advocated by Ross<sup>11</sup> for classification of heart failure (Table 12.4) and scoring its severity.

## MANAGEMENT OF HEART FAILURE

### General Measures

The management of heart failure in emergency settings in children depends on the age of presentation and the suspected pathology. Foremost, cardiopulmonary resuscitation should be instituted, if required, followed by general measures like oxygen inhalation, head end elevation (in relatively stable and older children) and

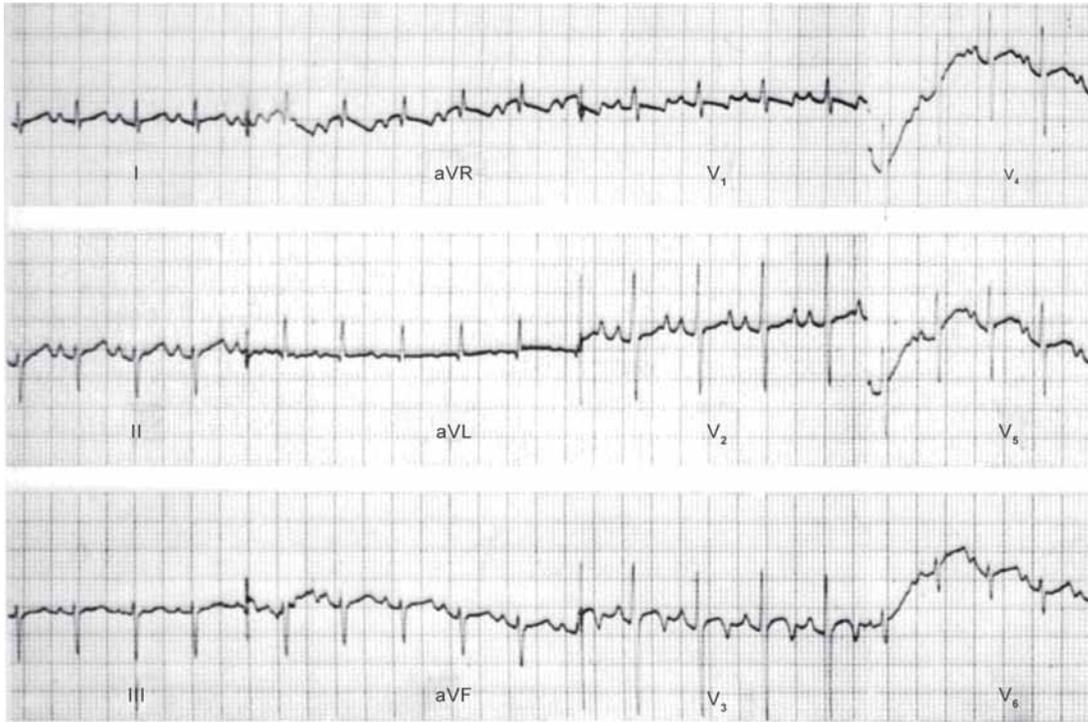


**Fig. 12.9:** Electrocardiogram of a child with ALCAPA showing presence of pathologic Q waves and ST-T changes (arrows) in lateral leads

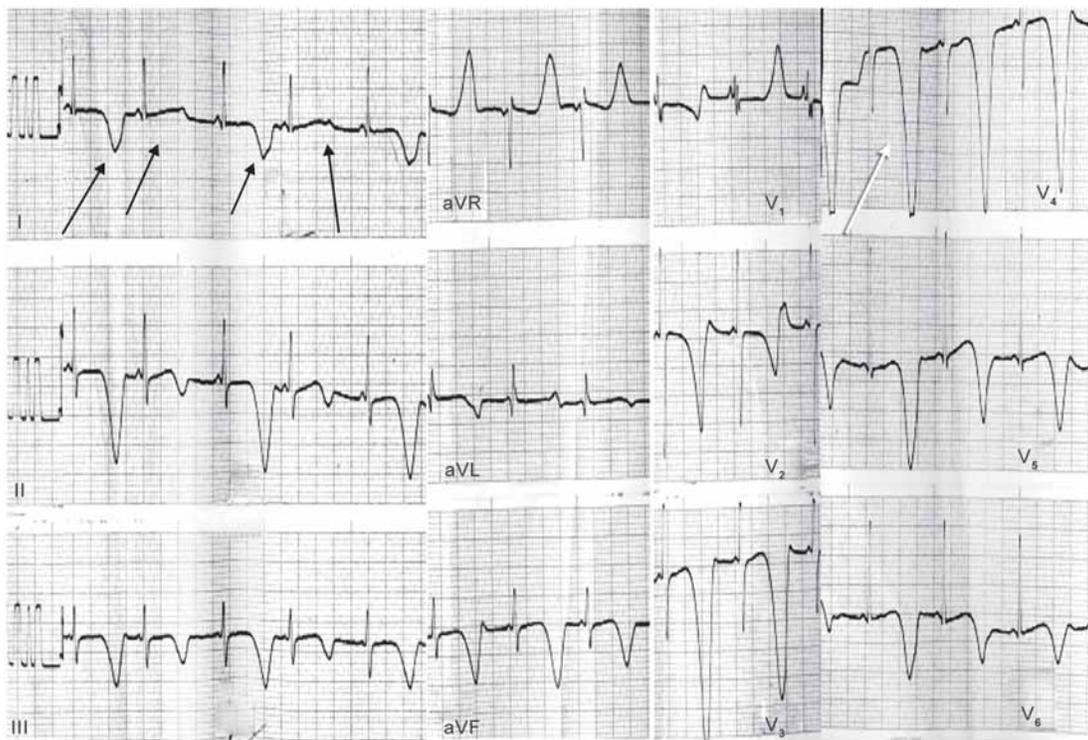
**Table 12.4: Ross classification of heart failure in infants**

Class I	No limitations or symptoms
Class II	Mild tachypnea or diaphoresis during feeding in infants Dyspnea on exertion in older children No growth failure
Class III	Marked tachypnea or diaphoresis during feeds or exertion Prolonged feeding times Growth failure
Class IV	Symptoms at rest with tachypnea, retractions, grunting or diaphoresis

correction of metabolic abnormalities, hypothermia, hypoglycemia and dehydration. It should be remembered that in children with evidence of peripheral shock or who are moving too much, pulse oximetry as a guide to oxygenation status may be unreliable. Furthermore in several lesions it is undesirable to aim for, and maintain, oxygen saturation of 90-100%. These include duct dependent lesions like left ventricular outflow obstruction (hypoplastic left heart syndrome, severe coarctation, interrupted arch) where high oxygen saturation can cause over circulation in pulmonary bed (with worsening of congestion) and may close the ductus. Similarly in children with obligatory admixture



**Fig. 12.10:** Electrocardiogram of a child with atrioventricular septal defect showing left axis deviation and right ventricular hypertrophy



**Fig. 12.11:** Electrocardiogram from a child with hypocalcemia showing long QTc interval and bizarre, inverted T waves (white arrow)

and high pulmonary flow like transposition or TAPVC physiology, it is wiser to aim for an O<sub>2</sub> saturation of 75-80% and PaO<sub>2</sub> of 50-60.

If there is severe tachypnea, oral feeding should be withheld, as there is risk of aspiration. The fluid and caloric intake should be adequate as the requirement is increased during heart failure. Intravenous fluid is generally restricted to 65-80 ml/Kg/day in newborns. It must be ensured that adequate calories are provided in restricted amount of fluids. Some sick neonates may have reduced intravascular volume at the time of admission to emergency room. They should be given fluid boluses of 5 ml/kg normal saline over 20 to 30 minutes till they improve.

### Treatment of Precipitating Causes

An attempt should also be made to address any possible precipitating cause for the acute or decompensated heart failure. These may be extracardiac like infection (especially chest infection), anemia, coexistent renal failure or due to arrhythmias (commonly seen with diuretic/digoxin/inotrope therapy), acute rheumatic fever (decompensating chronic RHD), infective endocarditis, myocardial depression due to drugs and others.

### Therapy for Acute Heart Failure

Acute therapy for heart failure consists of diuretics, inotropes and vasodilator agents besides specific measures targeted at the underlying pathology (like prostaglandin infusion). The doses of commonly used drugs in acute and chronic settings are given in Tables 12.5 and 12.6 respectively. In sick children, it is preferable to start the parenteral drugs on continuous cardiac monitoring because of their direct or indirect arrhythmogenic potential. Furthermore, evaluation of heart rate is very useful in assessing response to therapy.

### Diuretics

1. Intravenous furosemide is usually given in acute heart failure for diuresis and relief of pulmonary congestion and reducing preload. It should be used with caution in newborns who are prone to hypovolemia. There is some evidence to show that continuous infusion of furosemide may be better than intermittent bolus doses. Aggressive monitoring of electrolytes especially potassium is required while using parenteral diuretics. Hypokalemia in these settings can be fatal due to arrhythmias, especially with concomitant use of digoxin.

**Table 12.5: Treatment for acute heart failure**

Supportive measures	
Avoid hypothermia and hypoglycemia, check for hypocalcemia	
Maintenance of adequate oxygenation	Monitoring of blood gases if perfusion is poor Ventilate, if required, with modest PEEP to achieve PaO <sub>2</sub> of 50-60 mm Hg and SaO <sub>2</sub> of 75-85% to avoid pulmonary congestion
Adequate hydration	Stop oral feeds if severe tachypnea
Intravenous access	IV and CVP lines (umbilical vein cannula)
Intravenous inotropes for shock	Isoproterenol 0.5-2 mcg/kg/min Dopamine 5-20 mcg/kg/min Dobutamine 5-20 mcg/kg/min Avoid digoxin or use cautiously
Milrinone	Load with 25-50 mcg/kg/min. Maintain at 0.25-1 mcg/kg/min
Diuretics	Furosemide 2-4 mg/kg PO/IV 3-4 times a day Spironolactone: neonates 1-3 mg/kg/d in 1-2 divided doses Children 1.5-3.5 mg/kg/d in 1-2 divided doses
Vasodilators	Captopril 0.1-1 mg/kg/day PO q 8 hrly Sodium nitroprusside 0.5-4 mcg/kg/min IV nitroglycerin 0.05-20 mcg/kg/min IV infusion Careful monitoring of blood pressure necessary
Prostaglandin (PGE <sub>1</sub> ) infusion for ductus-dependent lesions	Start at 0.1 mcg/kg/min (uptil 0.4 mcg/kg/min if no response), taper to lowest dose possible (0.005 mcg/kg/min); monitor for apnea, keep minimum required dose

**Table 12.6: Drugs used to treat chronic heart failure**

Digoxin	10 mcg/kg/day (in two divided doses for children <5 years)
Furosemide	1-4 mg/kg/day (1-2 doses)
Spironolactone	2-4 mg/kg/day (2 doses)
Captopril	Neonates: (0.4-1.6 mg/kg/day) in 3 divided doses; Infants and children: 0.5-4 mg/kg/day in 3 divided doses
Enalapril	0.1-0.5 mg/kg/day (2 doses) avoid in neonates
Losartan	0.5 mg/kg/day once daily
Metoprolol	0.1-0.2 mg/kg/dose (2 doses) and increase to 1 mg/kg/dose or maximally tolerated dose over weeks or months
Carvedilol	0.05 mg/kg/dose (twice daily) and increase to 0.4-0.5 mg/kg/dose or maximally tolerated dose

2. Spironolactone is usually given orally in older children along with furosemide. It has potassium preserving action and also has been shown to confer mortality benefit in advanced heart failure in adults.
3. Torsemide is a relatively newer diuretic that has action similar to furosemide with better bioavailability and longer action. It is more potent and has some potassium sparing action.
4. Metolazone is a potent thiazide type diuretic that has been used in refractory cases of heart failure or volume overload at a dose of 0.2-0.4 mg/kg/day. It also helps in cases with diuretic resistance, but requires close electrolyte monitoring.

### Inotropes

While digoxin is used in less sick children as an inotrope, intravenous sympathomimetics are used in acute settings. These include dopamine, dobutamine, and epinephrine. They require close monitoring however because of their arrhythmogenic potential. Dobutamine is a good initial choice to support failing heart because it has less proarrhythmic properties but should not be used alone in cases with hypotension. In cases with failure and hypotension, dopamine initially should be used and dobutamine may be added later.

Milrinone is also a good choice in children in acute heart failure settings because it reduces afterload while increasing the contractility. None of these drugs has however been shown to have mortality benefit in adults or children.

### Vasodilators

These agents decrease afterload and thus are an important part of acute heart failure therapy due to failing myocardium or volume overload conditions. However, they should not be used in obstructive conditions like aortic stenosis, mitral stenosis, and coarctation of the aorta. Commonly used vasodilators

are ACE inhibitors, sodium nitroprusside (both drugs dilate systemic venous and arterial systems) and nitroglycerin (predominantly venous dilator). All these agents require careful monitoring of blood pressure while administration and should be used with caution in presence of renal dysfunction. Use of sodium nitroprusside should always be accompanied by invasive pressure monitoring. Among ACE inhibitors, captopril is favored in children owing to shorter period of action but still should be used carefully in neonates.

### Mechanical Devices

Ventricular assist devices, intraaortic balloon counterpulsation and extracorporeal membrane oxygenators have also been used in acute heart failure to temporarily unload the failing myocardium. However they are expensive and only available in select tertiary referral centers and are used mostly in post-operative settings.

### Newer Agents

Several new agents have been used in acute or decompensated heart failure; their role however is still investigational, in adults and in children. These include natriuretic peptides (e.g. nesiritide), calcium sensitizers (e.g. levosimendan), vasopressin antagonists (e.g. tolvaptan), renin inhibitors (e.g. aliskiren), endothelin antagonists (e.g. sitaxentan), etc. Nesiritide is used in decompensated heart failure but is not widely available and its incremental benefit over standard regimen is not clear. Several other classes of drugs including anti-inflammatory molecules and vaso-peptidase inhibitors have either not been found useful or have unacceptable side effects.

Management of CHF in children, whether acute or long-term, is complex because of frequent presence of structural heart disease (on which medical treatment has little effect) and variable presentation and spontaneous resolution of some diseases. Most of this

evidence base has been generated in adults in whom randomized trials usually happen earlier. Conducting such trials in children has been difficult on account of ethical issues and logistical problems. These dilemmas are exemplified by the recently published randomized controlled trial for carvedilol in children<sup>15</sup> with heart failure, where beta-blockade did not improve outcomes over those with placebo. While smaller uncontrolled studies earlier had shown significant benefit with carvedilol, the neutral results of this trial were presumably due to inadequate sample size (due to high rate of spontaneous improvement in placebo group) and heterogeneous effect of drug on type of systemic ventricle (benefit seen in systemic left ventricle only).

### Specific Therapy for Various Etiologies

Specific management of heart failure in children can be divided into following categories:

#### 1. CHD presenting with acute shock, where definitive immediate treatment (pharmacologic, percutaneous, or surgical) is required

In neonatal period several causes of heart failure can present with acute circulatory collapse or progress to shock if not recognized early. These can be due to:

- **A closing ductus** where antegrade systemic flow is compromised (e.g. tight coarctation of aorta, interruption of aortic arch, critical AS, hypoplastic left heart syndrome), and TGA with intact septum and restrictive inter-atrial communication. These disorders require maintenance of duct patency with prostaglandin infusion till the time more definitive treatment can be employed. This consists of percutaneous procedures for critical AS (valvuloplasty), TGA (balloon atrial septostomy) as well as surgical procedures. In cases where surgery for coarctation of aorta is not possible due to severe comorbid conditions, a balloon dilatation is performed, although the restenosis rates are likely to be higher.
- Conditions like mitral atresia (requiring emergency atrial septostomy) and obstructed TAPVC (requires emergency surgery) can cause severe elevations in pulmonary venous pressure.
- Non-cardiac cause of neonatal heart failure, tachyarrhythmias and neonatal myocarditis can also rapidly progress to shock if not managed early.
- Lesions like AS, PS and coarctation of aorta, if associated with corresponding ventricular dysfunction or heart failure should undergo urgent relief of obstruction, irrespective of magnitude of gradient at baseline.

As these children are generally sick, they should be transferred to tertiary centers with expertise in their care, after initial resuscitation and prostaglandin infusion (if required). They require intensive monitoring because of frequent co-morbidities and likely requirement of ventilation (due to pulmonary edema, chest infections or due to apnea as an adverse effect of prostaglandin therapy).

**Prostaglandins in congenital heart disease:** Prostaglandins are arachidonic acid metabolites, of which PGE<sub>1</sub> is used as an infusion in duct dependent lesions. An increase in O<sub>2</sub> tension after birth reduces the dilatory effect of endogenous PGE<sub>1</sub> produced by fetal ductus (a physiological mechanism for ductal closure). Thus congenital lesions that require ductal patency for further survival can be fatal if ductal flow is not established in time. These include lesions that require ductal flow for severely restricted pulmonary blood flow (e.g. pulmonary atresia), for restricted systemic flow (examples given above) and for admixture lesions like TGA.<sup>12</sup> The timing of the infusion is crucial because it does not open an anatomically closed ductus (usually 7-10 days after birth). It is given as a continuous infusion through an infusion pump (dosage, Table 12.5) intravenously with initial requirement for higher dosage. Once the desired response is achieved, the minimum rate required for sustaining the desired response should be used as a maintenance dose. It should also be remembered that this infusion is only a 'bridge therapy' prior to a definitive management. Reasons for poor response include closed ductus, low birth weight (2 kg), older age (> 96 hours), high arterial pO<sub>2</sub> and hypoplastic pulmonary vasculature. Babies on prostaglandin infusion require intensive level of monitoring because of high incidence of adverse effects. Up to 12% children develop apnea (which is dose-dependent but more in low weight and cyanotic children), which may require artificial ventilation, while other significant side-effects are bradycardia, hypotension, lethargy, jerks and increased rates of infection. Prostaglandin E<sub>1</sub> should be avoided in obstructed TAPVC where it may actually aggravate the heart failure.

**CHD awaiting surgery** where medical treatment is applied for stabilization and alleviation of symptoms—**short-term medical therapy.**

This is a very common group because, most of CHD causing heart failure require surgical intervention. The exceptions may be some patients with VSD and PDA in premature babies which may close spontaneously. These children present with heart failure and frequently have co-morbidities like sepsis or chest infection. They tolerate repeated bouts of heart failure and chest

infection (which enters into a vicious cycle with heart failure) poorly and should undergo surgery or non-surgical catheter intervention promptly after stabilization of medical condition.<sup>13</sup> These conditions include:

- Large VSD/PDA/AVSD/Persistent truncus arteriosus with uncontrolled CHF or history of life threatening infection
- Severe AS or coarctation of aorta
- TGA with intact ventricular septum
- Unobstructed TAPVC

A special group is that of intractable or severe heart failure due to non-closing ductus in premature babies. These children require a trial of prostaglandin antagonists like indomethacin or ibuprofen. However it should be remembered that these drugs, beyond their recommended duration, have no effect on patency of the ductus and it is futile to merely observe these sick babies while expecting the PDA to close with prolonged drug administration. These babies should be promptly sent for surgical ductal ligation, which often dramatically improves their status.

**2. CHD requiring long term medical therapy** Several causes of heart failure in children require prolonged medical therapy because of tendency for spontaneous resolution or a cure for the condition in long-term or due to the fact that the surgical treatment is problematic. These babies often have recurrent episodes of heart failure, mostly exacerbated by chest infection:

- Ventricular septal defect is one of the commonest causes for heart failure after the neonatal period, in infancy. About 10% of non-restrictive VSD die in 1st year of life, primarily due to heart failure. However up to 30-40% of small or moderate sized defects close spontaneously (mostly by 3-5 years of age) and 25% decrease in size.<sup>14</sup> A minority of

VSD with large L-R flow can also close spontaneously.<sup>15</sup> Thus, at least some VSD presenting in infancy with less than severe heart failure can be judiciously followed on medical therapy and watched for spontaneous closure. Similarly, small PDA in term babies upto 3 months of age, and those in premature babies not in heart failure (with or without the use of indomethacin) may be observed for spontaneous closure.

- Myocarditis in children is a potentially reversible cause of heart failure provided the acute phase is cared for with the best available medical care (ventricular assist devices, if necessary). Similarly some uncommon causes of cardiomyopathies (e.g. carnitine deficiency) can be treated effectively with supplementation.
- Some conditions like congenital mitral stenosis are problematic to manage in infancy and it is prudent to defer surgery till later if the child is growing normally.

**3. Long-term therapy** in cases with irreversible myocardial dysfunction or where no other definitive therapy can be offered.

Finally, there is the group of conditions causing heart failure where there is established myocardial dysfunction. This can be due to cardiomyopathies (primary and secondary), decompensated systemic ventricle (single ventricle physiology, corrected transposition), valvular diseases where surgery is not an option, and following palliative surgeries. This group displays the whole spectrum from asymptomatic ventricular dysfunction to decompensated heart failure and requires long term medical therapy. Treatment options and a step-wise guide for managing chronic heart failure are suggested in Tables 12.7 and 12.8.

**Table 12.7: Treatment options for chronic heart failure**

<i>Established</i>	<i>Investigational</i>
Pharmacotherapy	
• ACE Inhibitors	• Angiotensin receptor blocker
• Beta-blockers	• Nesiritide
• Digoxin	• Levosimendan
• Diuretics	
• Aldosterone antagonists	
• Anticoagulants (with severe ventricular dysfunction)	
Cardiac transplantation	
<i>Surgery</i>	
Definite (for structural disease)	Ventricular remodeling
Ventricular assist devices	Cardiac resynchronization therapy
Extracorporeal membrane oxygenation	
Intermittent inotrope infusion	Stem cell therapy

**Table 12.8: Stepwise guide to management of heart failure**

<b>Step 1</b>	In acute decompensation: bed rest, propped up position, humidified oxygen. Sodium and, if required, volume restriction.
<b>Step 2</b>	Start digoxin (not in myocarditis) Assess reversible causes and precipitating causes
<b>Step 3</b>	Add ACE inhibitor. In case of ACEI induced cough, switch to losartan (angiotensin receptor blocker) Switch to nitrates if above therapy not tolerated
<b>Step 4</b>	Add carvedilol in compensated heart failure especially in cases with tachycardia
<b>Step 5</b>	Once or twice weekly dobutamine therapy Consider stem cell coronary infusion
<b>Step 6</b>	Cardiac transplantation • Ventricular assist device as bridge therapy

Management of acute and chronic heart failure: Important issues in the management of CHF in children are:

- Treatment of heart failure in children, like in adults, should consist of treatment of the cause, precipitating factors (like anemia, infective endocarditis, infections, acute rheumatic fever, non-compliance with drug or diet, arrhythmias) and treatment of the congested state.
- Digoxin has a very narrow safety window in children and adults alike. It can be used in emergency settings in mild cases but should be avoided in premature babies, those with renal compromised state and cases with acute myocarditis. Electrolytes ( $K^+$ ,  $Ca^{++}$ ,  $Mg^{++}$ ) should be carefully monitored to avoid potentiation of toxicity and development of arrhythmias (which are more often bradyarrhythmias in children).
- Generally, initial total digitalization is not performed. One can start directly with oral maintenance dose at 10 mcg/kg/day (The available digoxin elixir has 50 mcg/ml, hence the dose is 0.1 ml/kg twice daily).
- Continuous infusion of diuretics is recommended in cases of acute decompensated heart failure. Monitoring and supplementation of  $K^+$  is necessary at higher doses, as deficiency is associated with increased risk of arrhythmia.
- During early infancy supplementation with potassium is usually not required upto 2 mg/kg of dose or equivalent. In cases requiring higher doses of furosemide and in older children, usually a combination of frusemide of loop diuretic and spironolactone (or other potassium sparing diuretics) is used. In cases requiring chronic therapy, development of diuretic resistance is quite common. Addition of low dose dopamine

may help in this situation by increasing renal blood flow.

- ACE inhibitors should be avoided in heart failure caused by lesions having pressure overload physiology, e.g. in aortic stenosis, as they might interfere with compensatory hypertrophy. The incidence of ACE inhibitor induced cough is much less in children as compared to adults.
- Beta blockers should not be administered in acute decompensated heart failure. They should be started once child is stable, at low dose initially, and slow up-titrations (once every two weeks through 4 levels according to pediatric carvedilol study group trial<sup>16</sup>) should be done as this determines the occurrence and degree of side effects. In case up-titration is not tolerated, lower doses should be continued rather than discontinuing the drug. In the carvedilol trial, overall about 20% children had worsening of heart failure in both carvedilol and placebo population, of which 11% each withdrew from the study.
- Persistently high heart rates (>180/min in older children) with absence of normal variability during sleep or exercise should always be investigated to rule out tachycardiomyopathy as the cause of heart failure.

### Myocarditis/Cardiomyopathy

The management of acute myocarditis and cardiomyopathy is a challenge.<sup>8</sup> Several small studies have been conducted with immunoglobulin and immunosuppressive therapy in children with acute myocarditis. However, robust trials are few, with the outcome that there is still no consensus on use of these therapies.<sup>17,18</sup> Of note, studies in myocarditis indicate a high prevalence of resolution of cardiomyopathy in

2 years to the tune of 50-80%.<sup>19</sup> Children with fulminant myocarditis with a high chance of recovery, do well when put on extracorporeal membrane oxygenation (ECMO) and ventricular assist devices.<sup>20,21</sup> These findings suggest that a diagnosis of myocarditis is a positive prognostic factor in children with heart failure even if requiring mechanical support.

### Cardiac Transplantation

Heart transplantation has been used for treatment of end-stage heart disease in children for nearly 4 decades with first infant transplant done in late 1960s. Around 350 pediatric cardiac transplantations are done annually, mostly in developed countries, representing about 10% of total cardiac transplantations. Majority of the transplantations are carried out for end-stage heart disease due to cardiomyopathies. Other causes include congenital heart diseases like hypoplastic heart syndrome and other complex CHD, single ventricle, palliated heart disease, etc. One year survival has approached 90% and estimated conditional graft half-life is about 17.5 years in younger children (in comparison immediate waiting list mortality is about 20%).<sup>19</sup> However, given the fact that the surgery is done in few centers globally and the available donor hearts have remained static over last many years to few hundreds, it is clear that heart transplantation can be a solution for a minority only.

### Stem Cell Therapy

A heightened interest has developed in stem cell therapy for heart failure. Several trials have been completed, or are ongoing in adults with heart failure, predominantly due to ischemic heart disease. Stem cell therapy has been also used for nonischemic cardiomyopathy at our center,<sup>22</sup> and is being investigated under experimental settings, for children with refractory heart failure who are not candidates for transplantation.

### Cardiac Resynchronization Therapy

Cardiac resynchronization therapy is a new treatment option for individuals with symptomatic and severe systolic dysfunction with ventricular dyssynchrony, and consists of pacing the right atrium, right ventricle and the left ventricle (through coronary sinus). It has shown significant mortality and morbidity benefit in adults<sup>23</sup> and is now being used in pediatric patients as well. While there are no large trials in children, available data suggest improvement in functional class and left ventricular function indices in those with

systemic left ventricle morphology and in those who have received prior right ventricular pacing.<sup>24</sup>

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Cardiac arrhythmias are relatively infrequent in infants and children compared to adults. Most of them are fortunately benign and do not signify underlying heart disease. Serious cardiac arrhythmias make up about 5 percent of total patients attending pediatric cardiology clinics.<sup>1</sup> The major risk of any arrhythmia is that of severe tachycardia or bradycardia resulting in decreased cardiac output, or the risk of progression to a more severe arrhythmia like ventricular fibrillation, leading to syncope and sudden death.

Arrhythmias in children are now being recognized with increasing frequency primarily because of the increased vigilance of pediatricians and pediatric cardiologists, combined with advances in the recording technologies of arrhythmia, such as 24 hours ambulatory ECG monitoring transtelephonic electrophysiological studies, etc.<sup>2</sup> Moreover, there has been an increase in the incidence of cardiac rhythm disturbances as more and more patients undergo complex cardiac surgery for congenital heart diseases such as transposition of great arteries and Tetralogy of Fallot.

Most cardiac arrhythmias can be diagnosed fairly easily by careful study of a standard 12-lead electrocardiograms with a long rhythm strip. We present a simplified approach for the diagnosis and treatment of common childhood arrhythmias.

### Anatomy and Physiology of the Conducting System

The specialized conducting tissues in the heart comprise the sinoatrial (SA) node, internodal tracts connecting the SA node to the atrioventricular (AV) node, bundle of His and Purkinje fibers. These tissues exhibit automaticity, which is ability to spontaneously generate impulses. The rate of impulse generation is fastest in the SA node, which normally dictates the rate and rhythm of the heart beat. The SA node is influenced by the vagus (cardio-inhibiting) and sympathetic (cardio-stimulating) nerves. The impulse

generated in the SA node spreads throughout both atria and to the AV node, from where it passes via the bundle of His to supply both ventricles through the Purkinje fibers.

If the SA node ceases to function, the intrinsic rhythmicity of the AV node takes over at a slower rate (50-60/min in older children and 100/min in infants). If the AV node and bundle of His also cease to conduct impulses, the ventricles produce their own idioventricular rhythm (30-40/min). Anomalous development or injury to any segment results in abnormal initiation or propagation of electrical activity resulting in cardiac arrhythmias. The notable causes of cardiac arrhythmias in children are summarized in Table 13.1.<sup>3</sup>

**Table 13.1: Causes of cardiac arrhythmias**

Structural heart disease	Congenital malformations Rheumatic heart disease Mitral valve prolapse Myocardial disease/ischemia Purkinje cell tumor Arrhythmogenic right ventricular dysplasia
Electrolyte/Metabolic derangement	Acidosis Hypoxemia Hyper- and hypokalemia Hypocalcemia Hypomagnesemia
Drugs	Digoxin Anti-arrhythmic drugs Catecholamines Salbutamol Theophylline Ephedrine Phenothiazines Tricyclic antidepressants
Cardiac catheterization/ Surgery	
Miscellaneous	Pre-excitation syndrome Prolonged QT syndrome

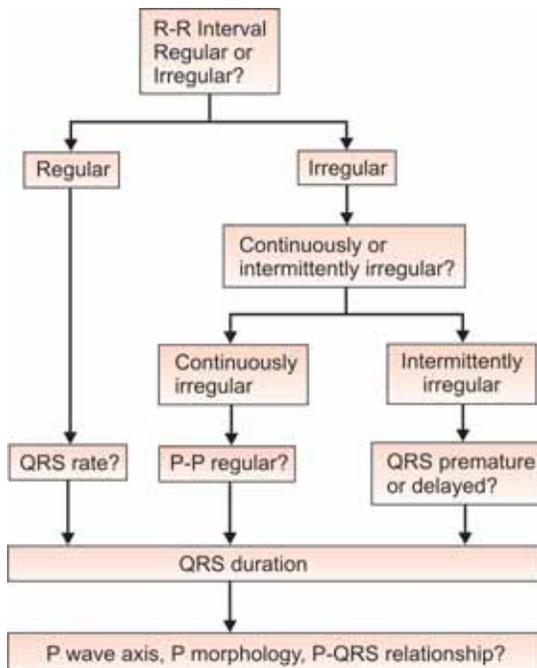
### Electrocardiographic Interpretation of Arrhythmias

In analyzing the ECG, certain questions must be answered sequentially (Flow chart 13.1).<sup>4</sup>

1. Is the R-R interval regular? If regular (less than 0.08 second variation), the answers to three further questions will categorize the rhythm.
2. Whether the ventricular rate is normal, decreased or increased for the patient's age and clinical condition? (Table 13.2).
3. Whether the QRS duration is normal or prolonged (normally under 0.08 seconds)? If the QRS duration is prolonged, the specific morphology must be determined.
4. Whether there are P-waves, flutter or fibrillation waves? If P-waves are visible, the P-wave axis must be determined. Normal sinus P-waves have an axis of 40 to 90°. Finally the relationship of atrial depolarization to the QRS complexes must be determined.
5. If the R-R intervals are regular, then it has to be determined whether they are regularly or irregularly irregular, or there is a basic regular R-R interval into which an irregular R-R interval is intermittently introduced.

Using this method of analysis, most of arrhythmias can be grouped into a particular category.

**Flow chart 13.1:** Interpretation of arrhythmias from the surface electrocardiogram



**Table 13.2: Normal heart rates for infants and children**

Age	Heart rate (beats/min)		
	Resting (awake)	Sleeping	Exercise
Newborn	100-180	80-160	Up to 220
1 week to 3 month	100-220	80-200	Up to 220
3 month to 2 year	80-150	70-120	Up to 200
2 year to 10 year	70-110	60-90	Up to 200
10 year to adult	55-90	50-90	Up to 200

### Features of Presentation

The pattern of presentation of arrhythmias in young patients is related to the age of the patient, the duration of arrhythmia, the heart rate and the presence of an underlying heart defect. Periods of fussiness, poor feeding, pallor and cyanosis are usually the presenting features in infants and are directly related to the duration of arrhythmia and degree of circulatory congestion secondary to the arrhythmia. Signs and symptoms of arrhythmias in patients over 5 years of age differ from those in infancy; palpitations and irregular pulse being one of the more common complaints. Syncopal attacks may occur as a result of hemodynamic compromise and are ominous because they are associated with sudden death.

Physical examination of children who have suspected arrhythmias is important but may be normal. Other disease processes such as fever, anemia or endocrine problems that can explain an adaptive arrhythmia (sinus tachycardia or bradycardia) should be ruled out. Any abnormality in the cardiovascular examination should be aggressively pursued because the prognosis and treatment of a particular arrhythmia are dependent on the cardiac structure.<sup>5</sup>

### Disturbances of Sinus Node Function

#### Sinus Tachycardia

Sinus tachycardia is a sinus rhythm at a rate faster than normal for age. It is commonly caused by conditions such as fever, hyperthyroidism, anxiety, etc. The rate varies periodically with respiration, crying and struggling.

#### Sinus Bradycardia

A slow sinus rate of under 90/min in neonates and less than 60/min thereafter is considered to be sinus bradycardia. It may be seen in athletes and normal individuals and has no pathological significance.

It must be differentiated from AV block by being abolished by exercise.

### *Sinus Arrhythmia*

Variation in the sinus rate is the commonest cause of irregular heart beat in childhood. There is a slowing of heart rate during expiration, and an acceleration, during inspiration. This is pronounced in premature infants, during recovery from febrile episodes and following drugs that enhance vagal tone. The ECG shows varying R-R intervals, but each QRS complex is normal and preceded by a normal P-wave with a constant PR interval. Tachycardia which can be induced by making a baby cry or in an older child by exercise, rules out a sinus arrhythmia.

### *Extrasystoles*

These are produced by a discharge from an ectopic focus located anywhere in the atria, ventricles or junctional tissue.

### *Premature Atrial Complex (PAC)*

These are common in childhood even in the absence of any cardiac disorder. They are usually asymptomatic and do not require any treatment. In infants, frequent contractions may trigger a supraventricular tachycardia or atrial fibrillation. The ECG findings include a premature P-wave having a different configuration from the normal sinus P-waves, preceding a normal QRS complex. Atrial extrasystoles usually reset the SA node pacemaker and hence there is no compensatory pause.

### *Premature Ventricular Complexes (PVC)*

They are characterized by premature, widened, bizarre QRS complexes that are not preceded by a P-wave. The PVC is usually followed by a compensatory pause. Isolated PVCs may be seen in up to 15 percent of normal newborns and one-third of normal adolescents in the absence of any cardiac pathology.<sup>6</sup> When PVCs are frequent, they may assume a definite rhythm; like alternating with normal beats (bigeminy) or occurring after two normal beats (trigeminy) PVCs in normal individuals may be caused by fever, anxiety, use of stimulants, caffeine, medications and electrolyte imbalances. Most PVCs in normal individuals are benign and usually disappear during the tachycardia of exercise. PVCs that are likely to degenerate into a more severe arrhythmia require suppressive therapy and include those that are multifocal; two or more in a row; increase with exercise; R on T phenomenon;

underlying heart disease; associated with marked anxiety and syncope. Such patients need further investigation and treatment. More than 50 percent of pediatric patients with sustained or symptomatic ventricular arrhythmias have evidence of organic heart disease.<sup>6</sup> An intravenous lidocaine drip is the first line of therapy followed by maintenance with oral antiarrhythmics such as propranolol or quinidine.

## Tachyarrhythmias

### *Supraventricular Tachycardia (SVT)*

Supraventricular tachycardia is the most common sustained tachyarrhythmia in children, occurring with an incidence of 1 to 4 children per thousand.<sup>7</sup> In approximately 60 to 70 percent of patients, the heart is normal; the remainder have congenital heart disease (Ebstein anomaly, corrected transposition of great arteries, ventricular septal defect), mitral valve prolapse, myocarditis or bacterial sepsis. It can occur *in utero* and is a recognized cause of hydrops fetalis. Up to 80 percent of affected children have the first attack early in infancy. Between 75 to 90 percent of SVT in infants are related to accessory pathways, the Wolff-Parkinson-White (WPW) syndrome alone accounting for almost 25 percent of cases.<sup>3</sup> In teenage years, AV node reentry is more common.<sup>8</sup>

Infants with SVT present with features of congestive heart failure as the tachycardia tends to go unrecognized. Older children usually complain of palpitations, chest discomfort and dyspnea. SVT may be precipitated by an acute infection and is characterized by abrupt onset and cessation. The ECG shows a regular rate of 220-300/min with narrow regular QRS complexes and absent or abnormal P-waves (Fig. 13.1). In about 5 percent of children with SVT, conduction within the ventricles is abnormal and the QRS complex is widened, mimicking ventricular tachycardia. Between episodes of SVT, some children may exhibit ECG changes of one of the pre-excitation syndromes (e.g. WPW syndrome), including a short PR interval, and slow upstroke of the QRS complex (delta wave). SVT may be confused with very fast sinus tachycardia. However, a heart rate in excess of 220/min virtually excludes a sinus tachycardia and the abrupt onset and termination are diagnostic of SVT.

Brief attacks with few or no symptoms require no treatment. In children without pre-excitation and having a structurally normal heart, paroxysms of SVT are annoying but not risky. These children or their parents should be taught vagotonic measures to abolish the paroxysm much as straining, Valsalva maneuvers,



**Fig. 13.1:** Paroxysmal supraventricular tachycardia

drinking ice cold water or carotid sinus massage. Diving reflex is frequently successful in infants.<sup>9</sup> The safest and easiest way to do this involves filling a small plastic bag with ice and covering the infant's face with the plastic bag. These maneuvers may terminate an attack in 25-30 percent of older children but are relatively ineffective in neonates and young infants.<sup>3</sup>

In urgent situations where heart failure has occurred, electrical synchronized DC cardioversion (1-2 watt-sec/kg) is recommended as initial management. Once sinus rhythm has been restored conventional treatment for heart failure should be instituted. In stable patients, adenosine is the drug of choice for pharmacological cardioversion.<sup>10</sup> A starting dose of 100 µg/kg is recommended, followed if necessary by increments of 50 µg/kg every 2 minutes as intravenous bolus till a maximum of 250 µg/kg. Adenosine terminates SVT in 90-100 percent of cases, but may get reinitiated in 25-30 percent of cases.<sup>11</sup> Verapamil may be given in older children but may produce hypotension and cardiac arrest in infants.<sup>12</sup> Intravenous verapamil is given 0.1-0.3 mg/kg rapidly over 15-30 sec and a further half dose may be repeated after 10 min. Calcium chloride must be available to counteract any hypotension. In resistant cases, effective drugs include propranolol, quinidine, procainamide, amiodarone, flecainide and disopyramide.<sup>13</sup>

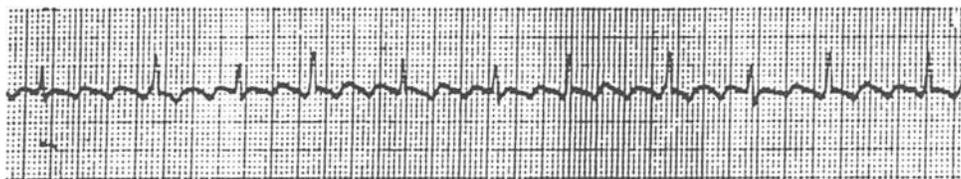
Recurrences of SVT are very common, especially in infants, 50-70 percent of whom may suffer a recurrence within 12 months.<sup>14</sup> To prevent this maintenance drug therapy for a period of 6-12 months is advised. There is a strong possibility of spontaneous resolution of SVT in patients with accessory connections and a structurally normal heart, if they present in the first year of life. However, if they continue to have or

present with SVT after the age of 5 years, or have structural heart disease, the chances of SVT disappearing are very low. In infants, digoxin is the mainstay of therapy.<sup>15</sup> In older children with a pre-excitation syndrome, it may however increase the rate of antegrade conduction through the bypass tract. Amiodarone is a very effective drug, used only in resistant cases due to its frequent toxic side effects. Flecainide has been used successfully in adults but has not been tried in children.<sup>13</sup> When there has been no recurrence after 6-12 months of therapy, the anti-arrhythmic agent may be tapered and the patient watched for signs of recurrence.

Radiofrequency ablation of the accessory pathway is another treatment option in patients with refractory or poorly controlled arrhythmias. An overall success rate of almost 85-95 percent has been reported.<sup>16</sup> Surgical excision of bypass tracts may also be effective.

#### *Atrial Flutter*

Atrial flutter is defined as a rapid atrial tachycardia of 300 beats/min or more, with characteristic saw-toothed flutter waves, best seen in II, III, aVF and aVL, usually produced by an irritable focus in the atrial muscle.<sup>17</sup> The ventricular response may range from 1:1 conduction to various degrees of second degree AV block (Fig. 13.2). Atrial flutter is most commonly seen in these groups of children: those with large stretched atria due to congenital or acquired heart disease as in tricuspid atresia, Ebstein anomaly and rheumatic mitral valve disease; in neonates, often with normal hearts; and postoperative, following palliative or corrective intra-atrial surgery as in Fontan, Mustard or Senning operations for transposition of great arteries. Heart failure will develop if atrial flutter is not corrected.



**Fig. 13.2:** Atrial flutter with variable conduction (2:1 and 3:1). The P-waves are replaced by very regular sawtooth waves without any isoelectric line

Treatment is always indicated. DC cardioversion is the treatment of choice, and the atrial flutter usually converts immediately to sinus rhythm. Digoxin prolongs conduction through the AV node, thereby slowing the ventricular response. The rhythm may occasionally change to atrial fibrillation after digitalization, and quinidine or procainamide may be added to revert to sinus rhythm. Treatment must be continued for at least a year if there is no recurrence. Older patients may benefit from a surgical procedure to improve the hemodynamic status, and only in this condition can the medication be safely withdrawn.

#### *Atrial Fibrillation*

Atrial fibrillation is due to irregular and rapid excitation of the atria (300-500/min), producing an irregularly irregular ventricular response and pulse rate. The ECG reveals absence of P-waves and completely irregular ventricular response with presence of fibrillatory waves. It occurs in the same group of patients with stretched atria as described in atrial flutter, especially in mitral valve disease. In a previously normal older child who presents with atrial fibrillation, pericarditis, thyrotoxicosis or pulmonary embolism should be suspected. Digoxin is very useful in slowing the AV conduction and controlling the ventricular rate.<sup>18</sup> Normal sinus rhythm may subsequently be restored with quinidine, procainamide or DC cardioversion. Re-institution of sinus rhythm may not be possible in patients where atrial fibrillation is associated with floricid AV valve disease and cardiomegaly. In such cases, chronic therapy with digitalis is usually required. Persistent atrial fibrillation may be an indication for corrective surgery in patients with an underlying cardiac disease.

#### *Ventricular Tachycardia (VT)*

Ventricular tachycardia is defined as three or more premature ventricular contractions in a row, with wide QRS complexes, a rate of 120-200/min and complete atrioventricular dissociation (Fig. 13.3). Capture and fusion beats are another indication of VT but are not necessary for diagnosis. VT in children is rare compared to the incidence of SVT, however, all wide

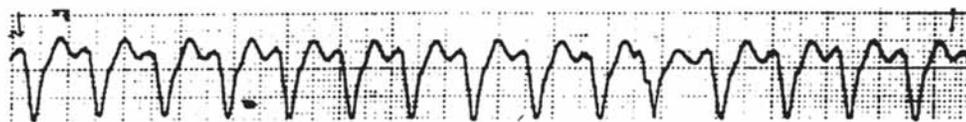
QRS complex tachycardias in children should be considered VT unless proven otherwise.

VT is a serious arrhythmia since acute cardiac decompensation may occur rapidly; it may degenerate into ventricular fibrillation; and lastly approximately 80 percent of children with VT have overt or occult structural heart disease.<sup>19,20</sup> The younger the patient, greater is the likelihood of an underlying heart disease. It may be associated with intramyocardial tumors, anomalous origin of a coronary artery, cardiomyopathies, metabolic disturbances (hypokalemia), myocarditis, prolonged QT syndromes, WPW syndrome and proarrhythmic drug ingestion. It may develop following corrective surgery for Fallot tetralogy and ventricular septal defect.

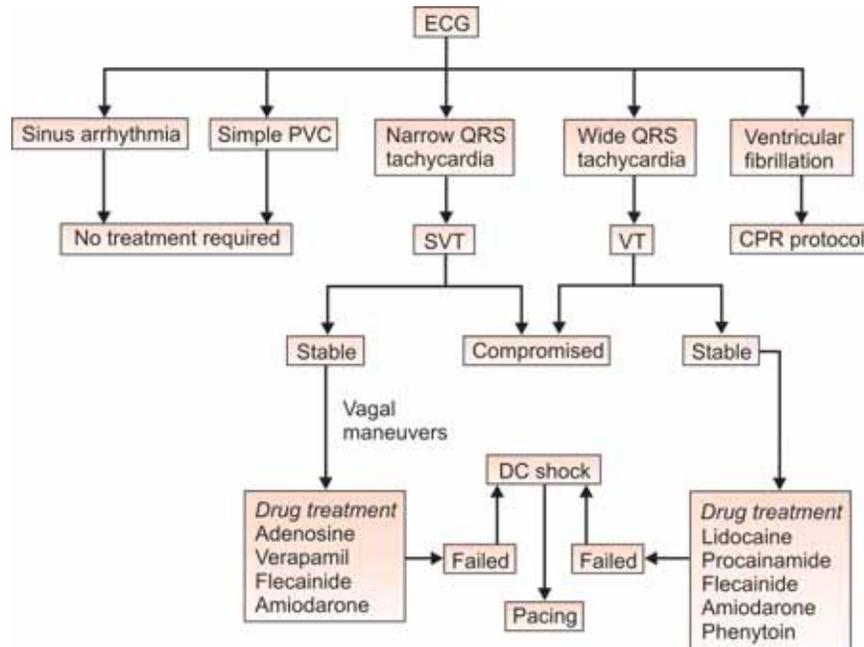
Prompt electrical cardioversion is indicated if there is hemodynamic compromise, and is effective in about 95 percent of cases provided any concurrent electrolyte and metabolic disorder has been corrected and hypoxemia alleviated. In the occasional unresponsive patient, cardioversion may be achieved by repeating DC shock after loading with lidocaine. Pacemaker insertion is a last resort for DC shock failures. Pharmacological cardioversion is recommended for hemodynamically stable patients and lidocaine is the drug of choice. If the first loading dose of 1 mg/kg is ineffective, it can be repeated twice at 5-10 min intervals, using 2 mg/kg and then 3 mg/kg. The bolus dose is followed by an infusion of 30-50 µg/kg/min. If unresponsive, procainamide or bretylium can be used. In prolonged QT syndrome (*torsade de pointes*) intravenous magnesium sulfate is the drug of choice. Maintenance therapy is necessary in all cases except in those where the cause of VT can be identified and treated. Quinidine, procainamide, disopyramide and amiodarone are commonly used agents.

#### *Ventricular Fibrillation*

This arrhythmia is of malignant magnitude and mostly terminates fatally. The ECG shows a series of low amplitude, rapid, irregular depolarization without identifiable QRS complexes. Usually DC defibrillation and external cardiac massage are mandatory because drugs have no effect on ventricular fibrillation. If the



**Fig. 13.3:** Ventricular tachycardia. Wide QRS complexes, P-waves distinguishable with difficulty

Flow chart 13.2: Algorithm for management of common arrhythmias<sup>3</sup>

fibrillation does not respond to first attempt at defibrillation or is recurrent, bretylium tosylate may be tried or an automatic implantable cardioverter-defibrillator may be inserted. Management after restoring sinus rhythm is directed at finding the underlying abnormality.

The commonly used anti-arrhythmic drugs are summarized in Table 13.3. A suggested algorithm for management of common arrhythmias is depicted in Flow chart 13.2.

## Bradyarrhythmias

### Sinus Node Dysfunction

*Sinus arrest* is a result of the failure of impulse formation within the sinus node and may cause a sudden pause in the heartbeat.

*Sinoatrial block* is caused by a block in the conduction of impulses between the SA node and the surrounding atrium. The above arrhythmias may or may not be symptomatic. Sudden decreases in the heart rate are poorly compensated, particularly in those with compromised cardiac function and may result in syncope. Though relatively rare in childhood, they may occur as manifestations of digoxin toxicity and following major atrial surgery.

*Sick sinus syndrome* results from abnormality in impulse generation from the SA node or impulse conduction through the atrium or both. This causes a

cardiac standstill for a few cycles after which a heart beat is initiated from an abnormal focus. Dizziness and syncope may occur during the periods of bradycardia and this may alternate with episodes of supraventricular tachycardia (bradycardia-tachycardia syndrome) with palpitations and exercise intolerance. This syndrome is commonly seen following surgical correction of major congenital cardiac defects, in particular the Mustard procedure for transposition of great arteries.<sup>21</sup> Treatment depends upon the severity of symptoms and needs to be individualized. Drugs used to control the tachyarrhythmias may worsen the SA node function and AV conduction. Therefore, it is usually necessary to combine the drug therapy (propranolol, quinidine, and procainamide) with cardiac pacing.

### Atrioventricular Block

AV block is caused by an interference in the normal conduction of impulses from the atria to the ventricles through the AV node. It can be classified into three major types.

**First degree block:** This is essentially an electrocardiographic diagnosis where the PR interval is prolonged (Fig. 13.4A). It may be seen in patients with rheumatic carditis, diphtheria, digoxin toxicity, and Ebstein's anomaly and L-transposition.<sup>22</sup> The block itself is asymptomatic and does not require any treatment.

Table 13.3: Antiarrhythmic drugs

Drug	Indications	Maintenance dose (oral)	Loading dose (IV)	Side effects	Drug interactions
Digoxin tab 0.25 mg Pediatric elixir Injection 0.5 mg/2 ml amp	PSVT, atrial flutter, atrial fibrillation	0.01-0.02 µg/kg/day	0.025-0.05 µg/kg/day q 4-8 h	PAC, PVC, bradycardia A-V block, nausea, vomiting, anorexia, prolongs P-R interval	Quinidine, amiodarone, verapamil increase digoxin levels, diuretic induced hypokalemia increases digoxin arrhythmias
Quinidine tab 200 mg Injection 80 mg/ml	PSVT, atrial flutter, atrial fibrillation, PVC, ventricular tachycardia	20-60 mg/kg/day q 6 h	10-15 mg/kg as 250 µg/kg/min	Nausea, vomiting, diarrhea, cinchonism, QRS and Q-T prolongation, A-V block, syncope, tinnitus, generalized muscle weakness	Enhances digoxin effects
Procainamide Tab 250 mg Injection 100 mg	PSVT, atrial flutter atrial fibrillation, PVC, ventricular tachycardia	50-100 mg/kg/day q 4-6 h	10-20 mg/kg as 300 µg/kg/min	P-R, QRS,QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coomb's positive hemolytic anemia, SLE, hypotension	Toxicity increased by amiodarone, cimetidine
Disopyramide cap 100 mg, 150 mg injection 10 mg/ml	PSVT, atrial flutter, atrial fibrillation, VPC	8-12 mg/kg/day q 6 hr		Anticholinergic effects, Q-T and QRS prolongation hepatotoxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia	
Phenytoin Tab 100 mg Syr 125 mg/5 ml Injection 50 mg/ml	Digoxin induced arrhythmias with heart block	3-6 mg/kg/day q12 hr	10-15 mg/kg as 250 µg/kg/min	Rash,gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, nystagmus, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, disopyramide increase toxicity phenytoin decreases effects of quinidine, furosemide, disopyramide
Lidocaine 50 ml vial 1 ml = 21.33 mg	PVC ventricular tacycardia	—	1 mg/kg; repeat q 5 min for 3 times; max 50-75 mg IV maintenance 30-50 µg/kg/min	CVS effects, convulsion, high degree A-V block, asystole, coma, respiratory failure, paresthesias	Propranolol, cimetidine, tocainide increase toxicity
Verapamil Tab 40 mg, 80 mg Injection 5 mg/2 ml	PSVT	4-10 mg/kg/day q 8 hr	0.075-0.15 mg/kg q 20 min for 2 times	Contraindicated in ventricular tachycardia, severe CHF and infants bradycardia, asystole, P-R prolongation hypotension, high degree A-V block, CHF	Use with beta-blockers or disopyramide exacerbates CHF. Increases digoxin levels and toxicity

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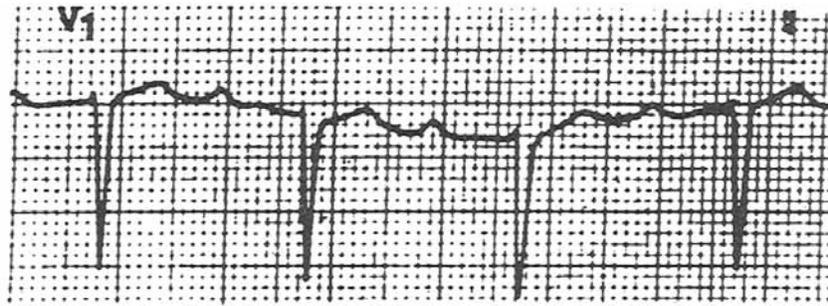
Drug	Indications	Maintenance dose (oral)	Loading dose (IV)	Side effects	Drug interactions
Propranolol Tab 10,40, 80 mg Injection 1 mg/ml	PSVT, PVC	1-4 mg/kg/ day q 6 hr	0.1-0.15 mg/kg	Bradycardia, loss of consciousness or memory, bronchospasm, heart block. CHF, hypotension, hypoglycemia	Use with disopyramide or verapamil exacerbates or precipitates CHF
Adenosine	PSVT	-	50-300 µg/kg; begin with 50 µg/kg and increase by 50-100 µg/kg/dose if no effect (rapid IV push)	Transient complete A-V block, sinus bradycardia, PVC, flushing, nausea, headache	Less effective in patients receiving theophylline. Increased heart block with carbamazepine
Bretylium Injection 50 mg/2 ml amp	Refractory ventricular tachycardia, ventricular fibrillation	-	5 mg/kg then 5-10 mg/kg q 6 h	Hypotension, sinus bradycardia, increased sensitivity to catecholamines with transient arrhythmias	Possible hypotension with concurrent sympathomimetic
Flecainide	Refractory PSVT, WPW syndrome, Ventricular tachycardia	3-6 mg/kg/ day	0.4-1.0 mg/kg max 2 mg/kg as slow infusion over 20 min	Nausea, dizziness, blurred vision, tremor, paresthesia, abnormal taste sensation, may precipitate arrhythmias in patients with cardiac disease	
Amiodarone 200 mg tab	Refractory PSVT, atrial flutter, atrial fibrillation, ventricular tachycardia	10 mg/kg day gradually reduce to 2-3 mg/kg day	5 mg/kg IV over 20-120 min then 15 mg/kg/day by IV infusion	Marked sinus bradycardia, complete A-V block, hypo and hyperthyroidism, pulmonary fibrosis, hepatitis, corneal microdeposits, blue-gray skin discoloration, IV admn may cause hypotension	Elevation of digoxin levels, potentiation of oral anticoagulants, beta-blockers and calcium channel antagonists; augment the action of amiodarone

CHF: Congestive heart failure; PAC: Premature atrial contraction; PSVT: Paroxysmal supraventricular tachycardia; PVC: Premature ventricular contraction; WPW: Wolf-Parkinson White

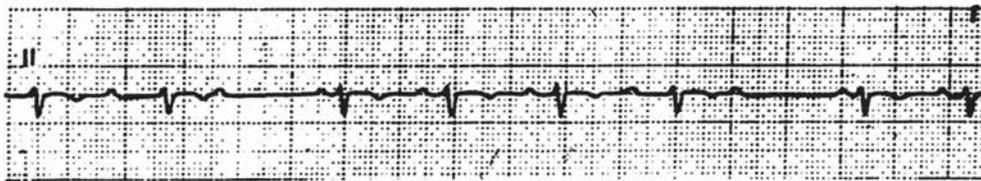
**Second degree block:** In this type of block, some of the atrial depolarizations are not conducted to the ventricles. This may occur irregularly or at regular intervals, resulting in a 2:1 or 3:1 block. In a variant of second degree block, known as the Wenckebach type (Mobitz type I), there is progressive lengthening of the PR interval, until a beat is dropped (Fig. 13.4B).<sup>23</sup> In Mobitz type II block, occasional beats are not conducted to the ventricles; this condition has more potential to cause syncope and may be progressive. These are associated with the same conditions as first

degree block and there is no treatment, other than that of the underlying heart disease.

**Third degree block (complete heart block):** Here, there is a complete lack of co-ordination between the atria and ventricles, and they beat independently of each other (Fig. 13.4C). It may be congenital is usually associated with systemic lupus erythematosus (SLE) in the mother and may produce hydrops fetalis. It is infrequent in older children, being usually associated with myocarditis, tumors, cardiomyopathies, myocardial abscesses due to endocarditis or idiopathic fibrous



**Fig. 13.4A:** First degree AV block; PR interval 0.36 sec



**Fig. 13.4B:** Second degree AV block (Wencheback). Gradual increase in PR interval until the absence of a QRS complex after a P-wave



**Fig. 13.4C:** Third degree AV block. Atria and ventricles beat regularly and independently

degeneration of the conducting system. It remains one of the most serious complications of surgical corrections of congenital cardiac defects involving the ventricular system (Fallot tetralogy, ventricular septal defect). The ventricular rate is usually 45-60/min and may increase to 65-80/min on exercise. The peripheral pulse is prominent due to a compensatory increase in ventricular stroke volume; along with a forceful left ventricular beat and ejection systolic murmur at the base. The jugular venous pulsations show cannon waves in the neck. Majority of patients with isolated heart block lead an asymptomatic life. A 24 hours Holter monitoring should however, be done to look for bradycardia, ventricular ectopics and widening of the QRS complex, all of which are adverse factors. These patients are likely to develop episodes of dizziness or syncope (Stokes-Adams attack) and are at risk for sudden death. The indications for implantation of a cardiac pacemaker include the development of

symptoms, prolonged pauses or the development or progressive cardiac enlargement.

Complete congenital heart block may be found in up to 1 in 20,000 to 25,000 live births and in 60-70 percent of cases it is the result of autoimmune injury of the fetal conduction system by maternally IgG antibodies. The primary autoimmune process responsible in majority of cases is systemic lupus erythematosus which may be overt or more often asymptomatic.<sup>24</sup> Rarely, rheumatoid arthritis, or Sjögren syndrome may be implicated. It may also be seen in neonates with complex cardiac defects like corrected 1-loop transposition of great arteries and single ventricle. Neonates with ventricular rates lower than 50/min, those having evidence of hydrops and those who develop heart failure after birth require cardiac pacing. Drugs such as atropine and isoproterenol are useful only in transiently increasing heart rates while awaiting pacemaker implantation. Mortality is common

in the first year, so these infants have to be monitored carefully during this period.

### *Fetal Arrhythmias*

The diagnosis and treatment of arrhythmias in the fetus has been one of the latest advances in the field of pediatric cardiology, made possible by the widespread use of electronic fetal monitoring by obstetricians, as well as technological advances in fetal echocardiography.<sup>25</sup> Fetal arrhythmias are associated with an increased incidence of congenital malformations and a high perinatal and neonatal mortality. The premature atrial and ventricular contractions are entirely benign. Tachycardias, especially SVT require special mention as they can lead to heart failure. Such cases can be successfully treated by giving digoxin or verapamil to the mother. Bradyarrhythmias, commonly complete AV block, are associated with the highest mortality, needing urgent temporary cardiac pacing at birth.<sup>26</sup> Knowledge of these fetal arrhythmias can prevent many late fetal and neonatal deaths by careful antenatal and postnatal management.

### **Radiofrequency Catheter Ablation**

Radiofrequency catheter ablation was first described in pediatric patients in the early 1990s. This treatment has in majority of cases, replaced arrhythmia surgery as the definitive cure for most arrhythmias. There are several advantages of this therapy when used in common indications: no exercise restrictions, no need for chronic drug therapy, and the avoidance of hospital visits for breakthrough episodes. For virtually every form of supraventricular tachycardia, as well as ventricular tachycardia, ablation has been attempted. Overall, the initial success rate for ablation is between 92 to 95 percent for all arrhythmias.<sup>27,28</sup>

Recommendations for radiofrequency ablation are dependent on several factors, including age and clinical status of the patient as well as experience and success rate of the institution. Indications usually include incessant tachycardias with decreased ejection fraction which are either refractory or poorly controlled on anti-arrhythmic therapy.<sup>29</sup> Risks of the procedure include bleeding, stroke, infection, and damage to cardiac valves, cardiac perforation, AV block and coronary spasm. A major complication rate of 3 percent and a minor complication rate of 8.2 percent have been reported<sup>28</sup> with a recurrence rate of 6 percent.

### **Surgical Therapy of Arrhythmias**

The success of radiofrequency ablation for most types of supraventricular and ventricular arrhythmias, particularly in young patients, has largely eliminated the role of surgical therapy of arrhythmias. However, there remains a set of arrhythmia patients in whom the catheter approach has not been successful and types of arrhythmias with high recurrence rates after initially successful catheter ablation procedures where surgery can provide more definitive therapy. In addition, the ability to incorporate the concepts of ablation into the simultaneous repair of structural heart diseases may be the optimal therapy for individual patients.<sup>30</sup>

### **Implantable Pacemakers**

Major advances have been made in pacemaker and pacemaker lead technology. Pacemakers which are now commercially available are small enough to allow successful implantation even in neonates.<sup>31</sup> All pacemakers now rely on lithium batteries, giving them a life span of 5 to 10 years. Most pacing wires are inserted intravenously (subclavian, cephalic or jugular veins) and the tip positioned in the right ventricle under radiographic control. The generator is then implanted in the pectoral region. Catheters are of polyurethane and not sialistic so that they are smaller with a lower coefficient of friction and less thrombogenicity. In children, dual chamber pacing (both atrial and ventricular leads are applied) and rate responsive pacing is to be preferred because of its capabilities of increasing cardiac output as per the needs of the body. In addition to its traditional use in sinus and AV nodal diseases, applications for cardiac pacing now include treatment of tachyarrhythmias after repair of congenital heart disease, reduction of left ventricular outflow tract in hypertrophic cardiomyopathy and prevention of sudden death in congenital long QT syndromes.<sup>29</sup> Programmable features such as rate-response and anti-tachycardia pacing contribute to pacemaker versatility and facilitate the achievement of normal hemodynamics in children requiring long-term pacing.

### **Cyanotic Spells**

Cyanotic spells are most commonly seen in patients with Tetralogy of Fallot (prevalence varies from 20-40 percent) and rarely in tricuspid atresia and pulmonary atresia with ventricular septal defect. They are seen during the first two years of life. The onset may be as

early as the first month of life, with a peak frequency between the 2nd and 3rd months. The episodes may occur at any time of the day but are particularly common in the morning. There is no correlation between the severity of cyanosis and the occurrence of spells.<sup>32</sup> In fact, infants who are mildly cyanosed are often more prone to develop spells.

The spells are characterized by increasing rate and depth of respiration, with deepening cyanosis, progressing to limpness, unconsciousness, occasionally ending in convulsions, and some may be life-threatening. Temporary disappearance or decrease in intensity of the systolic murmur is usual. Majority of the spells last for 15 to 30 minutes and are associated with a reduction of an already compromised pulmonary blood flow and an increase in right to left shunt. Crying, defecation and feeding are the most common precipitating events. These situations increase oxygen demands, and cause increased arterial pCO<sub>2</sub> and lowered pH and pO<sub>2</sub> all of which stimulate hyperpnea and initiate an attack. Hyperpnea is the crucial event in maintaining these spells.<sup>33</sup> It increases the shunt across the ventricular septal defect leading to an increase in the arterial pCO<sub>2</sub> and a decreased in pO<sub>2</sub> and pH. These changes in arterial composition tend to further stimulate respiration and a vicious cycle is begun. Wood<sup>34</sup> suggested that the spells are due to obstructive spasm of the right ventricular outflow infundibulum, which is considered to result from the release of endogenous catecholamines in the myocardium.<sup>35</sup> This decreases the pulmonary blood flow, increasing the right to left shunt and arterial hypoxemia which leads to rapid development of metabolic acidosis, stimulation of the respiratory center and results in hyperventilation.

### Management

A cyanotic spell is a medical emergency and should be treated with a sense of urgency. The measures to be taken are as follows:

1. *Posture:* The infant should immediately be placed prone in a knee-chest position.
  2. *Morphine:* The spell will respond dramatically to morphine (0.1 mg/kg, max 0.2 mg/kg, subcutaneously).<sup>36</sup> The effect is due to the depressant effect of morphine on the respiratory center.
  3. *Oxygen:* Oxygen should be administered though the effects are not dramatic.
  4. *Sodium bicarbonate:* If the attack has gone on for a considerable length of time and the patient has not responded to the above measures, it is quite probable that metabolic acidosis has developed.
- Treatment with sodium bicarbonate may help interrupt the attack.
5. *Propranolol:* Beta-adrenergic blockade with intravenous propranolol (0.1 mg/kg to max of 0.2 mg/kg) has proved to be of great value especially in spells accompanied by tachycardia. The favorable response is attributed to the negative inotropic effects on the infundibular myocardium.
  6. *Glucose supplementation:* This is useful since hypoglycemia may result from accelerated utilization and depleted glycogen stores.
- Occasionally general anesthesia will be necessary to interrupt the attack, probably by a generalized suppression of central nervous system activity and by depression of respiration. Exceptionally an emergency systemic pulmonary shunt will be required. Occurrence of even one cyanotic spell is an indication for surgery and maintenance propranolol (1-2 mg/kg in 3-4 divided doses) may be needed over the few days or weeks before surgery can be arranged. Several patients with iron deficiency anemia, have amelioration of spells after iron supplementation.

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# 14 Hypertensive Emergencies

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Severe hypertension, also called as hypertensive crisis, is uncommon in children. Such crises are potentially life-threatening, and call for immediate medical attention to prevent or limit end-organ damage. While the level of blood pressure determines the gravity of situation, the rapidity of rise of blood pressure and end-organ damage are more important than the absolute level of blood pressure.

Hypertension in children is classified based on age, gender and height percentiles according to the guidelines provided by the Indian Society of Pediatric Nephrology, which are in broad conformity with the Fourth US Task Force Report on Hypertension in children (Table 14.1).<sup>1,2</sup> Severe hypertension is defined as stage II hypertension that is accompanied by symptoms, with or without abnormalities on examination or biochemistry.<sup>3</sup> Usually, a diastolic blood pressure of more than 110 mm Hg in an adolescent is considered as severe hypertension.

Traditionally, hypertensive crises are further classified as hypertensive emergencies and hypertensive urgencies.<sup>4</sup> While the former term is reserved for severe hypertension associated with life-threatening symptoms and/or target-organ injury, the term 'urgencies' refers to hypertension with less significant symptoms and no target-organ injury. Hence, hypertensive emergencies include encephalopathy, cardiac

failure, retinal hemorrhage and renal dysfunction, while severe hypertension in the absence of clinical or laboratory evidence of end-organ damage is referred as hypertensive urgency. The implication of urgency is that if left untreated, it may progress to an emergency. However, the distinction is not absolute, and is based on clinical judgement.

## Etiology

An increasing proportion of children with hypertension, particularly adolescents in developed countries, are being diagnosed to have essential or primary hypertension.<sup>5</sup> However, the majority of children with hypertensive crises have secondary hypertension, with renal disease being the predominant cause. Hypertensive emergencies may occur in acute renal failure, particularly in rapidly progressive glomerulonephritis or atypical hemolytic syndrome, or in the course of known chronic renal disease, due to non-compliance to antihypertensive medications (Table 14.2). It may be the first presentation of end stage renal disease, often along

**Table 14.1: Definition and staging of hypertension in children**

Pre-hypertension	SBP or DBP 90th-95th percentile or > 120/80 mm Hg
Hypertension	SBP or DBP > 95th percentile
Stage I hypertension	SBP or DBP between 95th percentile and 99th percentile + 5 mm Hg
Stage II hypertension	SBP or DBP > 99th percentile + 5 mm Hg

SBP systolic blood pressure; DBP diastolic blood pressure

**Table 14.2: Important causes of severe hypertension**

### Renal

*Parenchymal:* Acute glomerulonephritis, hemolytic uremic syndrome, chronic glomerulonephritis.

Obstructive uropathy, reflux nephropathy

*Vascular:* Renal artery stenosis, vasculitis

Polycystic kidney disease, renal dysplasia, hypoplasia

Wilm's tumor

*Cardiovascular:* Coarctation of aorta, idiopathic aortoarteritis

*Endocrine:* Pheochromocytoma, neuroblastoma, Cushing disease, Conn syndrome

*Miscellaneous:* Therapy with corticosteroids or calcineurin inhibitors, Guillain-Barré syndrome

Medication non-compliance in known hypertension

Abuse of illicit substance (e.g. cocaine)

"Rebound" hypertension due to rapid withdrawal of clonidine or beta-adrenergic blockers

with evidence of fluid overload. Patients with chronic kidney disease stage V on maintenance dialysis may develop hypertensive crisis due to inadequate dialysis and poor compliance with fluid restriction.

### Clinical Features

Hypertensive emergencies are typically associated with a rapid rise in blood pressure. However, the presentation varies widely, from totally asymptomatic state to symptoms suggesting a primary cardiac, neurological or ocular disorder.<sup>6</sup> Patients may be detected to have elevated blood pressure without symptoms referable to hypertension; this underscores the importance of evaluating blood pressure in all ill children, particularly in those with cardiovascular, neurological, renal or ocular diseases. Chronic elevations of blood pressure may be surprisingly well tolerated, particularly in neonates. The presentation influences the management strategy; children presenting with severe symptoms need to be treated much more rapidly than those who are asymptomatic.

Findings on physical examination at presentation may include papilledema, congestive heart failure and pulmonary edema, usually only with hypertensive emergencies. Evidence of end-organ damage may be seen at presentation, in the form of left ventricular hypertrophy, congestive cardiac failure or hypertensive retinopathy.

### CNS Manifestations

Encephalopathy is one of the most common but severe manifestations of a hypertensive emergency.<sup>4</sup> The condition is caused by a failure of the autoregulation of cerebral blood flow, which leads to impaired cerebral perfusion. Symptoms include headache, vomiting, lethargy, confusion, altered sensorium, stupor, seizures and ataxia.<sup>7</sup> Focal neurological deficits such as hemiparesis, blindness and facial nerve palsy may be present.<sup>8</sup> Unless the blood pressure is recorded, hypertensive encephalopathy may be misdiagnosed as meningitis or encephalitis.

If a magnetic resonance imaging is performed, characteristic findings of posterior leukoencephalopathy may be seen predominantly in the parieto-occipital white matter; these changes are potentially totally reversible with correction of hypertension.<sup>9</sup>

### Ocular Symptoms

The child may complain of blurring or loss of vision. Examination of optic fundus may reveal papilledema

and retinal hemorrhages, but occasionally no abnormality is found.

### Cardiovascular Features

The child may present with congestive heart failure, particularly in patients with renal failure and fluid overload.

### Management

While adequate treatment of severe hypertension is required for prevention of serious sequelae, overzealous therapy may be equally hazardous in patients with long standing severe hypertension. In chronic severe hypertension, a gradual shift in cerebral autoregulation protects the brain from excessive perfusion in the hypertensive state (Fig. 14.1).<sup>10</sup> Ischemic complications are likely to occur if the blood pressure is reduced abruptly, causing it to fall below the new lower threshold of autoregulation. Thus, the aim of treatment of hypertensive crises is to prevent target organ damage due to severe hypertension or its rapid reduction. Therapeutic success is achieved by slow and controlled reduction of blood pressure.<sup>11</sup> However, there is no information on the safest rate of BP reduction in such children. The aim is to decrease the blood pressure by up to 25% over the first 8 hours of presentation and then gradually to the upper limit of normal (95th percentile) over 26-48 hours.<sup>7,11</sup> The drugs used for treating hypertensive emergency should be short-acting and administered intravenously, which allows easy modification of dose according to the therapeutic response. With these agents, invasive arterial blood pressure monitoring is desirable. The agents usually chosen for intravenous infusion include sodium nitroprusside, nitroglycerine, hydralazine, labetalol and nicardipine (Table 14.3). The latter two drugs are not yet approved by the Food and Drug

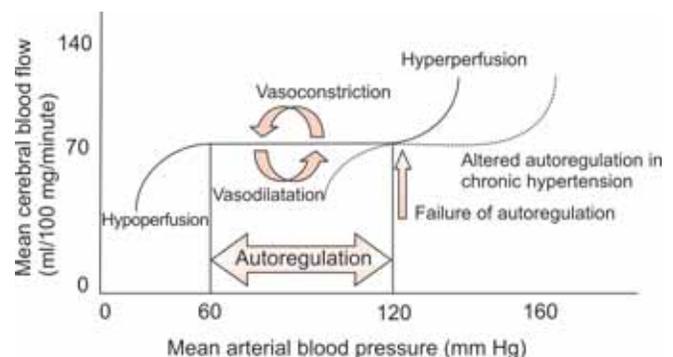


Fig. 14.1: Altered cerebral autoregulation in chronic severe hypertension

**Table 14.3: Intravenous agents used for treatment of hypertensive emergencies**

Drug	Dose, route	Onset	Duration of effect	Side effects
Sodium nitroprusside	0.5-8 µg/kg/min; IV infusion (in 5% dextrose)	30 sec	< 10 min	Nausea, vomiting, headache, tachycardia, cyanide toxicity (dizziness, confusion, seizures, jaw stiffness and lactic acidosis)
Sodium nitroglycerine	1-3 µg/kg/min; IV infusion	2-5 min	5-10 min	Methemoglobinemia, headache, tachycardia
Labetalol	0.25-3 mg/kg/hr as IV infusion; 0.2-1 mg/kg/dose q 5-10 min (max 40 mg) as IV bolus	5-10 min	3-6 hr	Orthostatic hypotension, bradycardia, pallor, abdominal pain, diarrhea
Nicardipine	0.5-4 µg/kg/min (max 5 mg/hr) as IV infusion; 30 µg/kg (max 2 mg/dose) as IV bolus	1-10 min	3 hr	Flushing, reflex tachycardia, phlebitis
Phentolamine	0.1-0.2 mg/kg (max 5 mg) as IV bolus, q 2-4 hr if required	2 min	5-15 min	Reflex tachycardia
Diazoxide	0.3-5 µg/kg/min as IV infusion; 1-3 mg/kg q 5-15 min	3-5 min	6-24 hr	Nausea, salt and water retention, hypotension, hyperglycemia
Esmolol	100-500 µg/kg/min; IV infusion	1 min	10-20 min	Bradycardia

µg – microgram; mg – milligram; IV – intravenous; sec – seconds; min – minutes; hr – hour; q – every.

Administration (FDA), USA for use in pediatric population, but are commonly used because of their efficacy and overall safety. Fenoldopam, though useful in adults with hypertensive emergencies, has limited efficacy in children.<sup>12</sup>

### *Sodium Nitroprusside*

The drug of choice for hypertensive emergencies is sodium nitroprusside.<sup>11</sup> It is metabolized to nitric oxide, an extremely potent vasodilator of veins as well as arteries which reduces both preload and afterload. Hence it is especially useful in case of congestive cardiac failure with severe hypertension. It is started as an intravenous infusion at dose 0.5 µg/kg/minute; this is gradually increased to achieve the desired blood pressure. The hypotensive action begins within seconds after the infusion is started, and disappears rapidly when it is discontinued. Because of its potent hypotensive effect, nitroprusside should be administered in an intensive care unit with blood pressure recording done continuously or at least every 5 minutes. The drug should be shielded from light to prevent degradation. The metabolic product of sodium nitroprusside is cyanide, which is converted into thiocyanate in the liver and almost exclusively removed by the kidneys. Cyanide poisoning, though rare, may occur in patients with renal insufficiency and in those in whom

nitroprusside infusion is given for prolonged duration (> 24-48 hours). Co-administration of thiosulphate or hydroxycobalamin minimizes this risk. Overt toxicity requires discontinuation of nitroprusside infusion, treatment with administration of amyl nitrate and sodium nitrate, and hemodialysis. Tachyphylaxis is another problem associated with prolonged use of nitroprusside.

### *Sodium Nitroglycerine*

This drug is an alternative to nitroprusside, especially in children with myocardial dysfunction. Like nitroprusside it has a rapid onset and short duration of action when used as an intravenous infusion, allowing easy titratability. Adverse effects include headache, tachycardia and methemoglobinemia. Tachyphylaxis is noted with prolonged use.

### *Labetalol*

Labetalol is an effective and safe parenteral drug for hypertensive emergency, which has both alpha and beta-adrenergic blocking activity.<sup>11</sup> It causes vasodilatation without significant effect on cardiac output. However, it is important to note that the alpha-to-beta blocking ratio of the intravenous preparation is 1:7, whereas it is 1:3 for the oral preparation. Hence, the

infusion should be avoided in patients with asthma, acute left ventricular failure and heart block.

### *Nicardipine*

More recently, nicardipine has been used as a continuous infusion in hypertensive emergency in children.<sup>10</sup> It exerts a prompt hypotensive effect, which can be titrated by adjusting the infusion rate. Its onset of action and efficacy is comparable to nitroprusside. There is selective vasodilatation of the cerebral and coronary vasculature; hence the drug is beneficial in situations of myocardial ischemia, but should be avoided in patients with raised intracranial pressure, e.g. intracranial space occupying lesions and head trauma.

### *Other Intravenous Agents*

Diazoxide causes direct vasodilatation by increasing vascular smooth muscle cell permeability to potassium that interrupts voltage-gated calcium transport. A mini-bolus frequent dosing regimen is recommended to avoid the significant hypotension associated with administration of large doses. However, the blood pressure reduction is unpredictable and hyperglycemia is a concern.<sup>13</sup> Phentolamine is used in the setting of pheochromocytoma, and is given 1-2 hours prior to surgery to control the blood pressure peri-operatively. Because of its ultra-short acting, cardioselective  $\beta$ -1 adrenergic blockade, esmolol is well suited as an intravenous infusion, especially for management of intraoperative hypertension.<sup>14</sup> Its efficacy in children has not been studied. Intravenous enalaprilat has been shown to be useful in patients with renin mediated hypertension, but the high incidence of renovascular hypertension in children, the lack of safety information in pediatric population, and the reported adverse effects like prolonged hypotension and oliguria make it an unlikely first choice for management of hypertensive emergency in children.<sup>15</sup> Diazoxide, enalaprilat and esmolol are not available in our country.

Intravenous frusemide is helpful in lowering blood pressure in patients with salt and water retention (e.g., acute glomerulonephritis) and adequate renal function.

### *Newer Agents*

Fenoldopam (0.2-0.8  $\mu$ g/kg/min), a peripheral DA1 receptor agonist, has efficacy and safety similar to nitroprusside in the treatment of hypertensive crisis in adults, with the advantage of maintaining or increasing renal perfusion. However, there is limited experience with its use in children.<sup>2</sup>

Clevidipine is a new ultra-short-acting dihydropyridine calcium channel blocker with a high specificity for vascular smooth muscle. Its action is seen within 2 minutes of infusion initiation, and the effect lasts only a few minutes beyond discontinuation.<sup>16</sup> Efficacy in adults is comparable to nitroprusside; studies in pediatric population are awaited.

Urapidil is a peripheral postsynaptic alpha-adrenoceptor antagonist with a central agonistic action at serotonin 5-HT receptors. Its rapid onset of action, along with strong vasodilating properties, such that it does not increase myocardial oxygen demand, heart rate and intracranial pressure, give this drug an edge over other vasodilators. Its efficacy is proven in adults with hypertensive emergencies, perioperative hypertension and eclampsia.<sup>17</sup> However, pediatric experience with this drug is limited.

### *Intravenous Bolus Administration*

If continuous infusion of an antihypertensive agent is not immediately available, IV bolus dosing of labetalol, enalaprilat and hydralazine can be used for management. However, boluses provide less minute to-minute control of blood pressure compared with continuous infusion therapies. Hydralazine, which interferes with intracellular calcium metabolism to cause arterial vasodilation by unclear mechanisms, may be administered intravenously or intramuscularly as a bolus. Adverse effects include reflex tachycardia, and sodium and fluid retention.

### *Oral Agents used in Management of Severe Hypertension*

Agents with relatively rapid onset of action when administered orally may be used in management of severe hypertension, particularly in hypertensive urgencies and where intravenous administration is not possible. These include nifedipine (0.1-0.25 mg/kg), clonidine (0.05-0.1 mg/dose), minoxidil (0.1-0.2 mg/kg/dose), labetalol (0.2-1 mg/kg/dose), isradipine (0.05-0.1 mg/kg/dose), captopril (6.25-25 mg) and hydralazine (0.2-0.6 mg/kg/dose).

Sublingual nifedipine has been widely used for treatment of hypertensive urgency and emergency. Oral administration is equally effective. Sublingual administration is by puncturing and squeezing the contents of the 5 mg capsule under the tongue. The dose may be repeated twice at 10 minute intervals. There is some concern about sublingual absorption of nifedipine, with reports suggesting that the absorption occurs predominantly after swallowing.<sup>18</sup> The overall

response rate to the first dose of nifedipine is 70-75%. The use of immediate release nifedipine for hypertensive emergencies has been criticized in adults for its unpredictable effect, and association with an increased risk for adverse cardiovascular outcomes in adults. In children, however, nifedipine seems to be effective and safe for management of hypertensive emergencies except those with hypertensive encephalopathy.<sup>19</sup>

#### *Additional Evaluation, Monitoring and Supportive Care*

Children with hypertensive emergency should preferably be treated in an intensive care unit under continuous blood pressure monitoring. Pupillary reactions, sensorium and neurological findings should be monitored carefully. In case hypotension occurs, intravenous saline should be promptly infused.

At presentation, an assessment of volume status is essential. Volume status can be depleted (due to decreased oral intake and pressure natriuresis), causing stimulation of the renin-angiotensin system, worsening the hypertension. Volume repletion may lower renin levels, help restore tissue perfusion, and prevent a precipitous fall in blood pressure that may occur with antihypertensive therapy.

Therapy with oral antihypertensive agents should be commenced as soon as patient can take orally, in order to permit intravenous therapy to be withdrawn over the next 24 hours. Oral drugs such as sustained release nifedipine, angiotensin converting enzyme inhibitors and beta-blockers may be used. Since it is extremely rare for primary or essential hypertension to result in hypertensive emergency in children, a thorough evaluation for the underlying cause should be carried out. Important investigations include abdominal ultrasound and Doppler evaluation of renal vessels, urinalysis, electrocardiography, and often, a dimercaptosuccinic acid (DMSA) scan.

#### *Special Situations*

The treatment of severe hypertension has to be modified in special situations. Sodium nitroprusside and labetalol are recommended and safe in patients with neurological impairment. Nicardipine should be used with caution in patients with intracranial space occupying lesions and atelectasis. The drugs of choice for hypertensive crisis due to pheochromocytoma are phentolamine, sodium nitroprusside with beta-blockers and labetalol. Patients with unilateral renovascular disease benefit from use of angiotensin converting enzyme inhibitors. In patients

with mineralocorticoid excess and rare endocrine disorders including Liddle syndrome, severe hypertension may not respond adequately to any therapy other than triamterene or amiloride. Patients with end stage renal failure with volume overload show blunted response to antihypertensive agents and require repeated dialyses to remove excess fluid.

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Acute renal failure (ARF) is an important emergency where prompt and appropriate management is life saving, whereas injudicious treatment may result in life-threatening complications. ARF is characterized by a rapid deterioration of normal renal function resulting in retention of nitrogenous wastes and other fluid and electrolyte derangements, which are usually felt to be reversible.<sup>1</sup> Oliguria (urine volume < 0.5 ml/kg/h) is a prominent feature. In a small proportion of patients, the urine output may be normal or only slightly reduced (non-oliguric renal failure); elevated blood levels of urea, creatinine suggest the diagnosis in such cases. ARF usually occurs in patients with previously normal renal function but may occasionally be superimposed on pre-existing renal disease (acute-on-chronic renal failure).

The incidence of ARF in neonatal and pediatric units varies between 1-25%, depending upon criteria used for its definition.<sup>2,3</sup> Despite advances in therapy the mortality due to the condition is still high (30-40%) and a proportion of patients may progress to chronic kidney disease and dialysis dependency.

### NOMENCLATURE AND CLASSIFICATION

In the absence of a universally accepted definition and in recognition that ARF actually includes a spectrum of clinical conditions, the term acute kidney injury (AKI) has recently been proposed for the entire spectrum of the syndrome.<sup>4</sup>

AKI is considered in the presence of functional or structural abnormalities of the kidneys including abnormalities in blood biochemistry, urine or biopsy findings or imaging studies of less than 3 months' duration. Diagnostic criteria for AKI include an abrupt (within 48 hr) reduction in kidney function, defined as 50% or greater increase in serum creatinine or oliguria (< 0.5 ml/kg/hr for > 6 hr). In 2004, various nephrology and critical care groups proposed an empiric working definition of AKI.<sup>5</sup> Staging of AKI was further proposed by the group based on the glomerular

filtration rate, serum creatinine and urine output (RIFLE classification). The acronym RIFLE stands for (R for risk of renal dysfunction; I for renal injury; F for failure of renal function; L for loss of renal function and E for end stage renal disease). A reduction in estimated creatinine clearance by 25% or urine output less than 0.5 ml/kg/hr for 6 hours is defined as risk while a further reduction of clearance by 50% and urine output less than 0.5 ml/kg/hr for 12 hours indicates injury. A decrease in creatinine clearance by 75% or urine output less than 0.3 ml/kg/hr for 24 hours or anuria for 12 hours suggests failure. Requirement of renal replacement therapy for more than 4 weeks is defined as renal loss and more than 3 months as end stage renal disease. In 2007 the acute kidney injury network (AKIN); a group comprising of experts from critical care and nephrology societies modified the staging of AKI to suit the needs of a wide age range of patients.<sup>6,7</sup> Currently, the AKIN classification defines 3 stages of acute renal failure (Table 15.1). These classifications have been validated in adult and pediatric renal injury models. The appropriate use of staging of AKI will help in uniform reporting and comparing the incidence and outcomes of renal injury in different centers.

**Table 15.1: AKIN classification of acute renal failure**

Staging	Serum creatinine	Urine output
I	Creatinine elevated by 1.5-2 times baseline or more than 0.3 mg/dL increase	Less than 0.5 ml/kg/hr for 6 hr
II	Creatinine elevated by 2-3 times baseline	Less than 0.5 ml/kg/hr for 12 hr
III	Creatinine elevated > 3 times baseline or serum creatinine > 4.0 mg/dL with acute rise of at least 0.5 mg/dL	Less than 0.3 ml/kg/hr for 24 hr, or anuria for 12 hr

Only one criterion (creatinine or urine output) need be fulfilled to qualify for a stage. Patients on renal replacement therapy are classified into stage III (Adapted from reference 6, 7)

## BIOMARKERS

The currently used marker of renal damage serum creatinine takes a longer time to rise from the actual time of renal injury. It takes about 50% loss of renal function to occur before an increment in serum creatinine is seen. Besides measurement of serum creatinine is highly dependent on the laboratory methodology. To prevent the progression of ARF it is important to detect even mild renal dysfunction early. This has triggered a search for serum and urinary biomarkers of early renal damage including serum and urinary neutrophil gelatinase associated lipocalin (NGAL), urinary interleukin 18 (IL-18), kidney injury molecule (KIM-1) and serum cystatin levels.<sup>8</sup> NGAL is a 25 kDa protein that is expressed in kidney, lung, stomach and colonic tissue in small amounts. However with renal injury especially hypoxic and nephrotoxin mediated, the levels of NGAL are markedly elevated in urine and serum. IL-18 is a proinflammatory cytokine that is induced and processed in proximal tubule cells. Increased levels of IL-18 are seen in hypoxic/ ischemic damage to renal tubules. KIM-1 is a transmembrane protein that is overexpressed in renal tubules after a hypoxic and nephrotoxic injury to tubules. Human and animal studies have shown that these biomarkers may be detected in serum and urine within 6 hours of the onset of renal injury, enabling early detection of AKI. Cystatin C is a cysteine protease inhibitor that is produced by all nucleated cells. It is freely filtered by the kidneys and completely reabsorbed by the proximal tubules. Unlike serum creatinine, cystatin C levels are not age, gender or muscle mass dependant. The serum levels correspond well with glomerular filtration rates and rise of cystatin C is seen earlier than that of creatinine in a situation of ARF. Commercial kits based on these biomarkers are not yet available.

## NEONATAL ARF

Published studies estimate the incidence of neonatal ARF at 8-24%, and associated with high mortality.<sup>6</sup> The common causes of ARF in neonates are birth asphyxia, sepsis, structural abnormalities of urinary tract (obstructive uropathy), drug toxicity (aminoglycosides and amphotericin).<sup>3</sup> Other drugs like indomethacin, captopril and frusemide might contribute to the occurrence of neonatal ARF. Use of NSAIDs or ACE inhibitors during the antenatal period may cause hypotension and ARF in newborn. Other causes include hypovolemia, respiratory distress syndrome and intravascular volume depletion following surgery.

Bilateral renal artery thrombosis may occur after umbilical artery catheterization. Non oliguric ARF is more common in neonates and also the mortality due to sepsis related ARF is higher compared to non-septicemic causes.

## CAUSES OF ARF

The etiology of ARF may be pre-renal, intrinsic renal or post-renal.<sup>1,2,5</sup> Pre-renal failure is renal insufficiency due to inadequate systemic and/or renal circulation. Pre-renal failure can be caused by either systemic hypovolemia or renal hypoperfusion. Hypovolemic pre-renal failure, if treated early, responds to a fluid challenge with resumption of normal urine output and resolution of azotemia. 'Post-renal' failure occurs as a consequence of mechanical obstruction in the urinary collecting system. Both pre- and post-renal categories can, if prolonged, lead to parenchymal injury to the kidneys (intrinsic renal failure). Intrinsic renal disease can also occur due to other conditions, including hemolytic uremic syndrome (HUS) and glomerulonephritis (GN).

Intrinsic renal disease, including acute tubular necrosis (ATN), GN and HUS is the leading cause of ARF in children.<sup>2,5</sup> ARF related to overwhelming infection or following major surgery is common in hospitalized children. Many of these children have normal renal function at admission to the hospital but develop ARF later because of either the primary illness or its treatment. Table 15.2 lists the common causes of ARF in children.

**Pre-renal ARF:** In pre-renal ARF, the functional integrity of the kidney is preserved; renal failure is thus reversible with restoration of the underlying hemodynamic abnormality. Characteristically, there is decreased renal perfusion and glomerular filtration, but normal tubular function leading to oliguria and azotemia. The most common underlying cause is hypovolemia due to acute gastroenteritis or hemorrhage. Other causes include a severe fall in cardiac output due to congestive heart failure, third space losses like nephrotic syndrome, renal vasoconstriction as in hepatorenal syndrome, peripheral vasodilatation as in sepsis, and increased insensible fluid losses as in extensive burns and pancreatitis. Therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin converting enzyme (ACE) inhibitors adversely effect glomerular perfusion in patients with hypovolemia. Although various conditions that lead to pre-renal failure can progress to ATN, it is difficult to predict when the transition may occur or the duration of circulatory impairment necessary for its development.

**Table 15.2: Common causes of acute renal failure****Prerenal**

Hypovolemia (dehydration, blood loss, diabetic ketoacidosis)  
 Third space losses (septicemia, nephrotic syndrome)  
 Congestive heart failure  
 Perinatal asphyxia

**Renal***Acute tubular necrosis*

Prolonged prerenal insult (see above)  
 Medications, exogenous and endogenous toxins  
 (Table 15.3)  
 Intravascular hemolysis, hemoglobinuria  
 Tumor lysis syndrome

*Hemolytic uremic syndrome*: Diarrhea associated (D+) and atypical (D-) forms

*Glomerulonephritis (GN)*

Postinfectious GN  
 Systemic disorders: SLE, Henoch Schonlein syndrome, microscopic polyangiitis  
 Membranoproliferative GN  
 Crescentic GN

*Interstitial nephritis* (drug-induced, idiopathic)

*Bilateral renal vessel occlusion* (arterial, venous)

**Postrenal**

Obstructive uropathy (calculi, blood clots), posterior urethral valves, bilateral pelviureteric junction obstruction, neurogenic bladder

*A significant proportion of patients may have multiple causative factors.*

**Renal parenchymal causes:** Renal tubules are particularly susceptible to injury because of the large renal blood flow, and a large surface area for filtration, tubular reabsorption and urinary concentration. The common causes include renal hypoperfusion following volume contraction, severe renal vasoconstriction, nephrotoxic agents, sepsis, shock and hypotension.

Renal hypoperfusion leads to a spectrum of conditions ranging from pre-renal ARF (reversible by volume repletion and improved renal blood flow), to an intermediate stage (with decreased urine osmolality, variable urinary sodium and mild azotemia), which is slowly reversible over 1-3 days, and established ATN. In more extreme instances of renal ischemia, varying degree of cortical necrosis may be present.

The kidney is exposed to high concentrations of exogenous or endogenous toxins (Table 15.3). Snakebites may produce hemorrhagic manifestations such as epistaxis, hemoptysis, hematemesis, hematuria, hypotension and shock. ARF may develop due to intravascular hemolysis, shock and direct tubular injury. Epidemics of severe systemic toxicity and ARF from

**Table 15.3: Nephrotoxic substances****Exogenous**

Aminoglycosides, cephalosporins, sulfonamides, amphotericin, acyclovir, vanomycin  
 Chemotherapeutic agents  
 Radiocontrast media, intravenous immunoglobulin  
 Frusemide, NSAIDs, ACE inhibitors, cyclosporin A, tacrolimus  
 Organic solvents (diethylene glycol), heavy metals  
 Snakebite, other envenomations

**Endogenous**

*Pigments*: Hemoglobin, myoglobin, methemoglobin  
*Crystals*: Uric acid, oxalate, calcium  
 Tumor lysis syndrome

diethylene glycol-contaminated glycerin, used to manufacture cough expectorants have been reported.<sup>9</sup> The outcome of toxin-mediated ARF is usually satisfactory, as long as the offending agent is promptly recognized and discontinued.

Patients with G-6-PD deficiency, following exposure to a variety of drugs, most notably antimalarials, sulfonamides, nitrofurantoin and naphthaquinolones, and occasionally infections may develop acute intravascular hemolysis. Rapid onset of pallor, weakness, mild jaundice and hemoglobinuria is characteristic. Renal tubular damage is indicated by elevation of blood urea and creatinine.

HUS is an important cause of ARF in children.<sup>2</sup> HUS in India is mostly related to intestinal infection with *Shigella dysenteriae* or enterohemorrhagic *E. coli*.<sup>10</sup> Most patients have marked oliguria; severe renal involvement with cortical necrosis and high mortality is not uncommon. While the incidence of *Shigella* dysentery related HUS has shown a decline during the last few years, there has been an increase in the incidence of D-HUS. The major causes of D-HUS are acquired or inherited disorders of complement regulation and deficiency of von Willebrand protease (ADAMTS13 protein).<sup>11</sup> Deficiency of this protease results in large uncleaved aggregates of platelets resulting in increased capillary occlusion especially in the glomeruli resulting in HUS or thrombotic thrombocytopenic purpura.

GN following infection with *Streptococcus pyogenes*, occasionally *Staphylococcus epidermidis* and *S. aureus*, and rarely other organisms may result in sudden onset of oligoanuria, hypertension, hematuria and azotemia. Crescentic GN, characterized by a rapidly progressive renal failure may occur in a number of conditions (post-infectious, associated with vasculitis, membranoproliferative GN, lupus nephritis and rarely secondary to anti-glomerular basement disease).

Acute tubulointerstitial nephritis due to a hypersensitivity reaction to one of the several drugs (e.g., ampicillin, cephalosporins, sulfonamides, cotrimoxazole, quinolones, NSAIDs, cimetidine, captopril and phenytoin) may occasionally cause ARF. The patient may have fever, arthralgia, rash and eosinophilia; urine microscopy may show eosinophils. Several liver diseases (advanced cirrhosis, fulminant hepatitis and Reye syndrome) may lead to profound renal hypoperfusion and ARF (hepatorenal syndrome). Urine examination shows low urinary sodium and high urine osmolality. The prognosis is poor, because of the seriousness of the underlying hepatic disease. ARF is rarely a direct cause of mortality.

**Postrenal ARF:** Obstruction to the urinary tract occurs from congenital malformations like bilateral pelviureteric junction obstruction, bladder outlet obstruction due to posterior urethral valves and bilateral obstructive ureteroceles. Bladder or urethral obstruction may be secondary to calculi, blood clots and pus debris. It is important to identify post obstructive ARF early so that the obstruction is relieved promptly.

### CLINICAL FEATURES

The child with ARF may have altered sensorium and convulsions due to advanced uremia or hypertensive encephalopathy. The breathing may be rapid and deep due to acidosis. There may be peripheral or pulmonary edema. Blood pressure is often elevated, or there may be hypotension indicating volume depletion. Features that suggest an underlying cause include a history of fluid or blood loss with severe dehydration (ATN); edema, hematuria and hypertension (acute GN); dysentery, pallor and petechiae (HUS), or a history of sudden passage of dark red urine and jaundice (acute intravascular hemolysis). A history of interrupted urinary stream and a palpable bladder or kidney suggests obstructive uropathy and that of abdominal colic, hematuria and dysuria indicates urinary tract calculi. Anuria may occur in patients with urinary tract obstruction, renal cortical necrosis, bilateral vascular occlusion, severe GN or vasculitis. Non-oliguric renal failure is typically seen in ATN following the use of nephrotoxic antibiotics and radiocontrast agents. Polyuria may occur in partial ureteral obstruction, ARF with pre-existing tubular disorders such as diabetes insipidus, solute diuresis (secondary to hyperglycemia or mannitol infusion), or in hypercatabolic patients receiving a large protein load.

ARF may occasionally be superimposed on chronic renal disease. Features such as failure to thrive and

growth retardation, hypocalcemia, hyperphosphatemia, hypertensive retinopathy, renal osteodystrophy and small contracted kidneys indicate an underlying chronic renal disease. Urinary tract infections, use of nephrotoxic drugs, rapid increase in blood pressure and hypovolemia may precipitate ARF in such cases.

### DIAGNOSTIC APPROACH TO ARF

In a child having oligoanuria, it is important to look for pre-renal factors that lead to renal hypoperfusion. A history of diarrhea, vomiting, fluid or blood loss should be sought and an assessment of fluid intake in the previous 24 h made.

In prerenal ARF renal blood flow and glomerular filtration rate decline, but tubular reabsorption of salt and water continues. Thus, there is oliguria with low urine sodium, high urine osmolality, increased plasma urea/creatinine ratio and low fractional excretion of sodium. The rise in blood urea/creatinine ratio occurs because oliguria with decreased tubular flow results in greatly increased urea reabsorption while that of creatinine is not affected. The level of blood urea (and urea/creatinine ratio) is also elevated when there is increased urea production (e.g., due to excessive breakdown, infections or high-dose steroid therapy). In ATN in a setting of renal hypoperfusion, there is diminished tubular function with a high urine sodium and dilute urine. Of the several indices (Table 15.4) that might differentiate pre-renal from established renal failure, fractional excretion of sodium is most sensitive and reliable. These indices are, however, not useful in patients with non-oliguric renal failure and those receiving diuretics. Some useful investigations aimed at identifying the cause and complications of ARF are listed in Table 15.5. Appropriate investigations should be performed to confirm the diagnosis. A careful peripheral blood smear examination may suggest the diagnosis of HUS. Throat culture for streptococci, ASO titer and other streptococcal antibodies, and serum

**Table 15.4: Indices to differentiate prerenal from established (intrinsic) acute renal failure**

	Prerenal	Intrinsic renal
Urinary sodium (mEq/l)	< 20	> 40
Urinary osmolality (mOsm/kg)	> 500	< 300
Blood urea-creatinine ratio	> 20:1	< 20:1
Urine-plasma osmolality ratio	> 1.5	< 1.0
Fractional excretion of sodium*	< 1	> 3

$$*FENa (\%) = \frac{\text{Urine sodium} \times \text{serum creatinine}}{\text{Serum sodium} \times \text{urine creatinine}} \times 100$$

**Table 15.5: Investigations in patients with acute renal failure****Blood**

Complete blood counts  
 Blood urea and creatinine  
 Electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>)  
 Venous blood gas (pH, bicarbonate)

**Urine**

Urinalysis; culture (if symptoms of urinary infection)  
 Sodium, osmolality, fractional excretion of sodium

**Radiology**

Chest X-ray (for fluid overload, cardiomegaly)  
 Ultrasonography (identify obstruction, dilatation)

**ECG** for hyperkalemia

**Investigations to determine cause**

Peripheral smear examination, platelet and reticulocyte count; blood LDH levels; stool culture (suspected hemolytic uremic syndrome)  
 Blood ASO, complement (C3), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) (suspected acute, rapidly progressive GN)  
 Doppler ultrasonography (suspected arterial or venous thrombosis)  
 Renal biopsy in RPGN or non-resolving renal failure  
 Micturating cystourethrogram (suspected obstruction)

complement should be done in patients suspected to have acute GN. In glomerular and vascular disease, urinary protein is significantly elevated (>1 g/m<sup>2</sup>/24 h) along with red cells and casts. Presence of eosinophils in the urinary sediment suggests interstitial nephritis.

Ultrasonography is the ideal imaging tool in renal failure because of its non-dependence on renal function. It allows visualization of pelvicalyceal system, and assessment of the renal size, structural anomalies and calculi. Renal biopsy is rarely necessary.

**Role of Renal Biopsy**

A kidney biopsy is not needed in most patients with ARF and is rarely necessary in the first 2 weeks of illness. A biopsy is indicated in patients suspected to have rapidly progressive GN, nonresolving acute GN or interstitial nephritis where appropriate specific therapy might be beneficial. The procedure is also necessary in patients with clinical diagnosis of ATN, HUS or non resolving ARF beyond 4 weeks, to determine the renal histology for diagnosis and prognostication.

Patients with severe azotemia (blood urea >180 mg/dL, creatinine >3-4 mg/dL) are at risk of bleeding following renal biopsy. These patients should be dialyzed (peritoneal or hemodialysis), to reduce the

severity of azotemia. Hypertension should be adequately controlled; platelet count and bleeding, clotting and prothrombin time should be normal. Intravenous (0.3 µg/kg) or nasal (2-3 µg/kg) desmopressin (available as nasal spray), administered 60-90 minutes prior to the procedure, is useful in reducing the risk of bleeding.

**MANAGEMENT OF ARF**

In pre-renal ARF, expansion of the intravascular volume leads to improved renal perfusion and increase in urine output. Dehydration is corrected by infusion of 20-30 ml/kg of an isotonic solution (0.9% saline or Ringer's lactate) over 30-60 minutes. During this period, the child's vital signs are monitored and care is taken to avoid overhydration. Central venous pressure (CVP) should be measured to determine the adequacy of fluid replacement if clinical assessment of hypovolemia is difficult. If urine output increases and CVP is still low, infusion may be continued. Once fluid replacement is accomplished, frusemide (2-3 mg/kg) may be given intravenously. This should normally induce a diuresis (urine flow of 2-4 ml/kg over the next 2-3 h if renal tubular function is intact). If these measures fail to induce diuresis, a diagnosis of established ARF is made.

Dopamine, in low dosage (1-3 µg/kg/min), causes renal vasodilatation and increased renal perfusion. The efficacy of low-dose dopamine is controversial and its routine use for prevention of renal failure is not recommended.<sup>12</sup> A recent study on 40 adult patients, used a crossover design to study the effect of dopamine in doses of 2 µg/kg/min on renal resistive indices as measured by ultrasound doppler. The study concluded that while low dose dopamine improved renal vasodilatation in normal subjects, it actually decreased the renal perfusion in patients with acute renal failure.<sup>13</sup> Therapy with intravenous administration of 20% mannitol might result in fluid overload in patients with oliguria and is also not recommended.

**Treatment of Complications**

In a child with ARF, immediate attention should be directed towards detection and management of life-threatening complications. Clinical evaluation includes measurement of blood pressure, fundus examination and a search for signs of congestive heart failure, fluid overload, acidosis and anemia. Initial investigations include estimation of blood levels of hemoglobin, urea, creatinine, sodium, potassium and bicarbonate. An electrocardiogram is done to detect potassium toxicity and an X-ray film of the chest for pulmonary edema.

**Table 15.6: Conservative management of acute renal failure**

Complication	Treatment	Remarks
Fluid overload	<i>Fluid restriction:</i> Insensible losses (400 ml/m <sup>2</sup> /d); add urine output and other losses; 5-10% dextrose for insensible losses; N/5 saline for urine output	Monitor other losses and replace as appropriate, consider dialysis
Pulmonary edema	Oxygen; furosemide 2-4 mg/kg IV	Monitor using CVP; consider dialysis
Hypertension	<i>Symptomatic:</i> Sodium nitroprusside 0.5-8 µg/kg/minute infusion; furosemide 2-4 mg/kg iv; nifedipine 0.3-0.5 mg/kg oral/sublingual <i>Asymptomatic:</i> Nifedipine SR, amlodipine, prazosin or atenolol	In emergency, reduce blood pressure by one-third of the desired reduction during first 6-8 hr, 1/3 over next 12-24 hr and the final 1/3 slowly over 2-3 days
Metabolic acidosis	Sodium bicarbonate (IV or oral) if bicarbonate levels <18 mEq/l	Watch for fluid overload, hypernatremia, hypocalcemia; consider dialysis
Hyperkalemia	<i>Emergency</i> Salbutamol 5-10 mg nebulized Dextrose (10%) 0.5-1 g/kg and insulin 0.1-0.2 U/kg  Calcium gluconate (10%) 0.5-1 ml/kg over 5-10 minutes IV <i>Less urgent</i> Sodium bicarbonate (7.5%) 1-2 ml/kg over 15 minutes Calcium or sodium resonium (kayexalate) 1 g/kg per day	Shifts potassium into cells Shifts potassium into cells Requires monitoring of blood glucose Stabilizes cell membrane; required only in situations of arrhythmias or ECG changes
Hyponatremia	Fluid restriction; if sensorium altered or seizures 3% saline 6-12 ml/kg over 30-90 minutes	Limited role in management Given orally or rectally, can be repeated every 4 hours, effect slow Hyponatremia is usually dilutional; 12 ml/kg of 3% saline raises sodium by 10 mEq/L
Severe anemia	Packed red cells 3-5 ml/kg; consider exchange transfusion	Monitor blood pressure, fluid overload
Hyperphosphatemia	Phosphate binders (calcium carbonate, acetate; aluminum hydroxide)	Avoid high phosphate products: milk products, high protein diets

Table 15.6 summarizes the management of complications that might be present. Besides these measures, patients with fluid overload and uncontrolled hyperkalemia, acidosis and uremia require dialysis.<sup>14</sup>

### Standard Supportive Care

In a child with ARF in whom serious complications are absent or have been adequately treated, standard supportive care is instituted.<sup>1</sup> Management is based on close attention to the intake of fluid and electrolytes, provision of proper nutrition, prevention and treatment of infections, careful monitoring and dialysis.

#### Fluid and Electrolyte Balance

Fluid and electrolyte intake in a patient with ARF should be regulated. The daily fluid requirement amounts to insensible water losses (400 ml/m<sup>2</sup>), urinary output and extrarenal fluid losses. Insensible fluid losses are replaced with 10 percent glucose solution. Urine output should be measured without resorting to catheterization. Urinary losses and those from extrarenal

sources should have their composition analyzed and replaced accordingly. It is preferable to administer the required amounts of fluid by mouth. If there is persistent vomiting, intravenous route may be necessary. Potassium containing fluids should not be given to patients with oliguria.

Ongoing treatment is guided by intake-output analysis, daily weight, physical examination and serum sodium. If fluid in an appropriate volume and composition has been given, the patient should lose 0.5-1 percent of his weight everyday. This weight loss is a result of caloric deprivation and not inadequate fluid therapy. The serum sodium concentration should stay within the normal range. A rapid weight loss and increasing level of serum sodium suggest inadequate free water replacement. On the other hand, an absence of weight loss and reduced serum sodium indicate excessive free water replacement.

#### Diet

Patients with ARF are usually catabolic and have increased metabolic needs. Adequate nutritional

support is desirable with maximization of caloric intake. However, volume restriction necessary during the oliguric phase often imposes severe limits on the caloric intake. A diet containing 0.8-1.2 g/kg of protein in infants and 0.6-0.8 g/kg in older children and a minimum of 50-60 Cal/kg should be given. The latter requirement can be met by adding liberal amounts of carbohydrates and fats to the diet. Once dialysis is initiated, dietary fluid and electrolyte restrictions can be made more liberal. Vitamin and micronutrient supplements are provided.

### *Management of Infections*

Patients with ARF are more susceptible to infections because of depressed immune system induced by azotemia and concomitant malnutrition, and invasive procedures. Various infections (respiratory and urinary tract, peritonitis and septicemia) are the immediate cause of death in majority of patients. All procedures must be performed with strict aseptic techniques, intravenous lines carefully watched, and skin puncture sites cleaned and dressed. Oral hygiene should be ensured.

Sepsis is suggested by hypothermia, persistent hypotension, hyperkalemia and a disproportionate rise of blood urea compared to creatinine. The patient should be frequently examined to detect infection, which may be present without fever. Once infection is suspected, appropriate specimens are cultured and antibiotics started.

### *Use of Medications*

Drugs that increase severity of renal damage or delay recovery of renal function (e.g. aminoglycosides, radio-contrast media, NSAIDs, amphotericin B, glycopeptides) should be avoided. Medications that reduce renal perfusion, e.g. ACE inhibitors and indomethacin should be used cautiously. The dose and dosing interval of antibiotics particularly those, which are nephrotoxic, may need to be modified depending on the severity of renal failure.<sup>14</sup> It is necessary that standard charts be consulted for calculating the GFR appropriate doses.

There is no evidence that treatment with diuretics improves renal function or the prognosis of intrinsic renal failure. Diuretics may be useful in instances where a high urine flow is required to prevent intratubular precipitation as with intravascular hemolysis, hyperuricemia and myoglobinuria. Inappropriate use of loop diuretics may cause ototoxicity, interstitial nephritis, hypotension or persistence of patent ductus arteriosus in the newborn.

### *Dopamine and Other Therapies*

Dopamine at low doses (1-3 µg/kg) induces vasodilatation and a modest natriuresis and diuresis. Review of data, however, suggests that the use of dopamine does not improve renal function, reduce the need for dialysis or decrease mortality.<sup>12,13</sup> Its routine use is currently not recommended. Other experimental therapies including calcium channel blockers, antioxidants, thyroxine, peptide growth factors and cytokines have been used in order to attenuate renal injury or enhance recovery of renal function.<sup>15</sup> Treatment with atrial natriuretic factor and insulin like growth factor-1 has shown beneficial effects in animal studies, but results of clinical trials are disappointing.

### **Monitoring**

Patients with ARF should be closely monitored. Accurate record of intake and output and weight should be maintained. Laboratory tests are done depending upon the stability of the patient's condition, progression of ARF and presence of complications. Careful physical examination should be done at least twice a day or more frequently if necessary.

### **Diuretic Phase in ARF**

The clinical course of ARF is often characterized by 3 phases: oligoanuria, diuresis and recovery. The duration of oliguria may be a few hours to several weeks but in uncomplicated ATN, it usually lasts for 5-10 days. During the diuretic phase, there is a progressive rise in urine output that may reach 2-3 L per day. Such high output is often due to excessive replacement of fluids and overhydration, although, a profound diuresis may be seen following relief from obstructive uropathy.

During the diuretic phase, the levels of blood urea and creatinine usually continue to increase, and decline only after several days. The initial urine has low concentrations of urea and creatinine and contains large amounts of sodium and potassium. Complications such as infections, gastrointestinal bleeding, convulsions and electrolyte abnormalities are frequent during this period. The diuretic phase should be managed by replacement of urinary output with half isotonic saline. Excessive administration of fluid should be avoided.

### **Renal Replacement Therapy**

ARF requiring dialysis can be managed with a variety of modalities, including peritoneal dialysis, intermittent

hemodialysis, and continuous renal replacement therapies (hemofiltration or hemodiafiltration techniques). The choice of dialysis modality to be used in managing a patient is influenced by several factors, including the goals of dialysis, the unique advantages and disadvantages of each modality and availability of resources.

Indications for initiating renal replacement therapy include severe or persistent hyperkalemia ( $>7$  mEq/L), fluid overload (pulmonary edema, severe hypertension), uremic encephalopathy, severe metabolic acidosis, hyponatremia ( $<120$  mEq/L or symptomatic) or hypernatremia. The decision to institute dialysis should be based on an overall assessment of the patient keeping in view the likely course of ARF. A recent systematic review has shown that mortality due to ARF is reduced in critically ill patients if dialysis is instituted at blood urea nitrogen levels beyond 75 mg/dL.<sup>16</sup>

#### *Intermittent Peritoneal Dialysis (IPD)*

The initial renal replacement therapy of choice in sick and unstable patients is often IPD.<sup>16</sup> It is popular because of the ease of initiation and effectiveness in children of all ages, including neonates.

**Peritoneal catheters:** Peritoneal access, in most centers in India, is obtained using a stiff catheter and trocar. While peritoneal dialysis can be effectively performed with these catheters, they should be removed after 48-72 hr, beyond which the risk of infection is very high. The risk of injury to the viscera and infections is considerably less with soft sialastic (Tenckhoff or Cook) catheters, made of silicone rubber or polyurethane which therefore can be used for repeated dialysis for prolonged periods. The standard Tenckhoff catheter needs to be placed surgically but a temporary peel off catheter is available for bedside insertion. The Cook catheter (temporary catheter) is inserted using a guide wire by the Seldinger technique. The catheter should be of appropriate length to allow placement into the most dependant portion of the abdominal cavity without causing a bend or kink. Various intraperitoneal designs are created to prevent outflow obstruction of the dialysate. The soft catheters can easily be used for prolonged peritoneal dialysis up to a month or till renal recovery is achieved.

**PD prescription:** The dialysis prescription depends upon the clinical condition of the patient. The fill volume varies from 30-50 ml/kg (800-1200 ml/m<sup>2</sup>). The standard solution used for acute peritoneal dialysis is hyperosmotic (350-360 mOsm/kg) and formulated primarily to eliminate metabolic waste and maintain

fluid and electrolyte balance. Glucose is the chief osmotic agent and its concentration is about 1.7%. The fluid contains sodium in a concentration of 132-134 mEq/L, chloride 85-107 mEq/L and lactate 35-40 mEq/L. Calcium and magnesium are also present in the fluid. Most of the fluids used for acute PD are potassium free.

In patients with fluid overload, peritoneal dialysis solution containing 2.5-3% dextrose is used to increase ultrafiltration. The dextrose concentration of PD fluid can be increased by adding appropriate amounts of 25% dextrose to the standard PD solution. The initial dialysis cycles are of short duration (10 minutes each for inflow and outflow and 20-30 minutes dwell time). It is important to correctly measure indwell and the drain fluid to estimate the ultrafiltrate. After 10 cycles if potassium levels are normal, potassium chloride (2-3 mEq/L) may be added to the dialysis fluid. Patients who are sick and have severe lactic acidosis are dialyzed using a bicarbonate based dialysate. Heparin (500 U/L) needs to be added to the dialysate solution to prevent clogging of the catheter by fibrin strands and blood clots.

If the indication for dialysis is uremia then prolonged cycles (40-60 minutes) with larger amounts of dialysate fluid help in reducing the urea levels. In most situations 30-40 hours of IPD is sufficient to correct the fluid overload, dyselectrolytemias and uremia.

The dialysate effluent is checked for clarity, cell count and culture. Blood levels of urea, creatinine and electrolyte are measured at the baseline and then monitored frequently.

**Complications:** Complications of PD are primarily related to insertion of the stiff catheter. Bleeding, bowel and bladder perforation has been reported uncommonly. Catheter blockage occurs occasionally and might require maneuvering. The incidence of peritonitis is between 20-30% when the catheter is used for less than 72 hours, but increases significantly (70-80%) thereafter.<sup>17</sup> If the duration of ARF is prolonged and there is a need for renal replacement therapy arises, chronic PD may be performed, either manually (continuous ambulatory peritoneal dialysis; CAPD) or with the use of an automated device (continuous cycling peritoneal dialysis; CCPD). Various types of PD cyclers are available in the market.

#### *Hemodialysis (HD)*

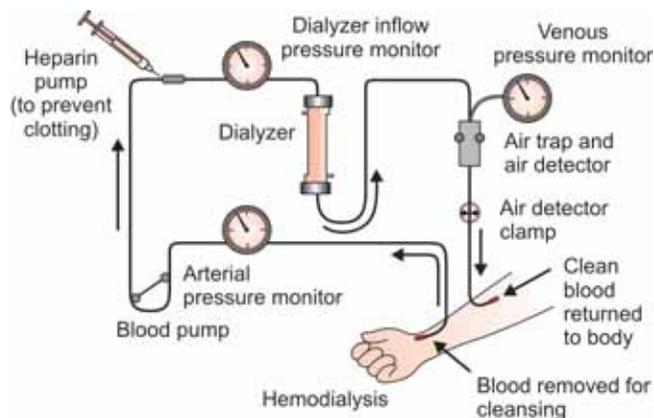
HD is more efficient for correction of fluid and electrolyte abnormalities.<sup>18, 19</sup> However, it is expensive to institute, requires expertise and skilled nursing and is

not available at most centers in our country. It is not suited for patients with hemodynamic instability and bleeding tendency.

**Technique:** The equipment required is the HD machine, pediatric dialyzer with tubings and dialysate fluid. An appropriate vascular access in the patient completes the circuit (Fig. 15.1). The dialysis machine has a blood pump, which regulates the outflow of blood from the child and delivers it to the dialyzer. In children the rate of blood flow is adjusted between 100-200 ml/min depending upon the size of the patient. Younger children (less than 15 kg body weight) may be dialyzed with flow rates of 50-75 ml/min (about 5 ml/kg/min).

Heparin is commonly used for anticoagulation during the procedure. An initial bolus dose of 30-50 IU/kg is given and the doses repeated at hourly intervals. A continuous infusion of heparin, delivered through a pump, can also be used. Heparin free dialysis can also be done in high-risk patients using saline washes or regional heparinization.

The blood flows on one side of the semipermeable membrane of the dialyzer while a concentrate of dialysate, mixed in a fixed proportion with pretreated water (1:38 mostly), flows at a rate of at least 1.5 times the blood pump rate on the other side. After dialysis the blood is returned back to the patient's circulation. The machine also has an ultrafiltrate controller, which determines the removal of free water. The maximum ultrafiltrate removed in children is about 500 ml/hr. Removal of larger amounts in younger children can result in hypotension. The availability of multiple alarms, which can be preset, allows the application of HD for even small children.



**Fig. 15.1:** Hemodialysis circuit. The blood flows out from the child and passes through the dialysis circuit and then is returned back to the patient. The system is equipped with multiple alarms to avoid complications and ensure adequate dialysis

**Vascular access:** The most common type of vascular access for children is a double lumen venous catheter inserted into internal jugular, femoral vein or subclavian vein. The femoral vein is the most easily accessible in children but is prone to infections. Acute complications associated with jugular or subclavian catheterization are almost similar and include pneumothorax, major vessel puncture, pleural or pericardial hemorrhage. Long term subclavian catheterization is associated with a risk of vascular stenosis. Internal jugular catheterization is preferable in most instances.

Temporary HD catheters are made of polyurethane, polyethylene or polytetrafluoroethylene. These materials are rigid at room temperature, which facilitates their insertion but at body temperature they are flexible. Tunneled, cuffed catheters are composed of silicone and silicone elastomers. Catheter lumen sizes vary from 7 to 16 French, their size is determined by the body weight of the child.

**Dialyzer:** The most commonly used dialyzer is the hollow fiber type. The semipermeable membrane is made into thousands of thin fibers bundled together and encased in a polyurethane container. The fibers are made of cellophane, cuprophane or cellulose acetate. Blood flows inside the fibers and dialysate flows around their outer surface. These dialyzers are easy to handle and can be reused up to 4 times after sterilization. However reuse decreases their clearance efficiency. Sodium hypochlorite or bleach and formalin are commonly used for reesterilization of dialyzers. Hollow fiber dialyzers are available in sizes of different surface area varying between 0.5-1.5 m<sup>2</sup>. The surface area of the dialyzer used should be at least 75% of the total body surface and the extracorporeal blood should not exceed 10% of child's blood volume.

**Dialysate:** An ideal dialysate should have a composition similar to extracellular fluid to prevent electrolyte imbalance. The sodium concentration of the fluid varies between 135-140 mEq/L, potassium between 0-4 mEq/L, calcium 3-3.2 mEq/L, magnesium 1-1.5 mEq/L and acetate/ bicarbonate 35-40 mEq/L.

**Dialysis prescription:** Most children are well maintained on dialysis duration of 3-4 hours, three times a week. Children require more dialysis in relation to their body size as compared to adults, due to their higher metabolic needs. Sick patients with fluid overload and hypertension often benefit from daily dialysis initially.<sup>20</sup> The dialysis prescription should be individualized depending upon the nutritional requirement of the child.

**Complications:** The major complications in HD for ARF are related to catheter insertion. Pneumothorax,

pneumomediastinum and hemothorax have been reported with subclavian and jugular catheter insertions. Infections both local and systemic can occur due to central venous catheterization. Besides these, the procedure related complications are hypotension, chills and rigors during the procedure and development of dialysis disequilibrium syndrome.

### *Continuous Renal Replacement Therapies (CRRT)*

CRRT is replacing IPD and conventional HD as the procedure of choice for treatment of AKI in intensive care units.<sup>21</sup> The technique involves the removal of solutes and water by hemofiltration (convection) or dialysis (diffusion) in a continuous mode. Apart from unwanted solutes like sodium, potassium, urea, creatinine, uric acid (particle size <50,000 daltons) the procedure also removes certain cytokines (interleukins, TNF etc). The removal of certain cytokines acts as adjuvant in the management of sepsis related AKI where these are contributing to the ongoing multiple organ damage.

CRRT is any extracorporeal blood purification therapy that can be applied over an extended period of time or aimed at being applied for, 24 hr a day. These therapies are gaining increasing popularity for the treatment of critically ill patients with ARF in developed countries. Various modalities include CAVH (continuous arteriovenous hemofiltration), CVVH (continuous venovenous hemofiltration), continuous venovenous hemodiafiltration (CVVHDF) and slow continuous ultrafiltration (SCUF). CVVHDF is the most preferred modality in ARF secondary to major surgical procedures, burns, heart failure and septic shock especially when conventional HD or IPD are not possible. Continuous hemofiltration provides smoother control of ultrafiltered volume and gradual correction of metabolic abnormalities in unstable patients. Special equipment (PRISMA system, modified hemodialysis machine) and trained staff is necessary to provide CRRT in children.

**CAVH:** The circuit consists of an arterial and venous access, a highly permeable hemofilter and a continuous availability of replacement fluid. The blood pressure of the patient provides the driving force while the hemofilter removes the ultrafiltrate. The filter is highly permeable hence a large volume of ultrafiltrate is produced per unit time. To prevent hypotension and electrolyte depletion a replacement fluid that mimics the extracellular fluid composition is reinfused into the circuit. Blood pumps are not required though

heparinization of blood is essential and this anticoagulation has to be provided throughout the procedure. The need for arterial access, lower mean blood pressures, higher hematocrits, small sized catheters in infants and children limit the use of this modality in pediatric population.

**CVVH:** It is useful in neonates and infants with cardiovascular and abdominal surgery, trauma, shock and multiorgan failure. It has also been used to treat acute metabolic derangements. The procedure involves the addition of blood pump to the circuit, which improves the ultrafiltration of the system. The vascular access is through a central vein (a double lumen hemodialysis catheter inserted in femoral, internal jugular or subclavian veins). A replacement fluid is needed throughout the procedure. Anticoagulation with heparin is also needed continuously.

**CVVHDF:** Use of high flux dialyzers converts the system to arteriovenous or venovenous hemodiafiltration, in which solute clearance is much better (especially urea and creatinine). The circuit is similar to CAVH or CVVH with addition of constant inflow of dialysate through the filter. The replacement fluid is also required in this procedure.

**SCUF:** In this modality slow ultrafiltration occurs through a low flux filter throughout the day. Both dialysate and replacement fluids are not required in this procedure. This modality is primarily useful in a situation of fluid overload in a sick child with relatively preserved renal functions.

CRRT is advantageous since it avoids rapid fluid and electrolyte shifts, provides hemodynamic stability, improves the adequacy of hemodialysis and allows unrestricted fluid and nutrient intake during the therapy. However it requires more experienced personnel, large amounts of dialysate and replacement fluid, and careful patient monitoring in an intensive care setup. The outcome of ARF in patients receiving CRRT in comparison to intermittent hemodialysis is almost similar.<sup>16</sup>

### OUTCOME

The derangements caused by ARF can be reversed by optimal management and appropriate renal replacement therapy. Despite advances in dialysis techniques, morbidity and mortality due to ARF remains high (mortality rates of 30-50%).<sup>22</sup> The eventual recovery and the long term outcome of patients with ARF mainly depend on the underlying condition. The prognosis is good in ATN, intravascular hemolysis, nephrotoxin

mediated damage and diarrhea related ARF, when complicating factors are absent. In D-HUS and crescentic GN, the outcome depends on the severity of the renal injury (poor prognosis with cortical necrosis). Factors associated with high mortality include sepsis, cardiac surgery, multiple organ failure and delayed referral.<sup>16</sup>

In uncomplicated ARF, the oligoanuria may last for 7-10 days at the end of which the urine output may improve and progressively increase. A large proportion of patients require only a single dialysis. If ARF is prolonged beyond 2-3 weeks, multiple dialysis sessions may be required. Maintenance of nutrition and prevention of infections is crucial in these patients.

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# Fluid and Electrolyte Disturbances

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The extraordinarily complicated functions of the human body depend on the preservation of a narrow range of volume and composition of the body fluids. Even slight variations can have dramatic manifestations and consequences. On the other hand, there is an immense capability to maintain homeostasis, i.e. the dynamic equilibrium between the intake of water, inorganic substances and organic molecules, their distribution between body compartments, and their excretion. Before considering the conditions that affect this delicate balance, it is important to discuss the principles of fluids and electrolyte balance in our body.

In children, the influence of growth on physiology is striking in terms of: (a) the body composition of fluids and electrolytes, (b) metabolic turnover, and (c) the progressive maturation of organ systems (e.g. the kidneys) with time.

## PHYSIOLOGY

### Body Water and its Distribution

Water is the largest component of the human body. Total body water (TBW) in healthy, term neonates at birth is 75-80 percent of the body weight; this gradually declines to 60-65 percent by 1 year of age. In adolescent boys, TBW is 60 percent of body weight, while in adolescent girls, it is about 55 percent of the body weight.<sup>1</sup>

The TBW is divided into two main compartments: the fluid inside the cells (intracellular fluid, ICF) and the fluid outside (extracellular fluid, ECF). The ICF remains relatively constant at 40 percent of the body weight, while ECF as a proportion of body weight reduces with age (Table 16.1). The ECF is further divided into the intravascular (or plasma) volume and the interstitial fluid by the capillary membrane. In addition, ECF also includes the transcellular fluid, i.e. cerebrospinal fluid, intraocular fluid, synovial fluid, and pleural and peritoneal fluids.

The composition of ICF is important, as it is the site of all metabolic activity. The ECF regulates the ICF and

**Table 16.1: Changes in body water (% body weight) with age**

Age	Total body water	Extracellular fluid	Intracellular fluid
<i>Neonate</i>			
Preterm	80-85	50-60	25-30
Term	75-80	40-45	35
1-year old	65	25	40-45
<i>Adolescent</i>			
Boy	60	20	40-45
Girl	55	15-20	40

composition, since both ECF and ICF are under osmotic equilibrium.

### Electrolyte Composition of Body Fluids

The electrolyte composition of these compartments is different. The major cation in plasma is sodium ( $\text{Na}^+$ ), with smaller contributions from calcium ( $\text{Ca}^{2+}$ ), potassium ( $\text{K}^+$ ) and magnesium ( $\text{Mg}^{2+}$ ); chloride ( $\text{Cl}^-$ ), bicarbonate ( $\text{HCO}_3^-$ ) and proteins are the major anions. In addition, there are a number of anions that are present, but are not routinely estimated; these undetermined anions constitute the anion gap.

Sodium is the focus of homeostatic mechanisms concerned with maintenance of intravascular volume. If osmolality is maintained, then the water movement tends to follow the  $\text{Na}^+$  movement across various compartments. Therefore, total body  $\text{Na}^+$  and TBW generally parallel one another. By contrast, the dominant cation in ICF is  $\text{K}^+$ , with small amounts of  $\text{Na}^+$  and  $\text{Mg}^{2+}$ . Most of the anions are organic phosphates, proteins, organic acids and sulfate.

It is important to understand three important concepts in fluid and electrolyte therapy namely, cell membrane permeability, osmolality and electroneutrality. Cell membrane permeability refers to the ability of the cell membrane to allow certain substances such as water and urea to pass freely, while charged ions such as  $\text{Na}^+$  cannot freely cross the membrane and are trapped on one side.

Osmolarity is defined as the number of osmotically active particles in 1 liter water in a solution (mOsm/l). Osmolality, on the other hand, refers to the number of osmotically active particles per kilogram water (mOsm/kg). The number of dissolved particles in a solution determines its osmolality and osmolarity. For instance, one molecule of sodium chloride will dissociate into two ions:  $\text{Na}^+$  and  $\text{Cl}^-$ . One mOsm sodium chloride thus yields a two mOsm solution.

Plasma osmolality can be estimated by the following formula:

$$\text{Osmolality (mOsm/kg)} = 2 \text{ Na}^+ + \text{K}^+ \text{ mEq/l} + \frac{\text{glucose mg/dl}}{18} + \frac{\text{urea nitrogen mg/dl}}{2.8}$$

As is evident, the concentration of  $\text{Na}^+$  is the major determinant of plasma osmolality. The normal plasma osmolality ranges from 280-295 mOsm/kg and changes of as little as 1 percent elicit regulatory mechanisms. Effective osmolality (tonicity) refers to the osmolality of a solution when a semi-permeable membrane separates it. Solutes, such as urea, which rapidly diffuse across the membrane and abolish any osmotic gradient, do not contribute to effective osmolality or tonicity. This principle is the major determinant of the balance between plasma and interstitial fluid. Effective osmolality depends on the size of the solute particle and the permeability of the membrane. Oncotic pressure refers to the total osmotic effect of a non-diffusible colloid such as plasma albumin.

Finally, the principle of electroneutrality implies that the total electrical charge of cations equals that of the anions. In conditions where there is loss of bicarbonate anions (e.g. in diarrhea or renal tubular acidosis), chloride is retained leading to a hyperchloremic metabolic acidosis.

### Regulation of the Water Balance

The TBW and plasma osmolality are maintained in a narrow range by regulating the intake and loss of water. Water is available to the body by oral intake, oxidation of fats and carbohydrates, and from release of water during tissue catabolism. The intake of water is governed by the thirst mechanism (controlled by the hypothalamic osmoreceptors that are sensitive to change in plasma osmolality and blood volume). Intravascular volume preservation takes precedence over osmolality. Thus, thirst may occur even when the body water is hypo-osmotic.<sup>2</sup>

The amount equivalent to the intake is lost by the way of insensible water losses (lungs, skin), urine and losses through the gastrointestinal tract. Under normal circumstances, there is no significant control over the extrarenal fluid losses. The renal excretion of water and solutes is under the control of antidiuretic hormone (ADH, the release of which is controlled by changes in plasma osmolality and volume) and natriuretic peptides. Hypovolemia is a stronger stimulus for release of ADH than hyperosmolarity. The renin-angiotensin-aldosterone axis contributes to the regulation of  $\text{Na}^+$ , and thereby, water excretion. In older children and adults, ADH is a more important regulatory mechanism than thirst as water intake is commonly influenced by social and cultural factors rather than physiological needs.

Changes in plasma osmolality, which are determined mainly by plasma  $\text{Na}^+$  concentrations, are sensed by the hypothalamic osmoreceptors. These receptors influence water intake by regulating thirst, and water excretion by regulating the release of ADH. Thus, osmoregulation is primarily achieved by changes in water balance without any significant changes in  $\text{Na}^+$  handling.

On the other hand, volume regulation aims to maintain tissue perfusion. Various sensors located in the carotid sinus, afferent arterioles, and atria detect changes in the effective circulating volume. Urinary  $\text{Na}^+$  excretion is modified to achieve changes in the volume by renin-angiotensin-aldosterone system, sympathetic nervous system, atrial natriuretic peptide and ADH. Thus, the osmoregulatory and volume regulatory pathways are essentially independent except for the overlap involving ADH.

### Normal Requirements of Fluids and Electrolytes

The normal requirements of water and electrolytes consist of the amounts necessary to replace the urinary and insensible water losses and provide water for metabolism. These can be calculated on the basis of body weight, body surface area or the metabolic rate. Of these, the metabolic rate is the most physiologic. The metabolic rate consists of several components: the basal metabolic rate, specific dynamic action, muscular activity and growth.

The 'caloric method' is the most accurate to determine the fluid and electrolyte costs of each activity. Holliday and Segar observed that the insensible loss of water and urinary water loss roughly parallel energy metabolism.<sup>3</sup> The insensible water loss (by evaporation from skin and lungs) is about 40-60 ml per 100 cal metabolized.

The renal water loss varies from 50-70 ml and the stool water loss is 5-10 ml per 100 Cal. On the other hand, the water produced during oxidation of carbohydrates, proteins and fats is about 12-17 ml and tissue catabolism contributes 3 ml per 100 Cal. The net requirement of water is thus 100-110 ml for 100 Cal metabolized. The approximate requirements for Na<sup>+</sup> are 3 mEq/100 Cal, K<sup>+</sup> about 2 mEq/100 Cal and Cl<sup>-</sup> 2 mEq/ 100 Cal that are utilized. Table 16.2 shows the maintenance requirements for fluids based on the caloric method and body weight.<sup>3</sup>

The maintenance requirements are met using N/5 saline in 5 percent dextrose with 1 ml of 15 percent KCl per 100 ml intravenous fluid. This fluid provides 30 mEq Na<sup>+</sup> and 20 mEq K<sup>+</sup> per liter of the solution. The above method does not take into consideration patients with high caloric expenditure or those with ongoing fluid losses. The fluid requirements should be modified in such situations (Table 16.3).

The maintenance fluid and electrolyte requirement can also be calculated using the body surface area. Based on body surface area, the daily fluid requirement is 1500 ml per m<sup>2</sup>, Na<sup>+</sup> 50 mEq per m<sup>2</sup>, K<sup>+</sup> 30 mEq/m<sup>2</sup> and Cl<sup>-</sup> 30 mEq/m<sup>2</sup>.

The following issues should be considered while calculating the requirements for maintenance fluids and electrolytes: (i) Is insensible water loss normal? (ii) Is the urine output as expected? (iii) Are there any abnormal losses? (iv) Is there an altered metabolic rate? (v) Is Na<sup>+</sup> and K<sup>+</sup> homeostasis normal?

The patient's age and weight are recorded and fluid requirement determined using Tables 16.2 and 16.3.

Oral fluid therapy is preferred provided the child is hemodynamically stable and is able to accept and retain fluids given orally. If this is not the case and/or there is significant electrolyte imbalance, fluids are administered intravenously. Intravenous fluids are usually administered to: (i) Expand the intravascular volume, (ii) Correct the fluid-electrolyte imbalance and/or (iii) Compensate for the ongoing losses.

**Table 16.2: Fluid requirements in relation to body weight**

Body weight	Fluid requirement
Up to 10 kg	100 ml/kg
11-20 kg	1000 ml plus 50 ml/kg above 10 kg
>20 kg	1500 ml plus 20 ml/kg above 20 kg

For acutely expanding the intravascular volume, intravenous fluid solutions that can be used safely, include normal (0.9%) saline and Ringer's lactate. These crystalloid solutions are limited by the short retention time of their solutes. When isotonic sodium-containing solutions are given intravenously, only 15-30 percent of administered salt and water remains in the intravascular space while the remainder contributes to the interstitial fluid.<sup>4</sup> Hypertonic solutions, such as 3 percent saline, permit greater expansion of circulating blood volume with lower fluid load and less edema. Infusion of colloids such as albumin or blood products, which have some oncotic pressure by virtue of their protein content, has a longer lasting effect. This issue is addressed in detail in another chapter.

**Fluid and Electrolyte Disturbances**

Of various fluid and electrolyte disturbances, diarrheal dehydration is the commonest. This is discussed elsewhere.

Regular clinical evaluation and relevant investigations are important for monitoring a child receiving parenteral fluid therapy. Investigations that are useful in working up a child with suspected fluid or electrolytes disturbance are listed in Table 16.4. Clinical evaluation of the hydration status and peripheral perfusion should be performed every 8-12 hours, and more frequently in an unstable child. Urine output charting should be done every 6-8 hours. In some patients, particularly those with low urine output, urine specific gravity may aid in fluid management. Serum electrolytes should be estimated every 24-48 hours and

**Table 16.3: Clinical states requiring modification of fluid requirements**

Condition	Problem	Compensation
Hyperventilation	Increased insensible respiratory water loss	Requirement increased by up to 20 ml/100 Cal
Tracheostomy	Increased insensible respiratory water loss	Increased requirement
Fever	Increased caloric expenditure and sweat loss	Increase 10% per °C above 38°C
Increased physical activity	Increased calorie expenditure	Increase up to 30% for extreme activity
Oliguria	Decreased renal losses	Decrease fluid based on reduction in urine output
Other fluid losses	Sweating, gastrointestinal or blood losses	Replace with equal volume of similar fluid

**Table 16.4: Work-up of a child with suspected fluid and electrolyte disturbance**

Serum electrolytes	Provide information about Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> and anion gap.
Blood urea, creatinine	Blood creatinine is a useful indicator of renal dysfunction. Raised blood urea may reflect intravascular volume depletion.
Urine examination	Specific gravity is related to the hydration status and presence of abnormal solute, e.g. glucose. Urinary electrolytes and specific gravity are useful in assessing patients with renal dysfunction.
Plasma and urine osmolality	Osmolal gap (difference between measured and calculated plasma osmolality) >10 mOsm/kg suggests presence of additional substances, e.g. mannitol. Plasma osmolality shows whether or not a patient is in an isotonic state. Urine osmolality helps in evaluation of the concentrating capacity of kidneys.
Serum protein and albumin	Total protein and albumin levels determine the intravascular oncotic pressure. Reduced in liver disease, nephrotic syndrome and malnutrition.
Blood gases	Provides information on blood pH, oxygen and carbon dioxide tension and bicarbonate.

more frequently, if there is dyselectrolytemia. Blood urea and creatinine levels should be measured every other day.

### DISORDERS OF SODIUM HOMEOSTASIS

The concentration of Na<sup>+</sup>, the main cation of ECF, determines the intravascular and interstitial volumes. The dietary intake of salt varies with food habits. Normal Na<sup>+</sup> losses in feces and sweat are small and kidney is the chief regulator of Na<sup>+</sup> excretion.

The ECF concentration of Na<sup>+</sup> is maintained around 135-145 mEq/l and the ICF concentration 10 mEq/l. The latter is achieved by active efflux of Na<sup>+</sup> from the cells mediated by magnesium dependent Na<sup>+</sup>-K<sup>+</sup>-ATPase system. Changes in Na<sup>+</sup> concentration of serum are followed by parallel changes in its concentration in ECF and interstitial fluid. The Na<sup>+</sup> concentration of transcellular fluids (gastrointestinal secretions, cerebrospinal fluid, pleural, peritoneal and synovial fluid) is highly variable, as these fluids do not have a simple diffusion relationship with plasma.

Retention or loss of Na<sup>+</sup> is usually accompanied by a proportionate change in water handling, leading to expansion or shrinkage of ECF volume, but with little changes in serum Na<sup>+</sup> concentration. In disease states, inappropriate retention or loss of water or Na<sup>+</sup>, or a combination of both may lead to hypo- or hypernatremia. Alterations in levels of serum Na<sup>+</sup> that arise slowly or are chronic in nature tend to be better tolerated clinically than acute alterations. Chronic or slow changes allow for maximal counter-regulation that involves loss or gain of organic osmolytes (idiogenic osmoles) and fewer clinical sequelae. On the other hand, profound acute alterations are often accompanied by neurologic complications.

### Hyponatremia

Hyponatremia, serum Na<sup>+</sup> level below 130 mEq/l is a common abnormality detected in children hospitalized after the newborn period.<sup>5</sup> In a majority of the cases, hyponatremia is mild and asymptomatic and does not require treatment. However, in occasional situations, especially when the serum Na<sup>+</sup> rapidly falls to very low levels, neurological symptoms and even irreversible brain damage may occur.

#### Causes

Important conditions that lead to hyponatremia are listed in Table 16.5. Hyponatremic dehydration is the most common condition, resulting from replacement of acute diarrheal fluid losses with plain water or very hypotonic solutions. Nephrotic syndrome, congestive cardiac failure and syndrome of inappropriate ADH

**Table 16.5: Causes of hyponatremia**

Circulating volume	Urinary Na <sup>+</sup>	
	<20 mEq/l	>20 mEq/l
Decreased	Gastroenteritis Chronic diuretic therapy Burns	Adrenal insufficiency Salt wasting states Renal tubular acidosis Obstructive uropathy Diuretic phase of ATN
Normal or increased	Congestive heart failure Cirrhosis liver Nephrotic syndrome	Renal failure SIADH Compulsive water drinking Excessive fluid therapy

ATN: Acute tubular necrosis; SIADH: Syndrome of inappropriate ADH secretion

secretion are the other important causes. Hyponatremia also is frequently observed in acute or chronic renal failure, when excessive fluids have been given.<sup>6</sup>

In the absence of accumulation of abnormal solutes, hyponatremia is associated with low serum osmolality. Occasionally, hyponatremia results from shift of water from cells due to solutes restricted to the ECF (e.g. mannitol); the osmolality is increased in these cases. Similarly, hyperglycemia, by causing water to move out of cells, leads to hyponatremia. An increase of blood glucose by 100 mg/dl reduces the serum  $\text{Na}^+$  concentration by 1.6 mEq/l. Excessive loss of  $\text{K}^+$  may also cause hyponatremia as  $\text{Na}^+$  shifts into the cells in exchange for  $\text{K}^+$ .

#### *Pseudohyponatremia*

Falsely low levels of serum  $\text{Na}^+$  may be obtained if it contains very high concentrations of lipids. The true  $\text{Na}^+$  value can be measured by separating the lipids and measuring  $\text{Na}^+$  in plasma water. Measurement of plasma osmolality is of help since the osmolality depends upon the number of solutes in plasma water and is not affected by hyperlipidemia. An accurate osmometer is used to measure plasma osmolality. If the measured osmolality exceeds the calculated osmolality (see above) by 10 mOsm/kg, either pseudohyponatremia is present or the plasma contains some unmeasured substance (e.g. mannitol, ethanol or acetone).

#### *Pathophysiology of Neurological Complications*

The intrinsic characteristics of the blood brain barrier cause the brain to respond to osmolal gradients as if it were a single cell. Most solutes, including  $\text{Na}^+$ , take several hours to equilibrate across the blood brain barrier. Because of the free movement of water, brain responds to hypo-osmolality by swelling and to hyperosmolality by shrinking. The brain when compared to the other organs is more likely to experience a change in its total size in response to an acute change in plasma osmolality.

Since skull is a rigid structure, increasing cerebral edema may lead to severe intracranial hypertension and brainstem herniation. In infants with open fontanelles and unfused sutures, there is relative protection from a rapid increase in intracranial pressure. Children are more prone to neurological damage due to hyponatremia since (i) the ratio of the brain to skull size is such that less room exists for expansion of the pediatric brain in skull than in adults, and (ii) the relative amount of cerebrospinal fluid is

lower in children than in adults. Adults thus have more space for brain to expand than do children.

The pathological findings in severe hyponatremia include cerebral edema, and demyelinating lesions in the basal ganglia, periventricular white matter and cerebral cortex. Central pontine myelinosis is characterized by demyelination within the central portion of basal pons with sparing of axis cylinders and neurons. Clinical manifestations of pontine myelinosis include spastic quadriplegia, pseudobulbar paralysis and behavioral changes without focal abnormalities. The lesions can be detected on CT and MRI scanning. There is considerable controversy on whether this condition occurs as a consequence of hyponatremia or its treatment, since it has been associated with both.<sup>7</sup>

In chronic hyponatremia brain water tends to gradually decrease. Initially there is extrusion of  $\text{Na}^+$  from the cells. Subsequently, there may be extrusion of idiogenic osmoles (e.g. taurine). Symptomatic hyponatremia usually occurs relatively acutely in a previously well patient or when serum  $\text{Na}^+$  rapidly falls further in a patient with chronic hyponatremia.

#### *Clinical Features*

Symptoms are related to the severity as well as the rapidity of development of hyponatremia. A very gradual fall in serum  $\text{Na}^+$  level may not cause any abnormality even at levels below 110 mEq/l. Apathy, anorexia, nausea, vomiting, agitation, headache, altered sensorium, convulsions and coma are the usual manifestations. With the development of cerebral edema and a rise in intracranial pressure, brainstem herniation may occur causing respiratory depression and apnea.

#### *Evaluation*

A careful clinical evaluation of the state of ECF volume is important. Serum and urinary electrolytes and osmolality should be measured (Table 16.4).

The rapidity of development of hyponatremia, whether acute or chronic, should be determined. Symptoms ascribed to low serum  $\text{Na}^+$  should be noted and the state of hydration assessed. Hypovolemia is indicated by thirst, dry mucous membranes, decreased skin turgor and hypotension. The urinary  $\text{Na}^+$  concentration is low, unless adrenal insufficiency or renal salt wasting has led to hyponatremia. The most common cause of normovolemic hyponatremia is the syndrome of inappropriate ADH secretion.

### Treatment

In a patient with hyponatremic dehydration, the foremost aim is to restore the circulatory adequacy with 20-40 ml/kg of normal saline or Ringer's lactate. In patients with symptomatic hyponatremia (presence of lethargy, altered sensorium, seizures) serum Na<sup>+</sup> level should be rapidly increased by intravenous infusion of 3 percent saline (514 mEq Na<sup>+</sup>/L), 5-6 ml/kg body weight over 10-15 minutes.<sup>8</sup> A rapid increase in the serum Na<sup>+</sup> level by 4-5 mEq/l usually causes relief of symptoms. If clinical improvement does not occur, an additional 3-4 ml/kg may be administered. The amount of Na<sup>+</sup> needed to raise the serum Na<sup>+</sup> by a given amount can be calculated by the formula.

$$\text{mEq Na}^+ \text{ required} = [\text{desired} - \text{actual serum Na}^+] \times 0.6 \times \text{body weight (kg)}$$

Further increase in serum Na<sup>+</sup> should be at a rate of 0.5 mEq/L per hour. The increase in plasma Na<sup>+</sup> concentration should not exceed 10-12 mEq/L in the first 24 hours. If neurological symptoms persist the possibility of some CNS pathology (hemorrhage, infections) should be considered.

Current evidence suggests that it is safe to raise the plasma Na<sup>+</sup> concentration in asymptomatic patients by 10-12 mEq/l on the first day and 18 mEq/l over the first two days.<sup>9</sup>

Water intake should be restricted in patients with an expanded ECF volume (e.g. cardiac or renal failure) or those who have received excessive fluids. In some patients, administration of diuretics is required. Some hyponatremic patients with congestive heart failure may benefit from a combination of a loop diuretic and an ACE inhibitor.<sup>10</sup>

### Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

SIADH is an important cause of hyponatremia in hospitalized patients.

#### Clinical Features

SIADH is characterized by hyponatremia and hyposmolality, oliguria, modest expansion of body fluid volume and mild urinary Na<sup>+</sup> wasting. The urine osmolality is inappropriately high. The blood pressure and renal function are normal and a cardiac or endocrine disorder is absent. There is no edema. There may be no abnormal clinical findings and hyponatremia is often detected incidentally. Occasionally the serum Na<sup>+</sup> levels are very low (below 120 mEq/l) and lead to sensorial disturbances and seizures.

**Table 16.6: Important causes of syndrome of inappropriate ADH secretion**

#### Neurologic disorders

Tuberculous meningitis	Pyogenic meningitis
Brain abscess	Tumor
Head injury	Subarachnoid hemorrhage
Guillain-Barre syndrome	Status epilepticus

#### Drugs

Cyclophosphamide	Vincristine
Barbiturates	Carbamazepine
Chlorpropamide	Indomethacin

#### Pulmonary disorders

Tuberculosis	Pneumonia
Chronic obstructive disease	Positive pressure ventilation
Acute respiratory failure	

#### Miscellaneous

Hodgkin's disease	Postoperative patient
Malignancies	

#### Causes

Intracranial infections and pulmonary diseases are the common causes of SIADH (Table 16.6). Hyponatremia in the postsurgical period might be due to SIADH caused by administration of anesthetic agents.

#### Diagnosis

The criteria for diagnosis of SIADH are: (i) Low plasma Na<sup>+</sup> and osmolality, (ii) Urine that is not maximally dilute (specific gravity >1.015), (iii) urinary Na<sup>+</sup> concentration >40 mEq/l, (iv) normal renal function, (v) normovolemia, and (vi) normal acid-base and K<sup>+</sup> balance. Other causes of hyponatremia such as cardiac failure, adrenal and thyroid deficiency and severe hypovolemia (which leads to excessive ADH release) should be excluded. Urinary Na<sup>+</sup> excretion is low in these conditions.

#### Treatment

The treatment of SIADH consists of restriction of water intake, which will gradually lead to a rise in the serum Na<sup>+</sup> level. However, if neurological abnormalities are present, 3 percent saline should be slowly infused to partly correct hyponatremia. Intravenous frusemide in a dose of 1-2 mg/kg will cause excretion of free water and increased levels of serum Na<sup>+</sup>. Drugs like lithium or demeclocycline that inhibit ADH effect on the kidney are not recommended in children. Urinary Na<sup>+</sup> and K<sup>+</sup> losses should be measured and replaced.

### Cerebral Salt Wasting

The syndrome of cerebral salt wasting (CSWS) is characterized by the development of excessive natriuresis and subsequent hyponatremic dehydration in patients with intracranial diseases.<sup>11</sup> Differentiation of this condition from the syndrome of inappropriate secretion of ADH is important.

The syndrome of cerebral salt wasting occurs in the setting of an acute disease involving the central nervous system, e.g. head injury, brain tumor, intracranial surgery, intracerebral hemorrhage and tuberculous meningitis. The exact mechanism underlying renal salt wasting is unclear. It is hypothesized that urinary  $\text{Na}^+$  loss results from an exaggerated renal pressure-natriuresis response caused by increased activity of the sympathetic nervous system and dopamine release. Another hypothesis involves the presence of circulating natriuretic factors in patients with cerebral salt wasting.

The clinical features are those of hyponatremia. The urine is dilute and its flow rate high (unlike urine that is concentrated and with reduced flow in patients with SIADH). Urine sodium concentrations are typically  $>40$  mEq/l. However, urinary sodium excretion (product of urine sodium concentration and urine volume) is high in patients with cerebral salt wasting and normal in SIADH. This results in a negative sodium balance in the former. Serum uric acid concentrations are low in patients with SIADH but normal in cerebral salt wasting.<sup>12</sup>

The management of CSWS comprises correction of volume depletion and hyponatremia, and replacement of ongoing urinary fluid and electrolyte losses using intravenous fluids. Once the patient is stabilized, enteral salt supplementation can be considered. Fludrocortisone, which enhances sodium reabsorption in the renal tubule resulting in expanded extracellular fluid volume, may be beneficial in some cases.<sup>13</sup>

### Adrenal Insufficiency

Hyponatremia is a common complication of adrenal insufficiency, chiefly attributed to cortisol deficiency, diarrhea, vomiting and renal losses (due to lack of aldosterone). Cortisol deficiency results in an increased release of ADH, reduced water excretion and hyponatremia. Replacement of cortisol improves water excretion and increases plasma  $\text{Na}^+$ .<sup>14</sup> A mineralocorticoid, such as fludrocortisone, may be required to correct the urinary  $\text{Na}^+$  losses and hyperkalemia that are commonly seen. Administration of fludrocortisone alone does not normalize renal water excretion and is not required in conditions that have normal aldosterone.

### Hypernatremia

Hypernatremia, defined as serum  $\text{Na}^+$  level above 150 mEq/l, represents net water deficit in relation to  $\text{Na}^+$  stores, which can result from a net water loss or hypertonic  $\text{Na}^+$  gain. Majority of patients with hypernatremia have net water loss; this may occur in absence of  $\text{Na}^+$  loss (pure water loss) or in its presence (hypotonic fluid loss). Hypertonic  $\text{Na}^+$  gain is usually due to therapeutic interventions or its accidental administration (Table 16.7).

The condition is mainly encountered in children with diarrhea and dehydration. It is more common in children who have been given oral or parenteral fluids having a high  $\text{Na}^+$  content. It is more common in summer months when insensible losses are increased. Other causes of hypernatremia include substitution of salt for sugar in preparation of formula feeds and accidental ingestion of salt. Excessive intake of  $\text{Na}^+$  leads to increase in body  $\text{Na}^+$  and extracellular fluid volume.

Hypernatremia results in a movement of organic acids and free  $\text{H}^+$  ions into the extracellular fluid, leading to acidosis. Hyperglycemia may occur due to inappropriately low levels of insulin. Hyperosmolality of the ECF causes a shift of water from the cells, which in the case of brain, leads to distension of cerebral vessels. These may rupture causing intracerebral, subdural or subarachnoid hemorrhage. Idiogenic osmoles are generated in the cells in patients with sustained and severe hypernatremia.<sup>15</sup> This is a protective phenomenon, which reduces the efflux of water, thereby preventing the consequences of hypernatremia.

**Table 16.7: Causes of hypernatremia**

#### Water loss

*Increased insensible losses*

Increased sweating, respiratory infections, burns

*Gastrointestinal loss*

Osmotic diarrhea, infectious diarrhea

*Renal loss*

Diabetes insipidus (central/nephrogenic), osmotic diuresis

#### Hypothalamic disorders

Primary hypodipsia

#### Sodium excess

Administration of hypertonic saline or sodium bicarbonate

#### Salt poisoning

Improperly prepared oral rehydration solution

### Clinical Features

Infants with hypernatremic dehydration have relatively well preserved extracellular fluid volume. Features of hypovolemia and shock are less prominent. Children with about 10 percent loss of body weight have reduced skin turgor and a characteristic doughy feel. Infants may be irritable or lethargic and have a high-pitched cry. Neurological complications and permanent cerebral damage are common. Seizures may be present before the institution of fluid therapy or develop subsequently.

### Evaluation

A detailed history, measurement of urinary osmolality and urinary  $\text{Na}^+$  excretion are useful in determining the etiology. Patients showing hypernatremia with urine osmolality less than 800 mOsm/kg usually have at least a partial defect in ADH release or action. In diabetes insipidus, urinary osmolality is usually less than 300 mOsm/kg. Desmopressin administration increases urine osmolality only if there is impaired endogenous secretion. Patients with nephrogenic diabetes insipidus or osmotic diuresis do not show increased urine osmolality following desmopressin administration.

Urinary  $\text{Na}^+$  is usually below 25 mEq/l when hypernatremia is due to water loss but well above 100 mEq/l if there is  $\text{Na}^+$  overload.<sup>16</sup> If diabetes insipidus is suspected, a water deprivation test should be carried out.<sup>17</sup>

### Treatment

The management of hypernatremia requires correction of the underlying cause and the prevailing hypertonicity. Patients showing features of severe dehydration or shock are managed with parenteral administration of normal saline or Ringer's lactate.

In most cases, hypernatremic dehydration can be treated with oral rehydration solution. Twice the clinically estimated deficit is administered either using the standard WHO oral rehydration solution, or the standard WHO solution and water in a ratio of 2:1 over 12-24 hours. Correction of hypernatremic dehydration with oral fluids is as effective as parenteral therapy but with considerably lower risk of complications.<sup>18</sup>

If there is persistent vomiting, a high purge rate or altered sensorium, intravenous fluid therapy is preferred. The volume to be administered is calculated by adding the estimated fluid deficit (containing 80-100 mEq/l  $\text{Na}^+$ ) to the maintenance fluid requirement for 48 hours. The total volume is then administered

over 48 hours. A solution containing 5 percent dextrose and 50 mEq/l  $\text{Na}^+$  as a combination of chloride and bicarbonate is usually sufficient. The aim is to decrease the serum  $\text{Na}^+$  level gradually, by not more than 15-20 mEq/l in 24 hours. Ongoing losses should be replaced appropriately. It is important to infuse the fluid slowly, monitor urine output and watch for evidence of expansion of the extracellular fluid volume, which may cause cardiac failure. In case seizures occur during rehydration, and serum  $\text{Na}^+$  level has been lowered too rapidly, 3-5 ml/kg of 3 percent saline may be slowly injected.

There can be another approach for calculating the fluid requirement. First, the fluid deficit is estimated. This can be done if the pre-illness weight is known or can be estimated by clinical examination. Of the total deficit, free water deficit is calculated.

$$\text{Free water deficit} = [\text{Observed Na}^+ - 145] \times 4 \text{ ml/kg} \times \text{body weight (kg)}$$

The remainder, i.e. the difference between total deficit and free water deficit is the solute fluid deficit (containing about 80-100 mEq/l  $\text{Na}^+$ ). The total fluid deficit (free water deficit and the solute fluid deficit) is added to the maintenance fluid requirement and administered over 24 hours.

For example, a 10 kg child has a deficit of 1 l and serum sodium of 160 mEq/l. The free water deficit in this child is  $[160-145] \times 10 \times 4 = 600$  ml. The remaining 400 ml fluid should have 100 mEq/l  $\text{Na}^+$ . Combining the two subgroups, we need to replace 1000 ml fluid containing 40 mEq  $\text{Na}^+$ . The maintenance fluid requirement for 24 hours, i.e. 1000 ml of N/5 saline in 5 percent dextrose is added to the deficit and the total fluid (2000 ml with 75 mEq  $\text{Na}^+$ ) infused over 24 hours. This method appears to be physiologically sound as it takes into account the severity of hypernatremia and free water deficit.

Hypocalcemia is an occasional complication during treatment of hypernatremia and should be treated with administration of calcium gluconate. Severe acute hypernatremia (as in salt poisoning) should be treated with urgent dialysis (see below).

### Hypernatremia in Diabetes Insipidus

Increasing the oral intake of water is usually sufficient in hemodynamically stable children. Administration of intravenous fluids containing 5 percent dextrose causes glucosuria and further loss of free water should be avoided. If there is peripheral circulatory failure, immediate measures are taken to expand the intravas-

cular volume with isotonic solution. Thereafter, administration of fluids as calculated above along with administration of desmopressin is recommended.

An appropriate dose of vasopressin or desmopressin is the cornerstone of management of central diabetes insipidus. Intranasal desmopressin may be used in conscious patients. In unconscious patients, intravenous vasopressin infusion is started at 0.5 mU/kg per hour and titrated upward to achieve the desired effect.<sup>19</sup>

#### *Salt Poisoning/Severe Hyponatremia (Plasma Na<sup>+</sup> >180 mEq/l)*

In cases of salt poisoning, peritoneal dialysis is performed using a 8-10 percent dextrose solution without electrolytes.<sup>20</sup> Three cycles one hour apart are usually sufficient. Simultaneously fluids calculated as above should be administered. In patients with hyponatremia that has developed rapidly over a period of hours, rapid correction improves the prognosis without increasing the risk of cerebral edema. Severe hyponatremia due to causes other than salt poisoning, particularly if present for some time should be corrected gradually using commercially available peritoneal dialysis fluid (1.7-3%).

### DISORDERS OF POTASSIUM HOMEOSTASIS

Potassium (K<sup>+</sup>) is the chief cation of intracellular space. Of the total body K<sup>+</sup>, over 90 percent is in the intracellular compartment, mostly in the muscle; the intracellular concentration is about 150 mEq/l of cell water. Its plasma concentration is closely maintained between 3.8-5.0 mEq/l (higher in newborn and preterm infants) and depends upon total body K<sup>+</sup> as well as its distribution between intracellular and extracellular compartments. The ECF K<sup>+</sup> modulates the electrical potential across cell membranes.

The high concentration of K<sup>+</sup> inside the cells is due to active influx of the ion mediated by the enzyme Na<sup>+</sup>-K<sup>+</sup>-ATPase. This enzyme is present in all cell membranes and pumps in two molecules of K<sup>+</sup> in exchange for 3 molecules of Na<sup>+</sup>. K<sup>+</sup> efflux from the cells is stimulated by exercise, decrease in extracellular pH and increase in plasma osmolality. Its movement into the cells is increased by a rise in extracellular pH and by insulin, epinephrine, thyroxine and growth hormone. Insulin increases Na<sup>+</sup>-K<sup>+</sup>-ATPase activity and stimulates K<sup>+</sup> uptake within minutes. Beta-adrenergic agonists, such as salbutamol and terbutaline stimulate movement of K<sup>+</sup> into the cells.

K<sup>+</sup> is chiefly excreted by the kidney. Fecal losses are small, but may increase with high K<sup>+</sup> intake or when

renal function is impaired. K<sup>+</sup> loss in sweating is normally negligible. Renal excretion of K<sup>+</sup> is slow with only 50 percent of an ingested load excreted in the first 4 hours. The major adaptation to a K<sup>+</sup> load is a shift of K<sup>+</sup> into the intracellular pool.

An intake of 2 mEq/kg/day of K<sup>+</sup> is adequate. Dairy products, foods from animal sources, some green vegetables and fruits are rich in K<sup>+</sup>.

### Hypokalemia

Important causes of hypokalemia (plasma K<sup>+</sup> below 3.5 mEq/l) are listed in Table 16.8. Common conditions such as protein energy malnutrition, chronic diarrhea, malabsorption and excessive diuretic use can easily be diagnosed. Diarrheal stools may contain as much as 15 mEq/l of K<sup>+</sup>, while gastric juice contains about 10 mEq/l. In hypokalemia due to gastrointestinal or other non-renal conditions (e.g. excessive sweating, severe burns), the urinary K<sup>+</sup> concentration is below 10-20 mEq/l. The hypokalemia that occurs with vomiting or nasogastric suction is not caused by extrarenal losses from the gastrointestinal tract alone but is also consequence of renal loss that occurs secondary to metabolic alkalosis and secondary hyperaldosteronism.

Important tubular disorders associated with excessive K<sup>+</sup> losses in urine (spot urinary K<sup>+</sup> >30 mEq/l) include Fanconi syndrome, distal renal tubular acidosis and Bartter syndrome. Excessive use of diuretics, mineralocorticoid excess and situations when large amounts of Na<sup>+</sup> are presented at the distal Na-K exchange sites lead to increased urinary K<sup>+</sup> losses and hypokalemia. Occasionally hypokalemia may result from a shift of K<sup>+</sup> from the extracellular to intracellular

**Table 16.8: Causes of hypokalemia**

<i>Shift from extracellular to intracellular compartment</i>
Insulin, beta-adrenergic agonists, alkalosis
Periodic paralysis (hyperthyroidism, familial)
<i>Decreased intake</i>
Protein energy malnutrition
<i>Gastrointestinal and skin losses</i>
Gastroenteritis, villous adenoma, congenital chloridiarrhea
Excessive sweating, severe burns
<i>Renal losses</i>
Medications: Diuretics, amphotericin B
Vomiting, nasogastric suction
Acidosis: Renal tubular acidosis, diabetes mellitus
Hyperaldosteronism: Primary, secondary
Bartter, Gitelman syndromes
Liddle syndrome
Magnesium deficiency

compartment, as in hypokalemic periodic paralysis. Treatment with  $\beta_2$ -agonists such as salbutamol and terbutaline, in usual doses may occasionally cause hypokalemia.

#### Clinical and Laboratory Features

Mild to severe muscle weakness is characteristic. It is initially noted in limbs before involving trunk and respiratory muscles. In infants, paralytic ileus and gastric dilation are common. Cardiac arrhythmia and eventually cardiac arrest may occur. ECG shows depression of ST segment, low voltage T waves and appearance of U waves; premature ventricular contractions are common and rarely complete AV block may occur (Fig. 16.1). Hyponatremia and alkalosis aggravate ECG abnormalities. Chronic hypokalemia leads to impairment of urinary concentrating capacity and urinary acidification. Tubular glutamine synthesis and ammonia formation is increased resulting in alkaline urine with a high ammonium content. The levels of plasma  $K^+$  by and large reflect the severity of its deficiency; levels below 2 mEq/l indicate a massive loss of intracellular  $K^+$ . Severe hypokalemia can cause paralysis and rhabdomyolysis.

Urinary  $K^+$  excretion is helpful in evaluation of a patient with hypokalemia. If urinary  $K^+$  is below 15 mEq/l, then extrarenal loss is likely. On the other hand, increased urinary  $K^+$  in the presence of normal urinary output implies renal wasting.

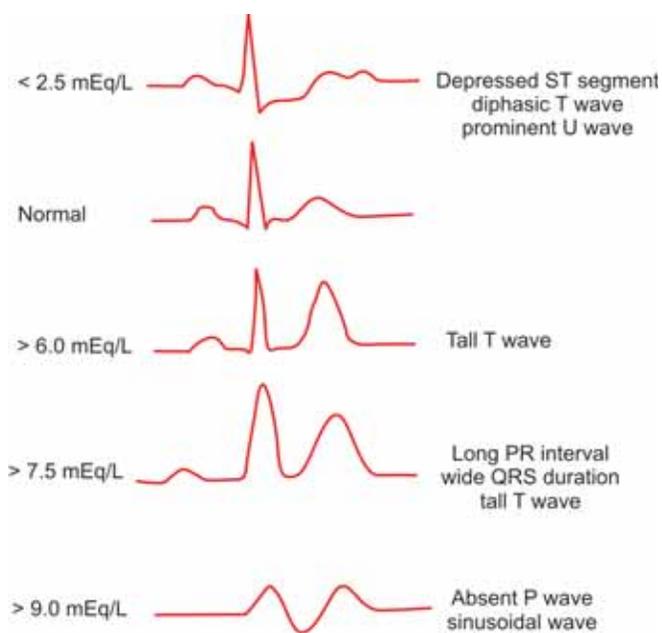


Fig. 16.1: ECG changes in potassium disturbances

#### Treatment

If severe muscle weakness, paralytic ileus or ECG abnormalities are present,  $K^+$  is infused intravenously in an amount not exceeding 0.5-0.75 mEq/kg body weight in the first hour. In severe hypokalemia that does not respond to the above, infusion rates of 1 mEq/kg body weight per hour may be used for short periods under cardiac monitoring. The concentration of  $K^+$  in the intravenous fluid should not exceed 40 mEq/l in a peripheral and 60 mEq/l in a central vein. In some situations, much higher concentrations of  $K^+$  in the intravenous fluid may be used provided there is facility for continuous cardiac monitoring.<sup>21</sup> Potassium should be infused using an infusion pump, using a large vein for the infusion, e.g. femoral vein. Some authors recommend against use of a CVP line whose tip is in the heart for administration of high concentrations as the local increase in the  $K^+$  concentration may have a deleterious effect on the cardiac conduction.  $K^+$  is given in saline without glucose, since the latter may cause of shift of  $K^+$  into the cells and aggravate hypokalemia. Continuous ECG monitoring and frequent estimations of serum  $K^+$  levels are done to detect hyperkalemia.

Oral supplementation of  $K^+$  may suffice if hypokalemia is relatively asymptomatic. Potassium chloride syrup (10%) contains 20 mEq  $K^+$ /15 ml solution. If hypokalemia is associated with metabolic alkalosis administration of chloride along with  $K^+$  is crucial. In the presence of metabolic acidosis,  $K^+$  should be administered as its acetate or citrate salt.

Patients showing lack of response to  $K^+$  replacement may benefit with magnesium supplementation (magnesium sulfate 50%, 0.2 ml/kg twice daily for 3 days).<sup>22</sup>

#### Hyperkalemia

Hyperkalemia (serum  $K^+$  level  $>5.5$  mEq/L) is a relatively common emergency in children with renal disorders. The blood sample for  $K^+$  measurement should be carefully obtained. Use of tourniquet, repeated clenching and opening of fist, and hemolysis (pushing blood sample through a fine needle) may cause a false rise in the level of serum  $K^+$ . Severe thrombocytosis and leukocytosis may also cause an increase in serum level of  $K^+$  during clot retraction.

#### Causes

Important causes of hyperkalemia are listed in Table 16.9. Excessive intake of  $K^+$  may lead to hyperkalemia if renal function is impaired, e.g. in the neonate or in

**Table 16.9: Important causes of hyperkalemia**

<i>Renal</i>	
	Renal failure
	Type IV renal tubular acidosis
	Renal immaturity in very low birth weight babies
<i>Endocrine</i>	
	Salt-losing congenital adrenal hyperplasia
	Addison disease
	Pseudohypoaldosteronism type I and II
	Spironolactone, amiloride, triamterene, cotrimoxazole
	ACE inhibitor therapy
<i>Increased K<sup>+</sup> load</i>	
	Drugs (potassium chloride, penicillin)
	Repeated blood transfusions
	Rhabdomyolysis, hemolysis, large tissue bleeds
	Hypercatabolic states (burns, surgery)
	Tumor lysis syndrome
<i>Shift of K<sup>+</sup> from cells</i>	
	Metabolic acidosis
	Hyperkalemic periodic paralysis
	Insulin deficiency
	β-blocker drugs

the presence of renal disease. In such situations infusion of stored blood and drug formulations with high K<sup>+</sup> content may result in hyperkalemia. Acute renal failure is a common cause of hyperkalemia. In chronic renal failure, serum K<sup>+</sup> levels are kept within the normal range because of an adaptive increase in aldosterone secretion that causes increased K<sup>+</sup> excretion from the remaining normal nephrons and colonic mucosa. These are overcome toward the terminal phase of chronic renal failure, when hyperkalemia is observed.

True hyperkalemia can occur from K<sup>+</sup> shift from the intracellular to extracellular space, as seen with acidosis and lack of insulin. Several adrenal disorders (salt losing type of congenital adrenal hyperplasia, Addison disease and hypoaldosteronism) are characterized by hyperkalemia. Administration of certain drugs such as β-adrenergic blockers and angiotensin converting enzyme inhibitors leads to K<sup>+</sup> retention. High serum levels of K<sup>+</sup> (7-9 mEq/L) may be observed in very low birth weight infants.

#### *Clinical and Laboratory Features*

Muscular weakness, paresthesia, flaccid paralysis and cardiac arrhythmia are the chief manifestations. Mild elevation in serum K<sup>+</sup> level (6.0-6.5 mEq/l) is associated with symmetrical peaking and increase in amplitude of T waves. At higher levels of serum

K<sup>+</sup> there is widening of QRS complex and prolongation of PR interval. At serum K<sup>+</sup> levels of 7-8 mEq/l there is broadening and ultimately disappearance of P waves and further widening of QRS complexes results in a sine wave pattern (Fig. 16.1). Arrhythmias include sinus bradycardia, atrioventricular block, idioventricular rhythm and asystole. A rapid rise in serum K<sup>+</sup> may cause ventricular asystole, tachycardia and fibrillation. Acidosis, hyponatremia and hypocalcemia increase the cardiac effects of hyperkalemia.

The transtubular K<sup>+</sup> gradient (TTKG) is a measure of net K<sup>+</sup> secretion by the distal nephron. The TTKG accounts for changes in urine osmolality that occur with water reabsorption in the collecting duct. It is expressed as:

$$\text{TTKG} = \frac{\text{urine K}^+ \times \text{serum osmolality}}{\text{serum K}^+ \times \text{urine osmolality}}$$

A value below 5-7 in the setting of hyperkalemia implies impaired distal tubular secretion of K<sup>+</sup> (aldosterone deficiency or resistance), whereas a value >10 suggests increased K<sup>+</sup> load and normal distal nephron handling of K<sup>+</sup>.

#### *Treatment*

The urgency of treatment of hyperkalemia depends upon its severity, best assessed by ECG abnormalities. These are largely related to serum K<sup>+</sup> levels, but wrong techniques in blood sampling and laboratory error occasionally create confusion. Serum K<sup>+</sup> levels below 6.0 mEq/l usually do not produce ECG changes, while higher levels cause peaking of T waves. When QRS widening or arrhythmias are present severe hyperkalemia must be inferred and immediate treatment initiated.

Measures to treat hyperkalemia are listed in Table 16.10. Infusion of 10 percent calcium gluconate has an instantaneous but brief effect. Calcium gluconate antagonizes the toxic effect of hyperkalemia by raising the depolarization threshold for myocytes. It should be administered very slowly with ECG monitoring. The dose may be repeated if ECG abnormalities persist. Infusion of sodium bicarbonate and insulin-glucose should follow the administration of calcium gluconate. Glucose-insulin infusion may lower plasma K<sup>+</sup> concentration by 0.5-1.5 mEq/l, an effect that begins within 1 hour and may last for several hours.<sup>23</sup>

β<sub>2</sub>-agonists, administered parenterally or by nebulization, are effective in lowering blood levels of K<sup>+</sup>. The dosage of salbutamol that is required for this effect is higher than used for bronchodilation.<sup>24,25</sup>

**Table 16.10: Treatment of acute hyperkalemia**

Drug	Dose	Onset of action	Duration of action	Remarks
Calcium gluconate (10%)	0.5-1 ml/kg IV	1-3 min	30 minutes	Give slowly under ECG control; bradycardia may occur
Sodium bicarbonate (7.5%)	1-2 mEq/kg IV	10-30 min	2 hr	Effect unpredictable; monitor ECG
Insulin and glucose	0.1-0.2 U/kg insulin 0.5-1 g/kg glucose	20-30 min	2-4 hr	Risk of hypoglycemia
Salbutamol	5-10 mg nebulized	30 min	4-6 hr	Tachycardia, tremor
Polystyrene sulfonate	1 g/kg/dose	4 hr	6-8 hr	Bowel obstruction may occur; use with sorbitol. Each g/kg reduces serum levels by 0.5-0.7 mEq/l

Measures to reduce total body  $K^+$  should be instituted. If the patient has normal renal function and is volume depleted, saline infusion (2-4 ml/kg/hr) will increase the distal delivery of  $Na^+$  and enhance  $K^+$  excretion. Loop diuretics (frusemide 1 mg/kg) may be administered if there is volume overload. If there is poor renal function,  $K^+$  clearance should be promoted either by enhancing its gut excretion (with  $K^+$  binding resins), or by dialysis. Hyperkalemia in acute renal failure is usually associated with acidosis and other complications. Dialysis should be promptly instituted in such cases. Hyperkalemia is usually corrected after 4-6 hours of peritoneal dialysis.

### Chronic Hyperkalemia

In chronic renal failure, preventive measures should be taken. Dietary  $K^+$  should be restricted, and  $K^+$  retaining drugs such as  $\beta$ -blockers, ACE inhibitors and spironolactone avoided. Dehydration should be promptly treated.  $K^+$  exchange resins [polystyrene sulfonate (Kayexalate) 1 g/kg/dose orally or rectally every 6 hours] decrease serum  $K^+$  by 0.5-0.7 mEq/L over 6-8 hours. The drug is administered with enough fluids and sorbitol or lactulose to prevent constipation.

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### PHYSIOLOGY

Acid-base homeostasis influences the functioning of all body proteins, including enzymes thereby critically affecting tissue and organ performance. According to the Bronsted and Lowry definition, an acid is a donor of hydrogen ion (or proton) and base is an acceptor or hydrogen ion.<sup>1,2</sup> The pH of the body must be maintained within a narrow range of 7.35 to 7.45. Most body systems function optimally at a pH of near 7.4. Deviations of systemic pH in either direction can have adverse consequences and, when severe, can be life-threatening. Yet it is the nature of the condition responsible for severe acidemia or alkalemia that largely determines the patient's status and prognosis.

As the pH changes, enzymes may cease to function, nerve and muscle activity weakens, and finally all metabolic activity becomes deranged.<sup>3</sup> The composition of the cell depends upon the pH for two reasons: (i) as the pH changes so will the degree of ionization and, hence, the concentration of ionized substances; (ii) if the degree of ionization changes greatly, a substance may cease to be ionized and move out of the cell. In practice we neither measure nor directly treat the pH inside the cell. It is much closer to neutral (pH 6.8 at 37°C) than the extracellular fluid, but it varies from one part of the cell to another.

The extracellular fluid provides nutrition and oxygenation to the cell and determines its temperature, and alkalinity. The normal pH (7.4) represents a hydrogen ion ( $H^+$ ) concentration of 40 nmol/L.<sup>4</sup> This is about one quarter its concentration inside the cell, 160 nmol/L. This four-fold concentration gradient favors  $H^+$  elimination from the cell, but is counter-balanced by the intracellular potential of -60 mV (which tends to retain the ion within the cell). Regulation of the  $H^+$  concentration at these low levels is essential for normal functioning of cells because of the high reactivity of  $H^+$ , particularly with the proteins.<sup>3</sup>  $H^+$ , because of its small size, is more strongly attracted to negatively charged portions of molecules and is more tightly bound than  $Na^+$  or  $K^+$ .

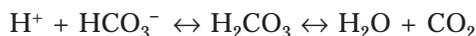
Under normal circumstance, the  $H^+$  concentration varies little from the normal value of approximately 40 nmol/L.<sup>4</sup> This maintenance of  $H^+$  concentration in a very narrow range occurs even though acids and bases are continually being added to the extracellular fluid. The process of  $H^+$  regulation involves: chemical buffering, control of the partial pressure of  $CO_2$  in the blood by alterations in the rate of alveolar ventilation and control of the plasma bicarbonate ( $HCO_3^-$ ) concentration by changes in the renal  $H^+$  excretion.

Buffers are the substances that maintain the pH in the normal range even when the acid or base is added to the body. The pH at which an acid or base is in half of the dissociated form is called dissociation constant and is depicted as pK. Weak acids and bases have pK close to 7.4 and accept or donate the  $H^+$  easily and hence they are best buffers.

The intracellular buffers include proteins, organic and inorganic phosphates, and hemoglobin within the erythrocytes. Bone also acts as an important buffering site.<sup>5</sup> Hemoglobin has a property that enables it to maintain pH within the capillaries. When combined with  $O_2$ , hemoglobin tends to release  $H^+$  that have attached to the imidazole chain (it becomes a stronger acid). When hemoglobin is exposed to acid and lower  $O_2$  concentrations in the capillaries, it gives up the  $O_2$ . It then becomes a weaker acid, taking up the extra  $H^+$ . This change maintains the pH in the capillaries despite the higher  $CO_2$  concentration. An opposite change occurs when hemoglobin is exposed to the higher  $O_2$  concentration in the lung. As it takes up oxygen, it becomes more acidic (more prone to release the  $H^+$ ). The  $H^+$  reacts with  $HCO_3^-$  to form carbonic acid, which in turn is converted to  $CO_2$  and released into the alveoli. Hemoglobin is therefore not only an  $O_2$  transporting molecule, but is also an acid-transporting system.

Other buffers exist in the human system of which the carbonic acid-bicarbonate buffer is the clinically most relevant. The carbonic acid-bicarbonate system is a classic chemical buffer. The body eliminates chemicals from either end of the chemical reaction to

maintain the pH. In the case of bicarbonate in this buffer, the chemical reaction is:



This buffering system is very effective because of the ability to convert carbonic acid to carbon dioxide (through the enzyme carbonic anhydrase) which is then removed from the body through respiration. Changes in carbonic acid concentration occur rapidly (seconds) in response to hypo- or hyperventilation. On the other hand, changes in bicarbonate require hours or days through the relatively slow process of elimination by the kidney. The ratio of bicarbonate to carbonic acid determines the pH of the blood. Normally this ratio is about 20:1. This relationship is described in the Henderson-Hasselbach equation:

$$\text{pH} = \text{pK} + \log (\text{HCO}_3^- / \text{H}_2\text{CO}_3)$$

(pK, the dissociation constant of the buffer is 6.10 at body temperature. The change in pK with temperature is the reason pH determinations must be adjusted for patients with abnormal temperatures).

As carbon dioxide is directly proportional to the carbonic acid ( $\text{H}_2\text{CO}_3$ ), and can be directly measured, it will be substituted into the above equation.<sup>6</sup>

$$\text{PaCO}_2 = 33 \times \text{H}_2\text{CO}_3 \text{ or } \text{H}_2\text{CO}_3 = 0.03 \times \text{PaCO}_2$$

By substituting,

$$\text{pH} = \text{pK} + \log [\text{HCO}_3^- / (\text{PaCO}_2 \times 0.03)]$$

Thus by measuring serum pH and  $\text{PaCO}_2$ , the serum bicarbonate can be calculated as in most blood gas measurements:

$$\log (\text{HCO}_3^-) = \text{pH} + \log (\text{PaCO}_2) - 7.604$$

### ACID ELIMINATION AND COMPENSATION

The body's own regulators of acid-base balance are the lungs and the kidneys, which are responsible for excreting the respiratory and metabolic acids respectively. The power of the lungs to excrete large quantities of carbon dioxide enables them to compensate rapidly. Unless the respiratory system is diseased or depressed, metabolic disturbances promptly stimulate partial respiratory compensation.

The elimination of acid is achieved by  $\text{H}^+$  secretion ( $\text{Na}^+ - \text{H}^+$  exchange in the proximal tubule and thick ascending limb of Henle; and active  $\text{H}^+$  ATPase pump in the collecting tubules). The hydrogen ions are produced in the body from dietary protein metabolism, partial metabolism of fats and carbohydrates and excretion of bicarbonate in stool which is more

significant in children with diarrhea. The daily acid load is not excreted as free  $\text{H}^+$  ions; the secreted  $\text{H}^+$  ions are excreted by binding either to filtered buffers such as  $\text{HPO}_4^{2-}$ , or to  $\text{NH}_3$  to form  $\text{NH}_4^+$ . The rate of  $\text{NH}_3$  production can be varied according to the physiologic needs. The excretion of daily acid load also requires almost complete resorption of filtered  $\text{HCO}_3^-$ , as  $\text{HCO}_3^-$  loss in the urine is equivalent to addition of  $\text{H}^+$  ions to the body.

There is a sequential response to  $\text{H}^+$  load in an attempt to restore the acid-base balance. Extracellular buffering of the excess  $\text{H}^+$  by  $\text{HCO}_3^-$  occurs almost immediately. Respiratory compensation begins within several minutes. The hyperventilation leads to decrease in  $\text{PCO}_2$  and increase of pH towards normal. In about 2-4 hours, the intracellular buffers, primarily proteins and organic phosphates, and bone provide further buffering. These responses prevent wide swings in the arterial pH until acid base homeostasis can be restored by the renal excretion of  $\text{H}^+$ . The corrective renal response begins early and is usually complete within 5-6 days. If there is metabolic alkalosis, the corrective renal action is more rapid, as the excess  $\text{HCO}_3^-$  is rapidly excreted in the urine.<sup>7</sup>

On the other hand, alterations in pH induced by changes in  $\text{PCO}_2$  elicit a different response. There is no extracellular buffering since  $\text{HCO}_3^-$  cannot effectively buffer  $\text{CO}_2$ . There is no compensatory change in alveolar ventilation, since the abnormality in gas exchange is the primary problem. The intracellular buffering is the initial response occurring in 10-30 minutes. The intracellular buffers increase plasma  $\text{HCO}_3^-$  concentration by only 1 mEq/l for each 10 mm Hg rise in  $\text{PCO}_2$ . The renal compensation, by excretion of  $\text{H}^+$  ions, begins within several hours, but takes a few days to complete.<sup>5</sup>

In respiratory alkalosis, there is reduction of plasma  $\text{HCO}_3^-$  because of intracellular buffering and decrease in net acid excretion.

These changes discussed above are compensatory but not corrective. Acid-base homeostasis cannot be restored unless the primary problem is taken care of. Table 17.1 shows the expected compensatory response.

### ACID-BASE DISORDERS

Acidemia is defined as a decrease in the blood pH or an increase in  $\text{H}^+$  concentration and alkalemia as an elevation in the blood pH. On the other hand, acidosis and alkalosis refer to processes that tend to lower and raise the pH, respectively. Usually, an acidotic process leads to acidemia and alkalotic process to alkalemia. However, in the mixed acid base disturbances, the final

**Table 17.1: Expected compensatory response to acid-base disorder**

Abnormality	Primary change	Expected compensatory change
Acute respiratory acidosis	↑ PaCO <sub>2</sub>	↑ HCO <sub>3</sub> <sup>-</sup> by 1 mEq/L for each 10 mm Hg rise in PaCO <sub>2</sub>
Acute respiratory alkalosis	↓ PaCO <sub>2</sub>	↓ HCO <sub>3</sub> <sup>-</sup> by 1-3 mEq/L for each 10 mm Hg fall in PaCO <sub>2</sub>
Chronic respiratory acidosis	↑ PaCO <sub>2</sub>	↑ HCO <sub>3</sub> <sup>-</sup> by 4 mEq/L for each 10 mm Hg rise in PaCO <sub>2</sub>
Chronic respiratory alkalosis	↓ PaCO <sub>2</sub>	↓ HCO <sub>3</sub> <sup>-</sup> by 2-5 mEq/L for each 10 mm Hg fall in PaCO <sub>2</sub>
Metabolic acidosis	↓ HCO <sub>3</sub> <sup>-</sup>	↓ PaCO <sub>2</sub> by 1-1.5 mm Hg for each 1 mEq/L fall in HCO <sub>3</sub> <sup>-</sup>
Metabolic alkalosis	↑ HCO <sub>3</sub> <sup>-</sup>	↑ PaCO <sub>2</sub> by 0.25-1 mm Hg for each 1 mEq/L rise in HCO <sub>3</sub> <sup>-</sup>

pH depends on the balance between the different disorders present.

Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

Evaluation of acid-base status begins with the pH. If the pH is greater than 7.44, the patient is alkalemic and pH less than 7.36, the patient is acidemic. If the HCO<sub>3</sub><sup>-</sup> is shifted in the direction of the pH, it may be the primary culprit. CO<sub>2</sub> is likely to be the primary culprit if it is shifted opposite to the pH. The pH is abnormal in majority of the patients with acid-base disturbance except in few circumstances where the pH will be maintained in normal range despite the acid base disturbance which includes, mixed metabolic acidosis and respiratory alkalosis in which the change in hydrogen ion concentration occur in the opposite direction in equal magnitude and the simple chronic respiratory alkalosis that can have adequate metabolic compensation.

After identifying the abnormal parameter (CO<sub>2</sub> or HCO<sub>3</sub><sup>-</sup>), the other value is assessed. If that other value is abnormal, but in a direction that would move the pH back towards normal, then compensation is present.

Diagnosis of mixed acid-base disorders can be made if one takes into account the expected compensatory responses (Table 17.1) and deviations from these.

### Metabolic Acidosis

Metabolic acidosis is characterized by low arterial blood pH, reduced plasma HCO<sub>3</sub><sup>-</sup> and compensatory hyperventilation. Low plasma HCO<sub>3</sub><sup>-</sup> alone is not diagnostic of metabolic acidosis since it may also result from the renal compensation to chronic respiratory alkalosis. These can be differentiated by measurement of the arterial pH. However, the plasma HCO<sub>3</sub><sup>-</sup> of 10 mEq/L or less is indicative of metabolic acidosis, as the renal compensation to chronic hypocapnia does not lead to such low levels of plasma HCO<sub>3</sub><sup>-</sup>.

### Etiology

Metabolic acidosis results from either an inability of the kidney to excrete the dietary H<sup>+</sup> load or an increase in the generation of H<sup>+</sup> or the loss of HCO<sub>3</sub><sup>-</sup>. Decreased H<sup>+</sup> excretion usually produces a slowly developing acidemia, while an acute increase in the H<sup>+</sup> load can overwhelm renal excretory capacity, leading to the rapid onset of significant metabolic acidosis. Rapid expansion of the extracellular fluid with a bicarbonate free solution may reduce bicarbonate concentration of extracellular fluid and cause acidosis. Loss of bicarbonate in gastrointestinal tract (diarrhea) and failure of its renal reabsorption (renal tubular acidosis) are common causes. The bicarbonate is replaced by chloride and serum chloride is elevated. Increased production of nonvolatile acids in the body such as phosphate, sulphate or organic acids (as in starvation, diabetes mellitus or renal failure) titrate bicarbonate and leads to metabolic acidosis. The blood chloride levels, in these cases, are normal. Several inborn errors of metabolism and poisonings are also important causes of metabolic acidosis. Table 17.2 shows the important causes of metabolic acidosis.

### Clinical Features

The clinical manifestations of the underlying disorder causing metabolic acidosis are more prominent. The clinical manifestations of the metabolic acidosis depend on the severity of the acidosis and the respiratory function. Mild metabolic acidosis with appropriate respiratory compensation is clinically manifested by rapid and deep breathing (Kussmaul respiration). Fall in serum pH below 7.2 is associated with myocardial dysfunction with impaired contractility and when arterial blood pH falls below 7.1 there is increased risk of fatal ventricular arrhythmias and attenuate response to catecholamines.<sup>8</sup> This myocardial dysfunction occur more so in children with underlying cardiac disease or when there is associated electrolyte abnormality is present. The decrease in ventricular function may have

**Table 17.2: Causes of metabolic acidosis**

<i>High anion gap</i>
Lactic acidosis
Ketoacidosis: diabetes, starvation
Renal failure
Toxins, medications: salicylates, ethylene glycol, methanol, paraldehyde
<i>Normal/low anion gap acidosis</i>
Gastrointestinal losses of bicarbonate
Diarrhea
External intestinal drainage
Ureterosigmoidostomy, small bowel loops
Drugs causing diarrhea
Renal tubular acidosis
Acetazolamide
Hypoaldosteronism
Ammonium chloride loading

a role in persistence of shock-induced lactic acidosis. In newborn period the metabolic acidosis causes pulmonary vasoconstriction which aggravates persistent pulmonary hypertension.

Neurological symptoms, varying from lethargy to coma have been described in metabolic acidosis. However, these abnormalities are more common in respiratory acidosis. Chronic acidemia, as with renal failure and renal tubular acidosis, can result in skeletal problems due to release of calcium ions and phosphate during bone buffering of the excess  $H^+$  ions. This also manifests in impaired growth. Other metabolic impairment that may occur with metabolic acidosis are hyperkalemia, insulin resistance, increased protein catabolism and reduced ATP synthesis that are seen more commonly with long standing metabolic acidosis. In infants and young children, there may be non-specific symptoms as anorexia, vomiting, weight loss, muscles weakness and listlessness.<sup>9</sup> Failure to thrive and recurrent episodes of respiratory distress are also common in infants with longstanding metabolic acidosis.

#### Laboratory Findings

The blood pH and  $HCO_3^-$  as well as  $PCO_2$  levels are decreased. For every 1 mEq/L fall in blood  $HCO_3^-$ , the  $PCO_2$  decreases by 1-1.5 mm Hg as a compensatory response; failure of that to occur indicates a respiratory contribution to acidosis. After confirming the presence of metabolic acidosis, calculation of the serum anion gap is a useful step in determining the underlying cause. The anion gap is equal to the difference between concentrations of the major cations ( $Na^+$ ) and the major measured anions ( $Cl^-$  and  $HCO_3^-$ ). The normal value

of the anion gap is  $12 \pm 2$  mEq/L. The normal value for anion gap should be revised downward by 2.5 mEq/L for every 1 g/dL decline in the plasma albumin concentration.<sup>10</sup> Table 17.2 lists the causes of metabolic acidosis according to the anion gap.

The plasma anion gap is useful in various clinical settings. In the first setting, the presence or absence of increased anion gap is useful for determining the cause of metabolic acidosis. Thus, metabolic acidosis with an increased anion gap is usually attributable to disorders associated with the accumulation of either endogenous organic acids (lactic acidosis, keto-acidosis, renal failure) or exogenous organic acids (methanol, ethylene glycol, salicylate). The magnitude of the increase in the anion gap is important. With an anion gap of  $> 25$  mEq/L, an organic acidosis is nearly always present.<sup>11</sup> However, mild increases in the anion gap may be relatively insensitive for detecting the presence of mild-to-moderate organic acidoses, such as the lactic acidosis encountered in critically ill patients. In even classic cases considered to be characterized by the presence of an increased anion gap metabolic acidosis, such as diabetic ketoacidosis, an increase in anion gap often cannot be demonstrated due to other acid-base disturbances and variations in fluid status.

The second setting in which the anion gap may be useful is when ascertaining if a mixed acid-base disturbance is present through the calculation of the ratio of the change in the anion gap and the change in the serum bicarbonate.<sup>12</sup> This calculation is based on the assumption that each milliequivalent of acid added to the body will reduce the serum bicarbonate by an equivalent amount. The normal value is between 1 and 2. Therefore, when the change in the anion gap is larger than the change in the serum bicarbonate, this implies an additional source of base (metabolic alkalosis). When the change in the anion gap is less than the change in the serum bicarbonate, this implies an additional source of acid (non-anion gap metabolic acidosis).

Measurement of urinary pH cannot reliably differentiate acidosis of renal origin from that of extrarenal origin. A useful method to distinguish extrarenal from renal causes of metabolic acidosis is to measure urinary ammonium excretion. Extrarenal causes of metabolic acidosis are associated with an appropriate increase in urine acid excretion, primarily shown by high levels of urinary ammonium. In contrast, the net acid excretion and urinary ammonium levels are low in metabolic acidosis of renal origin. Measurement of urinary ammonium excretion is, however, cumbersome and not a commonly available test in most

laboratories. One can, however, indirectly assess the amount of urinary ammonium by calculating the urine anion gap.<sup>13</sup>

#### Urinary Anion Gap

$$(UAG) = (U Na^+ + U K^+) - U Cl^-$$

Under normal conditions the urinary anion gap is positive, with values between 20-50 mEq/L. A negative value suggests presence of increased renal excretion of an unmeasured cation (other than Na<sup>+</sup> or K<sup>+</sup>). One such cation is ammonium. Metabolic acidosis of extrarenal origin is associated with an increase in urinary ammonium, and a negative urinary anion gap. If the metabolic acidosis is of renal origin like in renal tubular acidosis, urinary ammonium excretion is low and the urinary anion gap is positive.

Blood urea, creatinine, blood glucose, electrolytes and urinalysis are done to look for the cause of metabolic acidosis. The serum potassium level is most important as it is elevated abnormally and can cause fatal cardiac arrhythmia. If there is hypokalemia with metabolic acidosis, the differential diagnoses are narrowed which include, the diarrhea, renal tubular acidosis (proximal and distal) and use of diuretic acetazolamide.

#### Treatment

While in most conditions, correction of the acidemia can be achieved by the administration of NaHCO<sub>3</sub>, it is more important to correct the underlying disorder.

The initial therapeutic goal in patients with severe acidemia is to raise the systemic pH to above 7.1-7.2, a level at which arrhythmias become less likely. At this pH, the cardiac contractility and responsiveness to catecholamines is likely to be restored. Rapid administration of sodium bicarbonate is important only in patients with severe metabolic acidosis; this should be done only if ventilation is adequate. Exogenous sodium bicarbonate is usually not required if the initial arterial pH is greater than 7.20, the child is asymptomatic and the underlying process can be controlled.

The amount of HCO<sub>3</sub><sup>-</sup> required to correct the acidemia can be estimated by the formula:

$$HCO_3^- \text{ required} = 0.6 \times \text{body weight} \times HCO_3^- \text{ deficit}/l$$

The added HCO<sub>3</sub><sup>-</sup> produces a large increase in the plasma HCO<sub>3</sub><sup>-</sup> concentration within a few minutes. Thereafter, the change is attenuated as the exogenous HCO<sub>3</sub><sup>-</sup> equilibrates with the intracellular and bone buffers. Therefore, measurement of pH shortly after administration of HCO<sub>3</sub><sup>-</sup> may overestimate the final effect of the treatment.

Alkali therapy is usually not required in lactic acidosis or ketoacidosis where the metabolism of the organic anions will regenerate HCO<sub>3</sub><sup>-</sup>. Similarly, citrate salts of sodium or potassium may be preferable in the chronic treatment of renal tubular acidosis.

Metabolic acidosis due to diarrheal losses should be corrected by expansion of extracellular fluid with Ringer's lactate solution. Correction of the underlying disorder is the primary therapy in lactic acidosis. For example, reversal of circulatory failure will reduce the output of lactate and allow metabolism of lactate to HCO<sub>3</sub><sup>-</sup>. The role of sodium bicarbonate therapy in lactic acidosis is controversial.<sup>14</sup> Theoretically, the benefits of increase in arterial blood pH include improvement in tissue perfusion, by correction of vasodilatation and improvement in cardiac contractility. However, the potential adverse effects are volume overload, hypernatremia, hypocalcemia, hypokalemia, metabolic alkalosis and paradoxical intracellular acidosis. Current evidence does not support routine use of sodium bicarbonate in treatment of lactic acidosis.<sup>15</sup> However, a small amount of sodium bicarbonate may be administered to patients with severe metabolic acidosis to raise the pH to 7.10.

In diabetic ketoacidosis, insulin is the mainstay of therapy. However, sodium bicarbonate therapy may be beneficial if there is marked acidemia (pH < 6.9). It may also be useful in patients with relatively normal anion gap because of excretion of ketoacids in the urine; as in this condition, the quantity of sodium bicarbonate generated from metabolism of organic anions is likely to be low.

In renal failure, exogenous alkali therapy is not used routinely. Usually in most patients, the arterial pH is maintained close to 7.3 because of respiratory compensation. Attempts to increase pH in presence of hypocalcemia can precipitate tetany. There is also a risk of volume expansion. Sodium bicarbonate therapy is indicated if the plasma HCO<sub>3</sub><sup>-</sup> is less than 12 mEq/L, the patients are symptomatic or there is persistent hyperkalemia. In children, alkali therapy is used more frequently, as acidemia interferes with growth. In renal failure, the alkali of choice is sodium bicarbonate. Citrate may increase aluminum absorption in children receiving aluminum hydroxide.<sup>16</sup>

The aim of correction of acidosis in renal tubular acidosis is to allow normal growth, to minimize nephrocalcinosis, renal calculus formation and to prevent osteopenia due to calcium loss from the bone, and to diminish excessive urinary K<sup>+</sup> losses.<sup>9</sup> Patients may be treated with sodium bicarbonate or citrate salts.

Sodium bicarbonate administration is helpful in poisoning due to salicylates, tricyclic antidepressant, ethylene glycol and methanol as they help in eliminating the poisonous agent through renal route. Long term sodium bicarbonate therapy may be necessary in cases of inborn error of metabolism.

Dialysis, either peritoneal or hemodialysis, may be an option in treatment of severe metabolic acidosis due to renal failure or methanol or ethylene glycol poisoning.

### Metabolic Alkalosis

Metabolic alkalosis is characterized by an increase in the arterial pH, an increase in the plasma  $\text{HCO}_3^-$  concentration and compensatory hypoventilation. The kidney normally responds to an increase in  $\text{HCO}_3^-$  by rapidly excreting the excess alkali. Sustained metabolic alkalosis thus occurs when some additional factor disrupts the renal regulation of body alkali stores. Metabolic alkalosis commonly occur secondary to vomiting in children.

#### Etiology

Most of the conditions leading to metabolic alkalosis are characterized by enhanced renal reabsorption of bicarbonate due to depletion of volume, chloride or potassium<sup>17</sup> (Table 17.3). Removal of gastric secretions leads to metabolic alkalosis. Since there is no stimulus for pancreatic  $\text{HCO}_3^-$  secretion; this results in increase in plasma  $\text{HCO}_3^-$ .<sup>18</sup> Persistent vomiting is also associated with increased renal  $\text{H}^+$  loss. In conditions with mineralocorticoid excess, aldosterone promotes  $\text{H}^+$  secretion by stimulating the distal  $\text{H}^+$ -ATPase pump. In addition, hypokalemia, due to increased  $\text{K}^+$  losses plays an important role in metabolic alkalosis by causing volume contraction and increase in urinary  $\text{H}^+$  loss.

The causes of metabolic alkalosis can be divided into chloride responsive and chloride resistant.

Often alkalosis is seen in patients in whom chronic respiratory acidosis is corrected rapidly. The compensatory response to respiratory acidosis is increase in urinary  $\text{H}^+$  secretion and increase in plasma  $\text{HCO}_3^-$ . If such a patient is mechanically ventilated and  $\text{CO}_2$  brought down rapidly, the plasma  $\text{HCO}_3^-$  still remains high and leads to metabolic alkalosis.

The causes of chloride responsive metabolic alkalosis are vomiting or nasogastric suction, diuretics, low chloride intake and post-hypercapnia. These conditions can be reversed by administration of sodium chloride and water, by intravenous or oral route. These act by (i) reversing the depletion of volume and  $\text{Cl}^-$  thereby

**Table 17.3: Causes of metabolic alkalosis**

<b>Chloride responsive alkalosis</b> (Urine $\text{Cl}^- < 25$ mEq/l)
Vomiting or gastric drainage
Diuretics
After correcting prolonged hypercapnia
Low chloride intake
Cystic fibrosis
<b>Chloride-resistant alkalosis</b> (Urine $\text{Cl}^- > 40$ mEq/l)
Cushing syndrome
Primary hyperaldosteronism
Barter syndrome
Gitelman syndrome
Severe hypokalemia
Excessive bicarbonate therapy
Milk alkali syndrome

removing stimulus for renal  $\text{Na}^+$  retention, and allowing sodium bicarbonate excretion in the urine; and (ii) by increasing distal  $\text{Cl}^-$  delivery, which promotes  $\text{HCO}_3^-$  secretion.

The chloride resistant causes are the ones where  $\text{K}^+$  depletion, not hypovolemia, is responsible for alkalosis. These include edematous states, mineralocorticoid excess, severe hypokalemia and renal failure. In edematous states, frequent use of diuretics is responsible for metabolic alkalosis. Even though volume depletion contributes to the pathogenesis, saline administration is not indicated as it will increase the edema and the risk of pulmonary edema.

Hypokalemia is frequently observed in patients with metabolic alkalosis. This is because (i) many conditions cause both  $\text{H}^+$  and  $\text{K}^+$  loss; (ii) hypokalemia causes migration of  $\text{K}^+$  out of the cells and  $\text{H}^+$  into the cells; and (iii) hypokalemia increases urinary acid excretion and  $\text{HCO}_3^-$  reabsorption.

#### Clinical Features

The clinical features of metabolic alkalosis depend on the underlying cause. Mild metabolic alkalosis is well tolerated with no clinically significant adverse effects. The most serious effects of moderate metabolic alkalosis ( $\text{HCO}_3^- > 40$  mEq/L) occur due to associated hypokalemia and hypocalcemia. Chloride responsive metabolic alkalosis is associated with volume depleted and can have the manifestations of hypovolemia while chloride unresponsive metabolic alkalosis may have features of hypertension. With more severe metabolic alkalosis, hypoxemia can develop as a result of the hypoventilation. Patients may present with seizures, tetany and altered sensorium.

### Diagnosis

The finding of serum  $\text{HCO}_3^- > 28\text{-}30$  mEq/L in association with hypokalemia is diagnostic of metabolic alkalosis. Elevated plasma bicarbonate, hypercapnia, and hypoxemia may be seen in respiratory acidosis also, but this can be differentiated easily by the pH. However, a combination of respiratory acidosis and metabolic alkalosis may be difficult to interpret.

The etiology of metabolic alkalosis usually can be elicited from history. Measurement of urinary chloride is helpful in differentiating chloride responsive ( $\text{Cl}^- < 25$  mEq/l) from chloride resistant ( $\text{Cl}^- > 40$  mEq/l) forms. Primary hyperaldosteronism is characterized by a combination of hypertension and metabolic alkalosis. Measurement of plasma renin and aldosterone levels is useful in differentiating syndromes of mineralocorticoid excess from those with apparent mineralocorticoid excess. In a normotensive or hypotensive child with chloride resistant metabolic alkalosis, the diagnosis of Bartter or Gitelman syndrome is highly probable.

### Therapy

The aim of therapy is to correct the volume,  $\text{Cl}^-$  and  $\text{K}^+$  deficits. Efforts should be directed at correction of underlying disease. Oral or intravenous administration of sodium chloride and water is indicated in chloride responsive causes of metabolic alkalosis. With the exception of hypotension or shock or severe metabolic derangement, gradual correction is preferable to avoid complications of volume overload. The efficacy of such treatment can be assessed bedside by monitoring the urine pH. Urine pH, which is often below 5.5 before therapy, increases to beyond 7.0 once volume and chloride are replaced.

The administration of saline is usually ineffective in chloride resistant causes of metabolic alkalosis and can worsen hypertension. In patients with edematous states, withholding diuretics is the corrective therapy. Acetazolamide may be used to treat both edema and alkalosis, where withholding diuretics alone does not help.<sup>19</sup> Correction of severe hypokalemia (as in states of mineralocorticoid excess) leads to correction of alkalosis.

### Respiratory Acidosis

Respiratory acidosis is characterized by a reduced arterial blood pH, an elevated  $\text{PCO}_2$  and an increase in plasma  $\text{HCO}_3^-$  concentration.

**Table 17.4: Causes of respiratory acidosis**

#### Acute

- Pneumonia
- Pulmonary edema
- Severe asthma
- Pneumothorax
- Acute respiratory distress syndrome
- Neuromuscular disorders: Guillain-Barre syndrome, myasthenia gravis, severe hypokalemia, poliomyelitis
- Aspiration of foreign body/ vomitus
- Drugs: opiates, sedatives, anesthetics
- Central sleep apnea
- Obstructive sleep apnea

#### Chronic

- Extreme obesity (Pickwickian syndrome)
- Muscle weakness: spinal cord lesions, poliomyelitis
- Kyphoscoliosis
- Chronic obstructive pulmonary disease

### Etiology

Hypercapnia and respiratory acidosis are almost always due to a reduction in alveolar ventilation and not due to increase in  $\text{CO}_2$  production (Table 17.4). Hypoventilation, as seen in patients with reduced respiratory drive or neuromuscular dysfunction, leads to a generalized fall in the alveolar ventilation. On the other hand,  $\text{CO}_2$  retention in intrinsic pulmonary disease occurs primarily due to an imbalance between ventilation and perfusion.

If the ventilation is not improved, the cell buffers and increase in renal  $\text{H}^+$  secretion minimize the decrease in pH. However, the latter occurs over several days and the protection of the extracellular pH in acute respiratory acidosis is much less efficient than that seen in chronic respiratory acidosis.

The common causes of acute respiratory acidosis include severe pneumonia, asthma, pulmonary edema, acute exacerbation of existing pulmonary disease and suppression of the respiratory center following drug toxicity or administration of excessive oxygen to a patient with chronic hypercapnia.

Important causes of chronic respiratory acidosis in children are chronic lung disease, cystic fibrosis, extensive bronchiectasis and neuromuscular defects.

Upper airway diseases cause hypoventilation secondary to decreased air entry into lungs. Children with mild or moderate lung diseases cause respiratory alkalosis due to hyperventilation which occurs as a result of mild hypoxia or stimulation of lung mechanoreceptors. Severe lung diseases will have respiratory acidosis either due to hypoventilation

secondary to airway obstruction or respiratory muscle fatigue or due to severe ventilation: perfusion mismatch.

#### *Clinical Features*

The clinical features of respiratory acidosis depend on the underlying cause. In children with respiratory acidosis due to hypoventilation due to central nervous system depression or respiratory muscle fatigue and respiratory failure will have bradypnea, hypoxia and altered sensorium while respiratory acidosis due to pulmonary or airway obstruction will have tachycardia, tachypnea, respiratory difficulty and features of hypoxia. Severe acute respiratory acidosis may lead to symptoms of restlessness, anxiety, headache, blurred vision and excessive sweating.<sup>20</sup> Excessive CO<sub>2</sub> retention may lead to CO<sub>2</sub> narcosis as manifested by tremors, asterixis, delirium and excessive sleep. There may be features of raised intracranial pressure. Severe acidosis may also lead to significant vasodilatation and hypotension. With fall in arterial pH, the impairment in cardiac function, altered response to catecholamine and cardiac arrhythmia can also occur similar to metabolic acidosis. Rise in serum potassium can also occur in children with respiratory acidosis but less prominent compared to metabolic acidosis.

#### *Diagnosis*

The presence of acidemia and elevated PCO<sub>2</sub> is diagnostic of respiratory acidosis. In order to determine whether it is acute or chronic, an accurate history and good examination are essential. Children with altered sensorium may have severe central nervous system disease, drug intoxication or carbon dioxide narcosis. Tachypnea, respiratory distress, wheezing, crepitations and stridor may be present in pulmonary or airway diseases.

It is always important to remember the expected compensations in acute and chronic respiratory acidosis to determine presence of mixed metabolic and respiratory abnormalities.

Calculation of alveolo-arterial oxygen gradient [(A-a) DO<sub>2</sub>] can assist in determining the etiology. It is usually increased in patients with intrinsic pulmonary disease. A normal gradient usually excludes pulmonary disease and indicates central alveolar hypoventilation or abnormalities of chest wall or muscles of breathing.

#### *Treatment*

Patients with acute respiratory acidosis often have both hypercapnia and hypoxemia. While the hypoxemia can usually be corrected by increasing the FiO<sub>2</sub>, correction of hypercapnia requires increase in alveolar ventilation. This can be achieved by reversing the underlying condition or by mechanical ventilation. While the primary aim of therapy is to restore normal alveolar ventilation, some authors recommend infusion of small doses of NaHCO<sub>3</sub> to correct the pH, particularly in status asthmaticus.<sup>21</sup> This is done primarily to minimize the ventilatory settings in order to prevent barotrauma and air leaks, while accepting higher PCO<sub>2</sub> values. However, there are risks of volume overload, hypernatremia, and persistence or worsening of tissue acidosis.

Usually, the conditions leading to chronic respiratory failure are not entirely correctable. Hence, the goal of therapy is to maintain adequate oxygenation and if possible improve alveolar ventilation. Because of the efficient renal compensation, the pH is usually maintained. In children with cor pulmonale, use of diuretics may be helpful in raising the pH further. Attempts should be made to correct reversible components, e.g. appropriate use of bronchodilators, treatment of infections. Sedatives and excessive O<sub>2</sub> supplementation should be avoided as they act as respiratory depressants. Low flow O<sub>2</sub> therapy is useful in reversing hypoxemia and improving blood flow. Mechanical ventilation is usually limited to condition with an acute exacerbation. Here, PCO<sub>2</sub> should be lowered gradually, as a rapid decline can lead to alkalemia.

**Table 17.5: Causes of respiratory alkalosis**

#### **Associated with hypoxemia**

- Pneumonia
- Pulmonary edema
- Hypotension
- Severe anemia

#### **Without hypoxemia**

- Anxiety
- Fever
- Early sepsis
- Liver cell failure
- Central nervous system lesions: pontine tumors, cerebrovascular accidents
- Inappropriate mechanical ventilation

**Table 17.6: Terminology used in blood gas analysis reports**

Term	Explanation	Normal values
pH	Negative logarithm of H <sup>+</sup> ion concentration	7.36–7.44
PCO <sub>2</sub>	Partial pressure of CO <sub>2</sub> in blood	36–44 mm Hg
PO <sub>2</sub>	Partial pressure of O <sub>2</sub> in blood	80–100 mm Hg
Base excess (BE)	Actual base excess in variance from (above or below) total buffer base	–2 to +2 mEq/L
Buffer base (BB)	Buffer base represents the buffering capacity	48–50 mEq/L
HCO <sub>3</sub> <sup>–</sup>	Actual plasma bicarbonate concentration (derived from blood pH, PCO <sub>2</sub> )	22–26 mEq/L
Standard HCO <sub>3</sub> <sup>–</sup> (SBC)	Plasma bicarbonate value at PCO <sub>2</sub> 40 mm Hg and temperature 37°C	22–26 mEq/L
TCO <sub>2</sub>	Total CO <sub>2</sub> is the sum of HCO <sub>3</sub> <sup>–</sup> and the amount of CO <sub>2</sub> dissolved in plasma (for each mm Hg PCO <sub>2</sub> , 0.03 ml CO <sub>2</sub> is dissolved in 100 ml plasma)	23–27 mmol/L
Standard pH	pH adjusted for PCO <sub>2</sub> of 40 mm Hg and a temperature of 37°C. This represents pH purely due to metabolic status.	7.36–7.44
O <sub>2</sub> content	Sum of O <sub>2</sub> bound to hemoglobin and oxygen dissolved in plasma (For each gram of saturated hemoglobin, 1.34 ml O <sub>2</sub> is bound to it, and for each mm Hg PO <sub>2</sub> 0.003 ml O <sub>2</sub> is dissolved in 100 ml plasma)	

### Respiratory Alkalosis

Respiratory alkalosis is characterized by elevated arterial blood pH, a low PCO<sub>2</sub> and a reduction in plasma HCO<sub>3</sub><sup>–</sup> concentration.

#### Etiology

A decrease in PCO<sub>2</sub> will occur when the alveolar ventilation is increased beyond the level needed to eliminate the load of CO<sub>2</sub> produced. Primary hyperventilation leading to respiratory alkalosis can result from hypoxemia, anemia and pulmonary disease (Table 17.5). Pain, anxiety, stimulation of mechano-receptors within the respiratory systems, and direct stimulation of respiratory center by various conditions and chemicals can also cause hyperventilation.

#### Clinical Features and Diagnosis

The clinical features are due to the ability of alkalosis to impair cerebral function and to increase cell membrane excitability. Profound respiratory alkalosis can reduce cerebral blood flow. The symptoms include altered consciousness, paresthesiae, cramps and carpopedal spasms. In critically ill patients, supra-ventricular and ventricular arrhythmias may also occur. The diagnosis can be confirmed by the arterial blood gas result. Based on the clinical setting, history and examination, the underlying condition can be diagnosed.

#### Treatment

Hyperventilation is done in some patients with raised intracranial tension. Correction of alkalemia is not required and the management should be directed at the diagnosis and correction of the underlying disorder. In severely symptomatic patients, rebreathing into a reservoir (to increase PCO<sub>2</sub> in inspired air) may partially increase PCO<sub>2</sub> and relieve the symptoms.

Table 17.6 lists terminologies used in blood gas analysis reports.

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Hematuria is a common presenting feature of diseases or abnormalities of genitourinary system and systemic diseases like coagulation disorders. It rarely could be factitious. It is not uncommon for children to present to the emergency room with hematuria. The prevalence of gross hematuria, based on a retrospective review of children seen in an emergency clinic was 0.13 percent.<sup>1</sup>

The goals for the physician attending to a child with hematuria in the emergency are: (i) to recognize and confirm the finding of hematuria, (ii) to identify common etiologies for hematuria and (iii) to identify children with significant genitourinary disease who need further evaluation and management.

An orderly, comprehensive approach can simplify the diagnosis and ensure appropriate management. The chapter highlights the common causes of hematuria in children and suggests a systematic approach to evaluation of these children.

Hematuria is defined as more than 5 red blood cells (RBCs) per high-power fields in the urinary sediment.<sup>2</sup> Blood in the urine that is visible without microscopy is *gross hematuria* and finding RBCs in urine on

microscopy is termed *microscopic hematuria*. Hematuria can result from non-renal, and glomerular and extra-glomerular abnormalities. The list of common causes of hematuria is given in Table 18.1.

### CATEGORIZING THE PATIENT WITH HEMATURIA

Children with hematuria may come to the emergency room with:

- a. *Gross hematuria*: Gross hematuria can often be a frightening experience for the child and parents. A cause is identified in almost half the cases.<sup>3</sup> The common causes of gross hematuria include glomerulonephritis (e.g. poststreptococcal and IgA nephropathy), benign familial hematuria and bleeding disorders which are usually painless. Urinary tract infections, hemorrhagic cystitis, ureteropelvic junction obstruction, calculi, trauma and meatal stenosis with ulceration may present with painful gross hematuria. Recurrent hematuria with complete clearing of hematuria or persistent microscopic hematuria between the episodes of gross

Table 18.1: Causes of hematuria

Glomerular	Non-glomerular
Acute postinfectious glomerulonephritis	Nephrolithiasis*†
IgA nephropathy*	Hypercalciuria*†
Benign familial hematuria*†	Viral hemorrhagic cystitis
Systemic infections (malaria, leptospirosis, infective endocarditis)	Urinary tract infection@
Membranoproliferative glomerulonephritis	Vascular abnormalities
Focal segmental glomerulosclerosis	Renal vein or artery thrombosis@
Systemic lupus erythematosus	A-V malformations
Hemolytic uremic syndrome†	Ureteropelvic obstruction@
Henoch-Schonlein purpura	Renal cystic disease†@
Alport's syndrome*†	Bleeding, clotting disorder
Medications: NSAIDs	Medications: cyclophosphamide, anticoagulants

\* Causes of recurrent hematuria

† Hematuria with familial association

@ Common in newborns

hematuria is seen in IgA nephropathy, Alport syndrome and benign familial hematuria.

An important but underdiagnosed cause of gross hematuria is idiopathic hypercalciuria and the child may have gross or microscopic hematuria with symptoms of dysuria, frequency and urgency.

- b. *Clinical symptoms with findings of microscopic hematuria:* Many of the conditions mentioned above may also manifest with symptomatic microscopic hematuria. The clinical symptoms may be related to systemic illness or to the genitourinary tract.
- c. *Hematuria secondary to trauma:* Traumatic hematuria is seen due to injury to genitourinary system following vehicle accidents, fall or sports injuries. In fact, after the brain, the kidney is the most frequently injured internal organ in children. The degree of hematuria however is not a reliable indicator of severity of injury.
- d. *Blood spotting on diaper or underwear (urethrorrhagia):* Usually seen in pre-pubertal children.
- e. Asymptomatic microscopic hematuria is unlikely to be encountered in emergency clinics and is not discussed further.

### EVALUATING A CHILD WITH HEMATURIA

A detailed history, comprehensive physical examination and relevant laboratory tests are indispensable to the evaluation of hematuria (Flow chart 18.1).

**Presenting history:** Child may present with clinical manifestation that is general (e.g. fever, upper respiratory complaints, malaise), unrelated to urinary tract (e.g. rash, arthritis, bleeding from other sites), symptoms of upper urinary tract (e.g. facial puffiness, limb edema, decreased urine output, breathlessness secondary to fluid overload, headache or altered sensorium, seizures due to severe hypertension) or lower urinary tract (dysuria, urgency, frequency and flank pain).

**Drug history:** Many drugs (analgesics, cyclophosphamide, anticoagulants and quinine) can cause hematuria, hence a detailed history of drugs used by the child is useful.

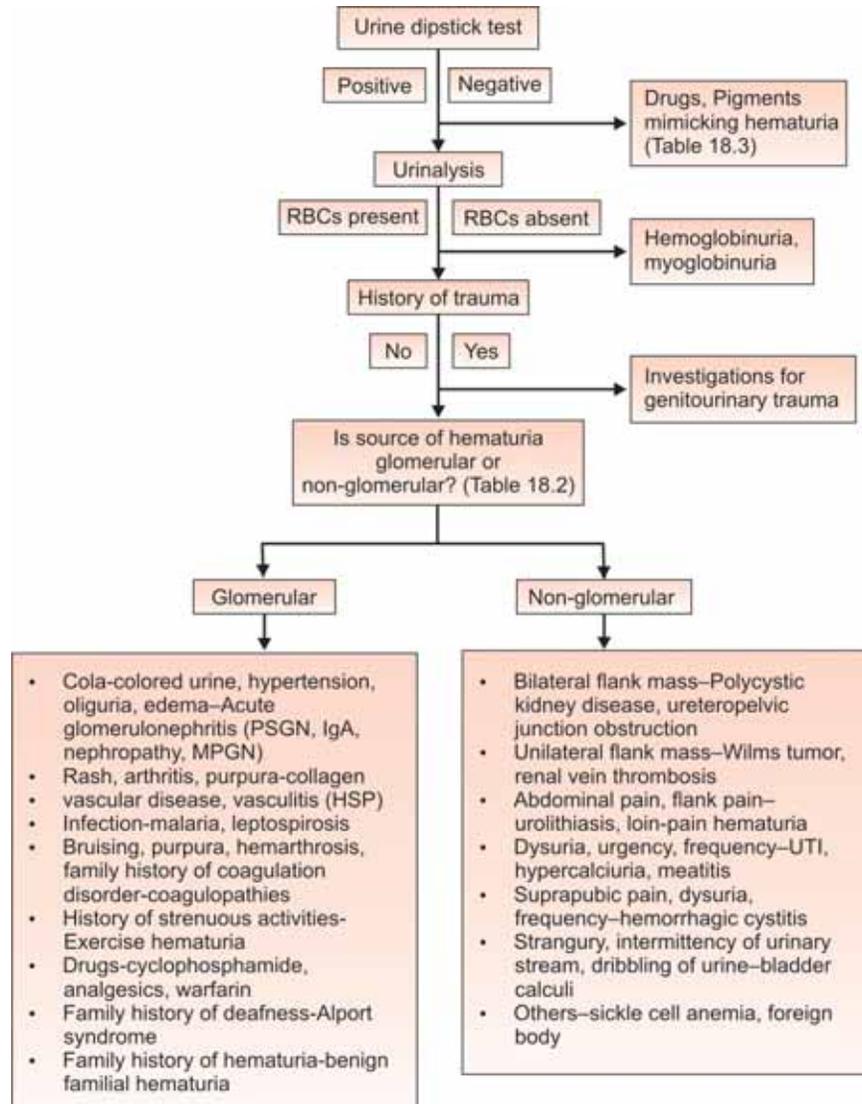
**Family history:** History of deafness, recurrent hematuria and kidney disease in family members should be enquired into.

**Physical examination:** Blood pressure should be measured and skin examined for rashes, bruises and palpable purpuric spots. Abdomen should be inspected for flank masses and bladder. Evaluation is not complete without examination of urethral meatus in males and vaginal introitus in females.

### Clues from History and Physical Examination

- An important step in evaluation is to distinguish bright red-urine from “cola-colored” urine as it indicates the source of bleeding (glomerular vs. lower urinary tract). The characteristics that help in distinguishing the two conditions are given in Table 18.2.
- Initial gross hematuria suggests a problem in the distal urethra, while hematuria throughout urination indicates upper urinary tract or bladder disease.
- Edema, decreased urine output, hypertension and cola-colored urine with a history of pyoderma or pharyngitis few weeks prior to onset of symptoms indicate poststreptococcal glomerulonephritis.
- History of upper respiratory infection followed within a few days by hematuria also suggests renal parenchymal disease.
- Bleeding disorder should be suspected in a child with bruising, purpura, hemarthrosis or a positive family history of coagulation disorder.
- A history of joint pains, skin rashes and prolonged fever in adolescents is suggestive of a collagen vascular disorder.
- Dysuria, urgency and frequency in older children are often seen in urinary tract infection or hemorrhagic cystitis.
- Family history of hematuria, stones, polycystic kidney disease, sickle cell disease or hearing loss (hereditary nephritis)
- Flank pain with hematuria may indicate calculi, pelviureteric junction obstruction, renal vein or artery thrombosis or very rarely loin-pain hematuria syndrome.
- History of strenuous activities like participation in athletic events or exercise suggests exercise hematuria.
- Strangury, intermittency of urinary stream and dribbling of urine indicates an obstructive process.
- The diagnosis of genitourinary trauma must be considered if a child has hematuria, decreased urine output, unexplained abdominal mass or pain and tenderness, penetrating abdominal trauma, fracture pelvis, blood at urethral meatus or scrotal swelling and hematoma.
- Wilms tumor (in younger children), polycystic kidney disease and pelviureteric junction obstruction are the differential diagnosis in a child presenting with a flank mass and hematuria.
- Blood spotting the underwear of an otherwise normal prepubertal child with dysuria and microscopic hematuria suggest idiopathic urethritis.

**Flow chart 18.1:** Algorithm for evaluation of hematuria PSGN post-streptococcal glomerulonephritis; MPGN membranoproliferative glomerulonephritis; HSP Henoch Schonlein purpura



- In adolescent girls with hematuria, it is important to elicit menstrual history at the time of evaluation; care should be taken to obtain an uncontaminated urine sample for analysis.

### Investigations

The goal of investigations is to confirm hematuria and identify the probable source.

**Urine dipstick:** The first step is to inspect the urine and perform a dipstick test as many substances may discolor urine and mimic hematuria (Table 18.3). It is important to briefly dip the strip in the urine, tap off

excess urine, and read the strip at the recommended time (usually one minute). Dipsticks have a sensitivity of 100% and a specificity of 99% in detecting one to five red blood cells (RBCs) per high power field.<sup>4</sup> The dipstick test will also be positive in hemoglobinuria and myoglobinuria. False positive test is obtained if urine is alkaline or in presence of oxidizing agents like povidone iodine.

**Urinalysis:** Hematuria is confirmed by microscopy. A positive dipstick reaction and an absence of RBCs and RBC casts on examining the urinary sediment suggest hemoglobinuria or myoglobinuria. The urine is also

**Table 18.2: Differentiating glomerular and non-glomerular hematuria**

Features	Glomerular diseases	Non-glomerular causes
<i>History</i>		
Dysuria	Absent	Present in urethritis and cystitis
Systemic complaints	Edema, fever, pharyngitis, rash, arthralgia	Fever (urinary infections), pain (calculi)
Family history	Deafness, hematuria in Alport syndrome	Positive with calculi and hypercalciuria
<i>Physical examination</i>		
Hypertension, edema	Usually present	Less common
Abdominal mass	Absent	Present in Wilms tumor, obstructive uropathy
Rash, arthritis	Lupus erythematosus Henoch Schonlein purpura	Absent, unless part of drug induced interstitial nephritis
<i>Urinalysis</i>		
Color	Brown, tea, cola	Bright red, clots may be present
Proteinuria	2+ or more	Less than 2+
Dysmorphic RBCs	More than 80%	Less than 20%
RBC casts	Common	Absent

**Table 18.3: Substances that color urine and mimic hematuria**

- *Red or pink urine:* Hemoglobinuria, myoglobinuria, beets and red dyes in food, porphyrins, chloroquine, phenazopyridine
- *Dark brown or black:* Methemoglobinemia, homogentisic acid, bile pigments
- *Dark yellow or orange:* Rifampicin, concentrated urine, pyridium

tested for protein excretion and the combination of hematuria and proteinuria (>100 mg/dL) indicates a significant renal disease of glomerular origin. Red blood cell casts is usually diagnostic of glomerulonephritis. White blood cells (WBC) and casts may suggest urinary tract infection or an inflammatory process. Examining red cell morphology by phase contrast microscopy may help to locate the site of bleeding. Presence of greater than 80% dysmorphic RBCs is suggestive of glomerular hematuria with a sensitivity of 96% and specificity of 93%.<sup>5</sup>

**Ultrasonography:** Ultrasonography should be performed in children with abdominal trauma, pelvic fracture, signs of obstruction of the urinary tract or in the presence of renal mass.

**X-ray KUB:** A plain X-ray of kidney and urinary bladder region in erect posture may be advised in

suspected cases of genitourinary trauma or in children with renal colic.

**Other investigations:** Obtaining blood for estimating levels of urea, creatinine and electrolytes should be individualized. Hemogram, platelet count and coagulation profile are obtained in suspected cases of coagulopathies or bleeding disorders. Urine sample for culture is taken if a urinary infection is suspected measurement of spot urine calcium-creatinine ratio is helpful in establishing hypercalciuria as a cause of hematuria. Serologic tests (C3, antinuclear antibodies) and ASLO titer may be requested in suspected cases of systemic lupus and poststreptococcal glomerulonephritis respectively.

### MANAGEMENT

A hemodynamically unstable or sick child with hematuria should be stabilized before specialist consultation is sought. A child with severe hematuria and passing clots should be catheterized, except in cases of urethral trauma. Children with evidence of acute nephritis, azotemia, renal failure or its complications, complicated UTI should be admitted and managed appropriately.

Patients with family history of deafness or nephritis, recurrent episodes of hematuria, systemic complaints like arthritis, rash and fever and isolated gross hematuria need to be referred for specialist opinion.

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Seizures account for 1 to 2 percent of all emergency department (ED) visits.<sup>1</sup> The focus of ED management is to stabilize the patient, terminate the seizure activity safely and quickly, identify and treat life-threatening conditions and to initiate follow-up.

Several times, a child may present with a condition that can mimic or be misinterpreted as an epileptic seizure. These conditions include convulsive syncope with or without cardiac dysrhythmia, decerebrate posturing, psychogenic events, dystonia, migraine and many others depending upon the age of the patient. A seizure has to be differentiated from these conditions as misdiagnosis can have significant therapeutic implications.

### Status Epilepticus

Status epilepticus (SE) is defined as single seizure or multiple episodes of seizures lasting more than 30 minutes without regaining consciousness in between.<sup>2</sup> This precise definition of SE although useful for epidemiological analysis and evaluation of therapeutic interventions does not address the urgency experienced by clinicians when confronted with a convulsing child, irrespective of how long the episode has lasted. It therefore seems more appropriate to take a pragmatic view and consider SE as the severe end of a continuum encountered during the progressive evolution of an unrelenting seizure, which may culminate with potentially life-threatening complications.

The classification of SE is given in Table 19.1.<sup>3</sup> Convulsive SE is the most important, as it is associated with significant morbidity and mortality. The determinants of neurological sequelae following SE are etiology, age at the time of seizure and duration of SE.<sup>4</sup> The risk of complications increases substantially if the SE lasts longer than 60 minutes.<sup>4</sup> Neurological residue includes mental retardation, focal neurological deficits, behavioral disorders and chronic epilepsy. The occurrence of further unprovoked seizures in patients with no prior seizure disorder is between 25 and 75 percent.<sup>5</sup>

The mortality rate is 10 percent; most deaths are attributable to the patient's underlying pathology. Only 1 to 2 percent of mortality is related to SE *per se*.<sup>6</sup>

In over 50 percent of cases, SE is the patient's first seizure.<sup>7</sup> It has been estimated that about 3 percent of epileptics will experience a SE in their lifetime.<sup>7</sup> Approximately one-quarter of childhood SE is idiopathic. Another quarter is idiopathic with fever. Another one quarter of patients have underlying congenital or developmental neurological abnormality or a history of acquired CNS insult. The final quarter of children present with SE as a symptom of acute disorder (meningitis, encephalitis, head trauma, stroke, drug intoxication, subarachnoid bleed, pyridoxine deficiency, of a metabolic abnormality like hypoglycemia or hyponatremia).<sup>5</sup>

**Table 19.1: Classification of status epilepticus**

#### Generalized

##### *Convulsive*

- Tonic-clonic
- Clonic
- Tonic
- Myoclonic

##### *Non-convulsive*

- Absence Spike and wave stupor, epileptic fugue, epileptic twilight state, minor SE

#### Partial

##### *Elementary*

- Focal motor status (epilepsia partialis continua)
- Somatomotor
- Dysphasia
- Others

##### *Complex partial*

- Epileptic fugue states, psychomotor SE, prolonged epileptic stupor

##### *Unilateral*

- Hemiclonic SE, hemiconvulsion-hemiplegia syndrome, hemigrand malstatus

### Pathophysiology of SE

Basis for SE is the failure of mechanism that aborts the seizure. This failure is either because of excessive and persistent excitation or ineffective recruitment of inhibition. Excitatory neurotransmitters that have a major role in SE include glutamate, aspartate, and acetylcholine, and the dominant inhibitory neurotransmitter is gamma-aminobutyric acid.<sup>8</sup> The blockage of N-methyl-d-aspartate (NMDA) channels by magnesium ions seems to be important in the pathogenesis of neuronal damage in SE.<sup>6</sup> There is also evidence that heat-shock protein is induced in some neurons in SE and that it may have a neuroprotective role.<sup>8</sup> Associated hypoxia, hypotension, acidosis and hyperpyrexia further exacerbate the neuronal damage.

### Evaluation in the Emergency Department

The history begins with a careful description of the event and its surrounding circumstances with documentation of the preliminary symptoms, progression of the clinical pattern, duration of the event including the postictal period (if the child presents in postictal phase), presence of incontinence or biting of the tongue. Every effort must be made to obtain a clear description of the event(s) from witnesses. The history helps to truly establish the event as an epileptic seizure.

Some children who are known epileptic may present with recurrence. Any change in the character of the seizure such as frequency or clinical features must be noted. Non-compliance/inadequate dosage of the anticonvulsants is the most common cause of recurrent seizures in this group of patients. Thus the use and doses of anticonvulsants must be ascertained. Seizures may also be exacerbated by several stress factors such as fatigue, systemic infection and fever. Identification of the stressors may explain an event and change the focus of management.

Prompt aggressive intervention is paramount but it is critical to stress the importance of taking the time to carefully observe the patient and to perform a physical examination (Table 19.2). Major systemic effects on cardiovascular, respiratory and renal system result from convulsive SE. These include tachycardia, cardiac arrhythmia, acidosis (metabolic as well as respiratory), hypoxia, dyselectrolytemia and hyperthermia. In addition the medications used to treat SE may contribute to these complications. For example benzodiazepines and barbiturates are potent respiratory depressants.

**Table 19.2: Physical examination**

- Vital signs (blood pressure, temperature, heart rate, respiratory rate)
- Mental status
- Pupil position and reactivity
- Signs suggestive of acute symptomatic seizure, e.g. rash, meningeal signs
- Motor activity if the child is still convulsing
- Automatism, e.g. lip smacking, swallowing, chewing movement
- Complete neurological examination to identify focal deficits
- Systemic examination to identify complications (if any)

Postictal confusion usually resolves over several hours and the failure to gradually improve must prompt a search for other causes such as hypoglycemia, CNS infection, CNS vascular event, drug toxicity, psychiatric disorders and non-convulsive SE. In particular, non-convulsive SE can present with subtle behavioral changes, which can be easily discounted unless the clinician maintains a high index of suspicion.<sup>9</sup> Non-convulsive SE can be diagnosed by continuous EEG monitoring.

### Investigations

#### Laboratory Studies

The laboratory tests indicated in the ED for patients presenting after having had a seizure for the first time, who are alert and oriented and who have no clinical findings is controversial.<sup>10</sup> At least, these patients need serum glucose estimation. All other tests have a very low yield in this group of patients. However, patients who have underlying medical disorder need detailed evaluation as indicated for the disease.

Patients with a known seizure disorder, who have a 'typical' event while taking medications but who are asymptomatic, alert and oriented only need a test for a serum anticonvulsant level. In these patients, it is important to investigate potential precipitants such as infections or new medications, which might have contributed to the event.

Patients who are in convulsive SE and those who are not actively convulsing but are persistently postictal require comprehensive diagnostic testing which includes a determination of serum glucose, electrolyte, urea, creatinine, calcium, magnesium (if indicated), a complete blood cell count, arterial blood gas analysis,

determination of anticonvulsant level (if on anticonvulsants) and liver function tests.<sup>2</sup>

### *Lumbar Puncture*

Lumbar puncture is strongly considered in those patients who are in status epilepticus, who have an unresolving postictal state, history suggestive of CNS infection (fever, headache, vomiting), meningeal signs, positive HIV history or who are otherwise immunocompromised. If meningitis is suspected but lumbar puncture cannot be performed, antibiotics should be administered immediately. There are no prospective studies that support performing a lumbar puncture as part of the diagnostic evaluation in the ED on patients who are alert, oriented, asymptomatic and not immunocompromised even if the seizure is a first time event.

### *Neuroimaging*

The indications and timing of computed tomography (CT) of the head, especially in patients with a first time seizure is controversial.<sup>11</sup> Of patients with a first time seizure, 3 to 41 percent have an abnormal head CT.<sup>12</sup> The proportion may be higher in developing countries because of high incidence of neurocysticercosis. The question remains whether identifying the abnormality in patients with non-focal neurological examination has an impact on outcome. A head CT is, however, strongly considered in the ED whenever an acute intracranial process is suspected in patients with a history of acute head trauma, malignancy, fever, persistent headache or appearance of a new focal neurological sign.<sup>13</sup> Brain imaging is eventually necessary in children with non-febrile SE and uncontrolled epilepsy. Skull radiograph is rarely of any use in the investigation of children with seizure unless a history of head trauma is elicited.

### *Electroencephalography (EEG)*

An urgent EEG in the ED is recommended for those patients with persisting altered mental status in whom non-convulsive SE is suspected. An EEG is also required when a patient's motor activity has been suppressed by either paralysis or barbiturate coma and assessment for ongoing seizure activity is needed.

## **Management**

There are four primary goals of therapy: (i) Ensure adequate systemic and cerebral oxygen delivery; (ii) Terminate seizure activity; (iii) Prevent seizure

recurrence; (iv) Establish a diagnosis and treat the underlying disorder if present.

### *Emergency Supportive Treatment*

Emergency /prehospital management of the patient who is convulsing focuses on securing the airway, maintaining oxygenation, maintaining blood pressure, obtaining intravenous access and protecting the patient from injury. Head and neck should be positioned to keep the airway open. An oral or nasal airway may need to be inserted. If necessary, airway should be suctioned. Oxygen should be administered by nasal cannula or mask. If the need for respiratory assistance persists after the patient has been supported by bag and mask, endotracheal intubation should be considered. The use of a padded tongue blade is contraindicated because it may induce emesis or break a tooth.

When a convulsing child is brought to the ED, after taking care of ABC of management, IV access should be rapidly secured. Immediate determination of blood sugar is required. Blood sample is also procured for other laboratory studies if indicated. If hypoglycemia is documented or the test is not available, 25 percent dextrose (2 ml/kg) should be given empirically. Hypotension can potentiate or exacerbate any derangement in cerebral physiology and function. Systolic blood pressure should be maintained at normal levels. Hyperthermia occurs frequently in SE and is primarily due to motor activity. Given the damaging effects of fever in patients with central nervous injury, hyperthermia should be treated promptly by passive cooling.

### *Anticonvulsant Treatment*

In the convulsing patient, initial supportive, therapeutic and diagnostic measures need to be conducted simultaneously. The goal of anticonvulsant treatment is the rapid termination of clinical and electrical seizure activity by the prompt administration of appropriate drugs in adequate doses, with attention to the possibility of complicating apnea, hypoventilation, and other metabolic abnormalities. The dosage schedule, route and rate of administration of the common anticonvulsant drugs used to treat acute seizures and SE are outlined in Tables 19.3 and 19.4. Early and effective treatment is essential to prevent the morbidity and mortality associated with prolonged seizures. Studies of prolonged seizures have established that the longer the duration of seizure episode before treatment, more difficult it is to stop and there is also a greater risk of long-term neurological sequelae.<sup>6,14</sup> Many anticonvulsant protocols and treatment guidelines have been reported from

**Table 19.3: Anticonvulsants used in the management of acute seizures**

Drug	Routes	Initial dose (mg/kg)	Rate of infusion	Remarks
Diazepam	IV	0.1-0.5	1 mg/min	Must be followed by phenytoin loading
	Rectal	0.2-1.0		
Lorazepam	IV	0.05-0.2	1 mg/min	Longer duration of action, less respiratory depression than diazepam Slower onset of action than rectal diazepam
	Rectal	0.1-0.4		
Midazolam	IV	0.05-0.2		Equally effective as rectal diazepam
	IM	0.1-0.2		
	Buccal	0.1-0.2		
	Nasal	0.1-0.2		
Valproic acid	Rectal/IV	20		Dilute 1:1 with sterile water
Paraldehyde	IM	0.15 ml/kg		Use glass syringe Dilute in 3:1 olive/coconut oil
	Rectal	0.3 ml/kg		
Phenytoin	IV	15-20	0.5-1 mg/kg/min	Mix only with normal saline May cause dysrhythmia and hypotension
Fosphenytoin	IV/IM	15-20 mg PE/kg	3 mg/kg/min	Less risk of hypotension, data not available for young children
Phenobarbitone	IV	10-20	1-2 mg/kg/min	Hypotension and respiratory depression especially if used after benzodiazepines

PE: Phenytoin equivalents

various institutions and groups. Most importantly, every institution should have a well established treatment protocol depending upon the local availability of drugs. A proposed management protocol is shown in Flow chart 19.1.

### Domiciliary Treatment

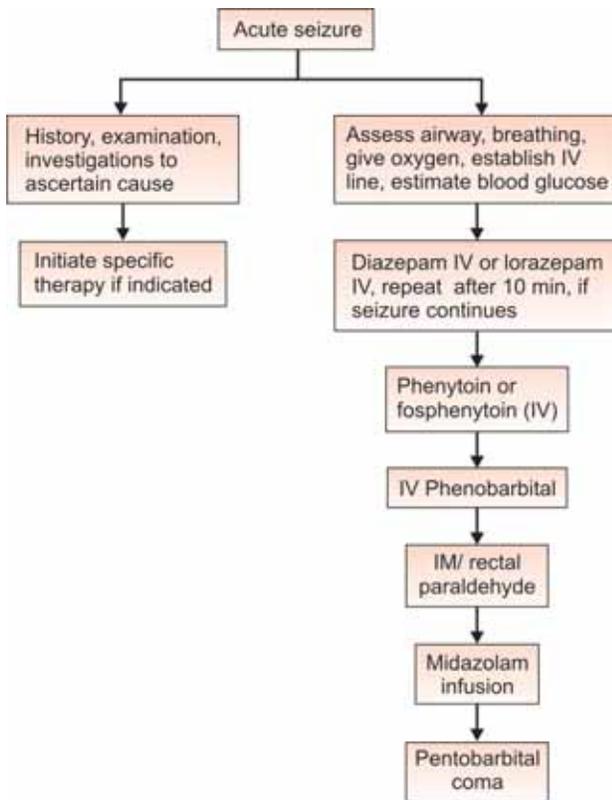
Prehospital treatment may be necessary for children with recurrent prolonged seizures. Home use of anticonvulsants for prolonged seizures in chronic

epileptics is effective and can decrease the cost spent on the evaluation and further treatment of these patients. The drug that is most commonly used is rectal diazepam.<sup>15</sup> Diazepam in the injectable (5 mg/ml) or syrup (2 mg/5 ml) form can be used. The usual rectal dose for diazepam is 0.2 to 1.0 mg/kg. A size 8 feeding tube after lubricating with xylocaine/paraffin is inserted per rectum up to 4 cm. The required dose of the drug is inserted through the feeding tube and then flushed with tap water. Only a single prehospital dose of rectal diazepam should be given by the caretakers.

**Table 19.4: Drugs used in the management of refractory status epilepticus**

Drug	Initial IV dose (mg/kg)	Maintenance infusion	Remarks
Pentobarbital	5-15	0.5-5 mg/kg/h	Titrate drip to seizure control/burst suppression on EEG
Propofol	1-3	2-10 mg/kg/h	Rapid infusion can cause apnea
Midazolam	0.15	1-5 µg/kg/min	Fewer hemodynamic adverse effects than pentobarbital
Diazepam	0.1-0.5	0.1-1 mg/kg/h	
Lidocaine	1-2	3-5 mg/kg/h	Proconvulsant at higher doses

**Flow chart 19.1:** Algorithm for management of status epilepticus



They should also be aware of the rare possibility of respiratory depression.

The rectal route of administration is not, however, always acceptable or convenient. A promising alternative is midazolam by buccal or nasal route. A few studies have found buccal and nasal midazolam to be equally effective as rectal diazepam in the acute treatment of seizures.<sup>16,17</sup> However, further studies are needed before it can be routinely recommended.

### Hospital Treatment

Any child who presents actively convulsing to ED should be assumed to be in SE and managed aggressively. The benzodiazepines are potent first line agents.<sup>18</sup> They should be administered only to patients with active convulsions. The drug routinely recommended is *diazepam*. It has onset of action within 3 minutes but a shorter duration of action (15 to 30 minutes). Therefore, when treating SE, a long acting anticonvulsant such as phenytoin must be administered concurrently with diazepam to prevent recurrent convulsions.<sup>19</sup> Diazepam should be administered by the intravenous (IV) route if IV line has been expeditiously established.

Diazepam stops convulsion within 5 minutes in 80 percent of patients. The usual IV dosage for diazepam is 0.1 to 0.5 mg/kg given at a rate of 1 mg/min. This dose can be repeated two or three times every 5 to 10 minutes if seizures persist up to a maximum dose of 10 mg. Many centers now prefer use of *lorazepam* compared with diazepam as a first line anticonvulsant as it has a longer duration of action (12-24 hours), less respiratory depression and repeated doses are less often required than with diazepam.<sup>20,21</sup> A second long-acting anticonvulsant is also not required because of longer duration of action. A maintenance drug such as phenytoin (5 mg/kg/day) should be added to control any further seizures. The dosing range of lorazepam by IV route is 0.05 to 0.2 mg/kg.

If IV access cannot be immediately obtained, then other routes of administration should be considered as prolonged attempts at access can jeopardize the patient. The rectal route is the preferred choice because intramuscular (IM) absorption of most medications is erratic and the intraosseous (IO) route requires an invasive procedure. Rectal diazepam is an effective treatment that can be used in prehospital and ED setup when presented with a child with difficulty in obtaining IV access.<sup>15</sup> Rectal lorazepam is not preferred as it has a slower onset of action compared with rectal diazepam. The liquid formulation of valproic acid per rectally in a dose of 20 mg/kg can also be used but response to rectal valproate is slower than with rectal diazepam.

Coupled with potent anticonvulsant properties and the ease of administration by intramuscular, nasal or buccal route, *midazolam* may prove to be an important drug for the initial management of acute seizure when IV access is not available.<sup>16,17</sup> The dose used is 0.1 to 0.2 mg/kg. These routes are also more socially acceptable than the rectal mode of administration. The safety, optimal dosing and the clinical utility of midazolam in initial management of SE, however, needs further evaluation.

*Phenytoin* is useful for maintaining a prolonged antiseizure effect after rapid termination of seizures with a benzodiazepine or when they fail. The loading dose is 15 to 20 mg/kg infused at a rate of 0.5 to 1.0 mg/kg/min (maximum 50 mg/min). A therapeutic effect can be seen in 20 minutes. Saline solution should be used for infusion because phenytoin can precipitate in dextrose solution. The side effects include hypotension, cardiac dysrhythmia, phlebitis and tissue necrosis from extravasation, movement disorder and cerebellar ataxia.

*Fosphenytoin* is a water-soluble ester of phenytoin that is rapidly converted to phenytoin by systemic

phosphatases. Fosphenytoin can also be thus administered intramuscularly. The dose of fosphenytoin is expressed in phenytoin equivalents (PE) and is 15-20 mg/kg, infused at a rate of no more than 3 mg/kg/min (maximum 150 mg/min). Phlebitis is less common with fosphenytoin but its primary disadvantage is high cost.

In case of no response to benzodiazepines and phenytoin, *phenobarbitone* is administered in a loading dose of 10 to 20 mg/kg at a rate of 1 to 2 mg/kg/min. It can also be used as a maintenance drug in dose of 3-5 mg/kg/day. Potential side effects include hypotension, respiratory depression, sedation and bradycardia. It must be used with caution in patients who have already received a benzodiazepine because respiratory depression may be exacerbated. Phenobarbitone is also the drug of choice in neonatal seizure, hypersensitivity to phenytoin and cardiac conduction abnormality.

If the patient is already receiving phenytoin or phenobarbitone, 5 mg/kg of the drug should be given before repeating the dose of diazepam or starting another drug because drug withdrawal is the most likely cause of SE in such cases. The caveat, however, is to determine the phenytoin level as soon as possible because phenytoin toxicity may also cause SE.

*Paraldehyde* can be administered per rectally (0.3 ml/kg diluted 3:1 in olive or coconut oil) or intramuscularly (0.15 ml/kg deep IM due to high incidence of sterile abscesses) in case seizures are still continuing. Paraldehyde should be given in a glass syringe as it dissolves plastic. If signs and symptoms of raised intracranial pressure are present, mannitol can be administered in a dose of 5 ml/kg (20%) IV over 10 minutes to decrease cerebral edema.

### *Refractory Status Epilepticus*

When the seizure has not responded to at least two doses of diazepam intravenously or rectally in succession followed by phenytoin or phenobarbitone or both or seizure lasting more than 60 minutes after treatment has been started, it is labeled as refractory SE.<sup>22</sup> It is associated with potentially fatal complications including severe hemodynamic and respiratory compromise. Patients with refractory SE must be ideally managed in a tertiary health care center with intensive care unit where facility for artificial ventilation is available. The modalities for treatment of refractory SE include barbiturate coma, midazolam or diazepam infusion, lignocaine, intravenous valproate, propofol, and inhalation anesthesia.

In a recent meta-analysis, midazolam infusion was found to be a good choice for initial treatment of refractory SE.<sup>23</sup> Compared with pentobarbital, midazolam has fewer hemodynamic consequences minimizing the need for invasive monitoring. The need for endotracheal intubation and mechanical ventilation is also less frequent with midazolam. Patient recovery is also quicker allowing earlier assessment after SE, and shortening the duration of ICU stay. A bolus dose of 0.15 mg/kg of midazolam is followed by continuous infusion at a rate of 1 µg/kg/min, increasing by 1 µg/kg/min every 15 minutes till a maximum of 5 µg/kg/min or seizure control. The optimum rate of infusion at which seizure control is achieved is maintained for a period of 48 hours. Subsequently the infusion rate is gradually decreased by 1 µg/kg/min every two hours. Any seizure activity during the weaning period requires an immediate resumption of the infusion to achieve again a seizure-free period of 48 hours.

Both pentobarbital and thiopental have been used for barbiturate coma. Patients requiring barbiturate coma must be intubated and mechanically ventilated with close hemodynamic and continuous EEG monitoring. Pentobarbital is given in a loading dose of 5 mg/kg followed by an infusion of 0.5-3 mg/kg/h. The patient is monitored for a burst suppression pattern by EEG. The patient remains in barbiturate coma for 12 to 24 hours. The patient is then weaned and observed for recurrence of seizure activity. If seizure recurs, the patient is placed back into the barbiturate coma and weaning is again tried after another 24 hours. Barbiturate coma is advantageous over the use of general anesthesia.

General anesthesia with isoflurane or halothane in conjunction with a neuromuscular blockade can also be used for refractory SE. Neuromuscular blockade results in muscle paralysis and facilitates mechanical ventilation. Continuous EEG is necessary to ensure that burst suppression has occurred when the patient is paralyzed.

### **First Time Seizure: When to Initiate Long-term Anticonvulsant Drugs**

The decision for therapy is based on the underlying cause of the seizure, the results of the head CT or MRI and EEG. All these data are rarely available before discharge from the ED; consequently the decision to initiate therapy must be based on the predicted risk for seizure recurrence which depends on the underlying etiology of the seizure.<sup>24</sup> When no etiology is identified and the EEG findings are normal, the

recurrence risk is 24 percent at 2 years.<sup>24</sup> Patients who have structural lesion on CT or patients with focal seizure that secondarily generalize have a risk of recurrence of up to 65 percent and are the group of patients that probably benefit from initiating anti-convulsant therapy in the ED.<sup>24</sup>

### Management of Febrile Seizures

Febrile seizures are events that occur between 6 months and 5 years of age, are associated with fever and have no underlying neurological cause. Simple febrile seizures are generalized tonic clonic events with no focality, lasting less than 15 minutes with a short postictal period. Complex febrile seizures either are multiple or have a focal onset or last longer than 15 minutes.

A diagnostic work-up even for first time events is not indicated when they occur in children older than 18 months.<sup>25</sup> Diagnostic studies instead are guided by general fever protocols. However, in patients less than 18 months of age, the signs of meningitis may be subtle or absent and thus lumbar puncture is strongly considered. The ED management of febrile seizures is same as for any other acute seizure.

### Management of Elevated Serum Anticonvulsant Levels

Current recommendations for the management of epilepsy emphasize the use of monotherapy with increasing single drug dosing to the point of seizure control or clinical toxicity.<sup>26</sup> Serum drug levels are, therefore, used only as a guide to therapy and must be interpreted in the context of the patient's clinical status. In addition, drug levels may vary depending on the patient's dosing schedule. For example, single dosing of phenytoin may result in a peak serum level that is two to three times that of the trough.

### Conclusion

The ED approach to the seizure patient begins with a careful assessment of the event with consideration given to the various disorders that can mimic epileptic seizure activity. The history, physical examination, and diagnostic tests are obtained to elucidate the seizure's etiology and to guide management. The morbidity and mortality attributable to this condition can be minimized through a rational therapeutic and diagnostic plan, and recognition and management of complications. The patient's social situation, resources and compliance must be taken into consideration before discharge. The parents should also be explained about the potentially dangerous situations, e.g. swimming or bicycling alone.

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A child presenting with coma is one of the most difficult diagnostic and management problems that may be encountered by a pediatrician. The gravity of the situation, the need to avoid further neurological damage, the wide range of possible causes call for a calm orderly approach to the situation at hand. Regardless of the etiology, initial management includes immediate attention to the ABCs in order to sustain life and prevent loss of brain function.

**Definition:** Coma or altered mental status implies a disorder of consciousness. It may be applied to a state or continuum of worsening consciousness from being fully alert and responsive to deep unresponsive coma.

Comatose states are indicative of diffuse impairment of cerebral functions, failure of brainstem activating functions or both. This may be caused by supratentorial lesions affecting deep diencephalic structures, subtentorial lesions affecting the brainstem or metabolic lesions diffusely affecting brainstem function (Table 20.1).

### GUIDELINES FOR DIFFERENTIATING CAUSES OF COMA

Although it is common practice to divide the etiology of coma as metabolic and structural causes, strict compartmentalization is not always possible as structural causes of coma may be associated with metabolic dysfunction, e.g. the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) complicating head injury.

See Table 20.2 for etiology of coma in children.

### EVALUATION OF A CHILD IN COMA

#### Immediate Considerations

- Assess and optimize airway, breathing and circulation in order to ensure that the brain is being adequately perfused.
- Obtain an immediate bedside capillary blood glucose level and correct if low.
- Brief relevant history of chronic and recent illnesses, trauma, medications in the home.
- Consider naloxone 0.1 mg/kg in suspected narcotic ingestions.

#### Secondary Considerations

A complete neurological examination is necessary with particular attention to 5 physiological variables. These may give valuable information about the level of the lesion in the brain, nature of involvement and direction of progression of the disease process.

These are:

- The level of consciousness
- Pattern of respiration
- Size and reactivity of the pupils
- Spontaneous and induced eye movements
- Motor responses.

#### Level of Consciousness

Numerous scoring systems have been developed to assess the level of consciousness. By far the most useful is the **Glasgow Coma Score (GCS)**, which was originally

**Table 20.1: Differentiating characteristics of structural and metabolic coma**

<i>Supratentorial lesions</i>	<i>Infratentorial lesions</i>	<i>Toxic, metabolic or infectious processes</i>
Initial signs focal	Initial signs of brainstem dysfunction	Confusion/stupor often precede motor signs
Rostrocaudal progression seen	Sudden onset coma	Symmetrical neurological findings
Asymmetric neurological signs at onset	Cranial nerve abnormalities common	Pupillary reactions preserved
Seizures may be present	Respiratory patterns often altered	Respiratory rate often altered

**Table 20.2: Etiology of coma in children**

The mnemonic "TIPS from the Vowels" is a useful method to remember the most common of the wide range of possible causes.

	Conditions	Comments
T	Trauma, head injury	Shaken baby syndrome: May present with non-specific history, retinal hemorrhages.
I	Intussusception	Mental status changes may precede abdominal finding.
	Insulin - hypoglycemia	Hypoglycemia secondary to accidental ingestion of oral hypoglycemic agents Ketotic hypoglycemia following prolonged fasting in thin built children.
	Inborn errors of metabolism	Coma may be associated with vomiting and seizures.
P	Psychogenic	Common in adolescents.
S	Seizures	Postictal states, non-convulsive status may masquerade as undifferentiated coma.
	Shock, stroke	Coma secondary to poor brain perfusion, arterial and venous infarcts.
	Shunt	Blocked or infected ventriculo-peritoneal shunts.
A	Alcohol ingestion, Abuse (Battered baby)	
E	Electrolytes	Disturbances of sodium, calcium, magnesium.
	Encephalopathy	Hypertension, Reye syndrome, hepatic failure, urea cycle defects, lead.
I	Infections	Encephalitis, meningitis, malaria.
O	Overdose, ingestion	Consider with unexplained loss of consciousness.
U	Uremic encephalopathy	

used to predict the outcome after head injury in adults. The **modified GCS** is applicable to younger patients and is the most frequently used general means of neurological assessment (Table 20.3).

An alternative method for assessing the level of consciousness is the **AVPU** score. This score, like the GCS, is also useful for the serial observation of the trends in the level of coma.

**A:** alert

**V:** responds to voice

**P:** responds to pain

**U:** unresponsive

### Respiratory Pattern

The control of respiration is governed by centers located in the brainstem (lower pons and medulla) and

**Table 20.3: The Glasgow coma score**

(< 5 years )	(>5 years)	
<i>Eye opening response</i>		
Spontaneous	Spontaneous	4
To speech	To speech	3
To pain	To pain	2
None	None	1
<i>Verbal response</i>		
Alert, coos, words - normal	Oriented	4
Irritable cry	Confused	3
Cries to pain	Inappropriate words	2
Moans to pain	Incomprehensible sounds	1
No response to pain	None	
<i>Motor response</i>		
Normal spontaneous movements	Obeys commands	6
Localizes (>9 months)	Localizes to supraorbital stimulus	5
Withdraws	Withdraws	4
Abnormal flexion (decorticate posturing)	Abnormal flexion (decorticate posturing)	3
Abnormal extension (decerebrate response)	Abnormal extension (decerebrate response)	2
None	None	1

modulated by forebrain cortical centers. Respiratory pattern abnormalities signify either metabolic derangements or neurologic insult.

#### Several Characteristic Respiratory Patterns Exist

- *Cheyne Stokes respiration (CSR)*  
This is a pattern of periodic breathing where hyperpnea alternates with apnea. The depth of breathing alters from breath to breath with a smooth rise to a peak and a smooth fall (decrecendo). CSR results from deep hemispheric or diencephalic dysfunction and may also be seen in children with metabolic abnormalities.
- *Central neurogenic hyperventilation*  
Sustained regular, rapid and deep respiration, which is seen in children with brainstem dysfunction.
- *Apneustic breathing*  
This pattern of breathing is characterized by inspiratory pauses lasting 2-3 seconds often alternating with end-expiratory pauses. Apneustic breathing is characteristic of pontine infarction and anoxic encephalopathy.

#### Pupillary Size and Reactivity

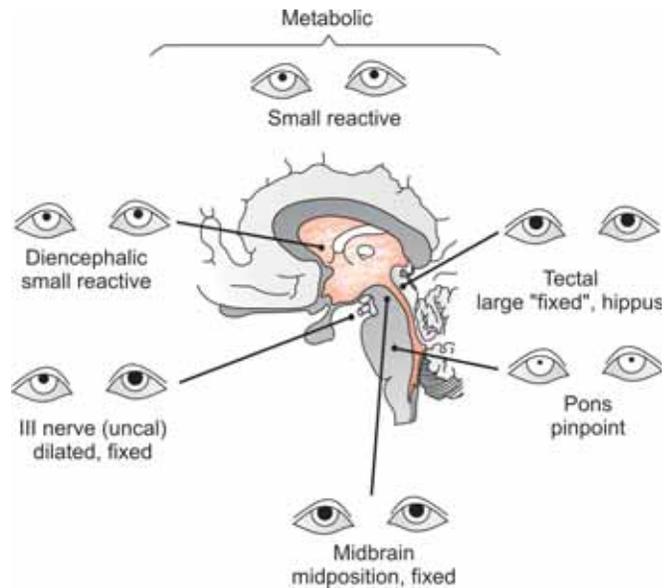
Pupillary reactions are controlled by a balance between the sympathetic and parasympathetic nervous system. As brainstem centers controlling consciousness are anatomically adjacent to those controlling pupils, pupillary changes are a valuable guide to the presence and location of brain lesions.

Additionally, **metabolic disturbances affect pupillary pathways late**. Consequently, the presence or absence of the pupillary reaction to light is one of the single most important differentiating features to distinguish between structural and metabolic disorders (Fig. 20.1).

#### Induced Eye Movements

Two specific eye movements are helpful in evaluating comatose children. One is the **oculocephalic** or **the doll's eye response**. This is performed by holding the eyelids open and rotating the head from side to side. The normal or positive response is conjugate deviation of the eyes in the opposite direction to which the head is turned.

The **oculovestibular** or **the calorie test** is performed by elevating the patient's head to 30° and slowly injecting 50 ml of ice water with a syringe. A perforated eardrum, wax in canal, or fracture base of skull should be excluded before performing this test.



**Fig. 20.1:** Pupillary abnormalities based on site of lesion (From: Plum F, Posner JB. *The diagnosis of stupor and coma*)

There may be three types of responses:

- Normal awake patients with intact brainstem:* Nystagmus with the slow component towards the irrigated ear and fast component towards midline
- Unconscious patient with intact brainstem:* Fast component abolished, eyes move towards stimulus and remain tonically deviated for >1 minute.
- Unconscious patient with brainstem dysfunction/brain dead patient:* No response to stimuli, i.e. eyes remain in the midline.

#### Motor Examination

Assessment of muscle strength, tone and tendon reflexes should be assessed for normality and symmetry. The ability of the patient to localize stimuli as well as the presence or absence of abnormal posturing helps in the assessment of severity of the neurological derangement.

**Decorticate posturing** with flexion of the upper extremities and extension of the lower extremities suggests involvement of the cerebral cortex and preservation of brainstem function.

**Decerebrate posturing** with rigid extension of the arms and legs is indicative of cortical and brainstem damage.

The **flaccid patient** with no response to painful stimuli has the gravest prognosis with injury sustained to deep brainstem lesions.

## LABORATORY EVALUATION

Laboratory evaluation of a patient in coma of indeterminate etiology may be divided into routine and specific investigations.

### Routine Investigations

- White blood count, coagulation screen
- Arterial blood gas, glucose, electrolytes, calcium, magnesium
- Serum and urine osmolality
- Urine for sugar, ketones, pH
- Infection screen, virology
- Chest X-ray

### Specific Investigations, where clinically indicated

- EEG, ECG
- CT scan
- CSF analysis if features of raised intracranial tension (ICT) not present
- Serum ammonia, lactate, pyruvate in suspected metabolic disorders
- Liver, renal function tests

### Additional tests, where appropriate

Thyroid function tests, lead level, skeletal survey, contrast studies of gastrointestinal tract.

## MANAGEMENT OF A COMATOSE PATIENT

The main goals of care include optimizing cerebral blood flow (CBF)/ cerebral perfusion pressure (CPP) and minimizing factors that can aggravate neuronal injury or trigger intracranial pressure (ICP) elevation.

### Assess the Airway, Breathing and Circulation (ABCs)

The airway should be stabilized and an assessment made for the need for intubation. Even if spontaneously breathing with normal gas exchange, many comatose children will benefit from intubation, especially if they have intracranial hypertension. Early intubation, ventilation and deep sedation are often overlooked as key interventions for ICP control.

A GCS below 8 has been the standard indication for intubation. Recent literature however states that intubation should be considered in patients with a GCS below 12. Other indications for intubation include deterioration in the level of consciousness, evidence of herniation and irregularities in respiration (Table 20.4).

**Table 20.4: Signs of cerebral herniation**

1. Glasgow coma score <8
2. Abnormal pupil size and reaction (unilateral or bilateral)
3. Absent doll's eye movements
4. Abnormal tone (decerebrate/decorticate posturing, flaccidity)
5. Hypertension\* with bradycardia\*
6. Respiratory abnormalities (hyperventilation, Cheyne-Stokes breathing, apnea\*, respiratory arrest)
7. Papilledema (rare, especially in infants)

\* (Cushings Triad) - Late findings

The blood pressure should be kept at the higher range of normal (for age). This requires ensuring appropriate fluid and inotrope management.

### Assess and Treat for Immediately Correctable Cause of Coma

Perform bedside capillary glucose test and correct if low, send samples to lab for routine hematological and biochemical testing.

### Assessment of the Depth of Coma

The standard assessment tool is the GCS in older children and modified GCS in children <5 years old or the AVPU.

### Assessment and Treatment of Raised ICP

The focus of contemporary ICP management has changed in recent years in two important aspects. Firstly, increasing emphasis on CPP (cerebral perfusion pressure) management in addition to ICP control and secondly, the increasing recognition of the potential for overzealous hyperventilation to aggravate cerebral ischemia by reducing CBF.

CPP = Mean arterial pressure (MAP) - Intracranial pressure (ICP)

Cerebral ischemia may result when CPP is lowered, either from raised ICP or lowered MAP (hypotension). When the ICP is critically raised, herniation syndromes (uncal, central or medullary herniation) can occur, which, along with hypoxic-ischemic damage from reduced CPP, are the most important causes of death. Table 20.4 describes the signs of herniation.

If raised ICP is clinically suspected, therapeutic measures should be immediately instituted as papilledema may not be seen in acutely elevated ICP and fatal herniation can occur even after a "normal" CT scan.

*Role of Mannitol (Table 20.5)*

Mannitol is indicated acutely for patients in whom there is a strong clinical suspicion of raised ICP or imminent herniation. Mannitol has two distinct effects. The immediate effect is related to its rheologic properties (decreased blood viscosity) resulting in a transient increased CBF followed by a more sustained fall in CBF. The delayed osmotic effects occur after 15-30 minutes and last for 4-6 hours. Urinary fluid losses should be replaced with normal saline to avoid volume depletion.

*Emerging Role of Hypertonic Saline (HTS)*

HTS acts like mannitol by establishing a constant osmolar gradient in order to draw fluid from the brain parenchyma but without the risks of dehydration and tubular damage as in the case of mannitol. In the hypotensive/hypoperfused patient, HTS may be the osmotherapy of choice for reducing ICP while maintaining MAP/ CPP. The beneficial effects of HTS with a low frequency of side-effects have been described in the setting of pediatric traumatic brain injury and cerebral edema occurring during DKA treatment in children.

**Anti-seizure Medications in Coma**

Convulsions can cause massive increases in CBF, consequent increase in ICP, can lead to secondary brain damage and may precipitate or be precipitated by cerebral herniation. Apart from generalized tonic clonic seizures (GTCS), some comatose children may have non-convulsive seizures (NCS) manifesting with subtle signs

such as eyelid twitching, eye deviation or nystagmus. A bedside EEG may be informative. If in doubt, empiric treatment of seizures may be justified and can result in improvement of consciousness.

**Neuroimaging**

Urgent imaging is indicated in afebrile coma and the presence of focal signs or papilledema, as the diagnosis includes stroke, intracranial bleed, tumor or hydrocephalus. However, any child who does not have a very obvious metabolic/toxic cause for the coma generally requires to be imaged. A CT scan may provide information about the cause of altered mental status and the presence of intracranial hypertension, however a normal CT scan does not rule out raised ICP.

An MRI may be more specific for early changes of herpes simplex encephalitis (where CT may be normal), posterior fossa and white matter pathology. A cranial ultrasound may miss subdural collections or even extensive infarcts and a CT or MRI is an essential investigation in a deeply comatose infant even when the anterior fontanelle is open.

**Lumbar Puncture (LP) in a Comatose Child**

The potential benefits of early LP include making an early diagnosis of CNS infection and identification of the pathogen and drug sensitivities. Contraindications to LP include signs of cerebral herniation, low GCS, focal neurological signs, or cardiorespiratory compromise. In an unconscious child with potential raised ICP, the decision is controversial with some authors stating that

**Table 20.5: Mannitol: Concerns and contraindications**

Concerns	Effects	How/when to avoid
Excess diuresis	Hypovolemia, fall in CPP	Lower doses 0.25-0.5 g/kg (1.2-2.5 ml/kg of a 20% solution) repeated 4-6 hourly*
Use in focal pathology with midline shift: (e.g., necrotizing encephalitis, edema surrounding intracranial hemorrhage, tumor, infarct)	Mannitol may cause "selective debulking" of normal brain parenchyma with increase in midline shift	Mannitol should be reserved for features of severely increased ICP or impending herniation
Rebound effect	Worsening edema after discontinuation	Limit use to less than 48-72 hours. Use smaller doses. Avoid concurrent hypotonic IV fluid or dilute enteral feeds
Contraindications		Hypotension Renal failure Serum osmolality > 320 mOsm/kg

\*Emergency therapy for herniation syndromes: 1.0-1.5 g/kg of 20% mannitol, Subsequent doses: 0.2.5-0.5 g/kg Q4-6H, measure serum osmolality

the risk of herniation far outweighs the benefit of knowing the pathogen from an early LP.

### Choice of Empiric Antimicrobials

If a CNS infection is suspected in a febrile child presenting in acute coma and seizures, empiric antimicrobial should include acyclovir in addition to a third generation cephalosporin until further confirmatory tests are available. The need for empiric anti-malarials and anti-mycoplasma therapy (IV macrolide) should be carefully assessed.

### Fluid Therapy

There is accumulating data that hypovolemia worsens outcome in children with meningitis, malaria and severe head injury. Hypovolemia (fluid restriction, diuretics) can lower the CPP and lead to worse ICP due to autoregulatory vasodilation. What must be restricted are hypotonic fluids such as N/5 saline in 5% dextrose (Isolyte P). The dextrose will be metabolized with a resultant hypotonic fluid that can exacerbate cerebral edema and ICP. Adult and pediatric literature stress the importance of avoiding both hyperglycemia as well as hypoglycemia since the former can also worsen neurological outcome.

Enteral feeds should be started at the earliest.

### Management of Persistent Raised ICP in the ICU

If despite the above treatment, the patient continues to show evidence of raised ICP, further measures to tackle refractory raised ICP must be instituted. Specific surgically correctible lesions should be attended to.

While steroids should not be used for ICP related to infarcts, hemorrhage or trauma, the use of dexamethasone for vasogenic edema related to tumors, granulomas and abscesses can lead to dramatic reduction in lesion volume.

Head end elevation by 30° (provided patient not hypotensive) and avoidance of neck kinking are important. Fever, agitation and seizures must be assiduously controlled as they can cause massive

increases in CBF and CPP. If ventilated, the PaCO<sub>2</sub> should be maintained between 30-32 mm Hg in order to prevent cerebral ischemia. More extreme hypocapnia can be employed as a short-term temporizing measure for acute deterioration.

Barbiturate coma and/or mild hypothermia are used in order to reduce the cerebral metabolic rate for oxygen (CMRO<sub>2</sub>) and thus the cerebral blood flow, although most references pertain to adults. Hypotension during barbiturate use may require vasopressors to optimize the MAP/ CPP.

In ICP refractory to medical measures, surgical decompression has been shown to improve survival and functional outcome.

### PROGNOSIS

The prognosis of a child in coma depends on the cause of altered mental status. In general, children have a better prognosis than adults. Prolonged coma after hypoxic-ischemic insult carries a poor prognosis, but children surviving infectious encephalopathies have a good outcome. Cortical blindness often recovers.

Neuroimaging may be useful in predicting prognosis: poor outcome is expected if there are large spread areas of low densities, suggesting global ischemia.

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# 21 Intracranial Hypertension

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Raised intracranial pressure is a life-threatening problem frequently encountered in pediatric emergency and intensive care units. It adds considerably to the morbidity and mortality of a diversity of illnesses. Reducing the raised intracranial pressure (ICP) and maintaining an adequate cerebral perfusion pressure is of vital importance in the management of such illnesses. An increased knowledge of the regulation of ICP and its pathophysiology as well as advancements in the techniques of measuring ICP and cerebral blood flow, have helped in developing appropriate therapeutic strategies.

## PATHOPHYSIOLOGY

Intracranial pressure is the pressure within the intracranial vault that contains the brain, cerebral blood volume and cerebrospinal fluid (CSF). An increase in volume of any one of these will produce an increase in ICP. For the ICP to remain stable, increase in volume of any one of the intracranial contents must, therefore be accompanied by simultaneous reduction in volume of one or more of the others. This concept is known as the *Monro-Kellie doctrine*. The compensatory mechanisms, however, fail beyond a certain limit after which decompensation occurs. Even small increase in any compartment will lead to large increase in ICP once decompensation has occurred.

The cranial cavity is compartmentalized into a supratentorial and infratentorial portion by the tentorium; the falx cerebri further divides the supratentorial portion into the right and left cerebral hemispheres. Compartmentalization of intracranial pressure prevents injurious movements of the brain. At the same time the unyielding character of the compartments limits the expansion of the intracranial contents. Thus, a primary neurological insult such as trauma, hypoxia and infection, that produces brain swelling leads to an increase in ICP with a consequent decrease in the cerebral blood volume and secondary ischemic injury to the brain. Also, pressure gradients

may develop between compartments leading to brain shifts and herniation of brain. The concept of ICP is more complex, and involves an understanding of each of the components of the intracranial vault.

## Brain

The brain constitutes 90 percent of the intracranial vault, 75 to 80 percent of the brain consists of water which is mainly intracellular in the gray and white matter. Only 15-20 percent of the water is extracellular. The blood-brain barrier consists of tight endothelial junctions that result in relative impermeability to proteins and solutes. The regulation of the blood-brain barrier is complex. Fluid balance of the brain is also controlled by a variety of hormones such as vasopressin, atriopeptin and angiotensin.<sup>1</sup> An increase in volume of the brain may occur because of edema, blood, tumors, etc.

### *Cerebral Edema*

There are three types of cerebral edema:<sup>2</sup>

*Vasogenic edema:* This is characterized by increased permeability of brain capillaries and is generally present in traumatic and inflammatory conditions such as meningitis and encephalitis, brain abscess and tumors. It does not reflect neuronal injury and is easily treated.

*Cytotoxic edema:* This is characterized by swelling of nerve cells secondary to cell injury caused by extraneous insults such as hypoxia, ischemia, trauma, infection or poisoning. It reflects failure of ATP-dependent sodium exchange and may involve all brain cells including neurons, astrocytes and oligodendroglia. States of irreversible cytotoxic edema are seen in diffuse axonal injury. Therapy does not significantly affect the outcome. Cytotoxic edema often coexists with vasogenic edema.

*Interstitial edema:* This is due to increased CSF hydrostatic pressure, as in obstructive hydrocephalus or situations with increased amounts of CSF. Treatment

involves surgical drainage or use of agents to decrease CSF production.

### Cerebrospinal Fluid (CSF)

The CSF accounts for 10 percent of the total intracranial volume; and is produced mainly in the choroid plexus at the rate of 0.35  $\mu$ l/min. CSF absorption is primarily through the arachnoid villi. A rise in ICP leads to compensatory increase in CSF absorption.

### Cerebral Blood Volume and Flow

The cerebral blood volume is the volume of blood contained within the intracranial vasculature. It constitutes about 10 percent of the intracranial volume and is an important contributor to ICP. Cerebral blood flow on the other hand is the amount of blood in transit through the brain and is not a primary determinant of ICP.<sup>3</sup> The normal adult cerebral blood flow is about 50 ml/100g/min; it is higher in children.<sup>4</sup>

### Cerebral Dynamics Overview

Cerebral perfusion pressure (CPP) is the net pressure at which blood is supplied to the brain tissue. This is determined by the resistance offered by the ICP, and the blood pressure, and is calculated as

$$\text{CPP} = \text{MAP} - \text{ICP}$$

where  $\text{MAP} = 1/3 \text{ systolic BP} + 2/3 \text{ diastolic BP}$

This is an oversimplification and may lead to the wrong assumption that an elevated ICP is always associated with a decrease in cerebral perfusion and that low ICP always indicates adequate perfusion. However, this may not always be true; in case of cerebral vasodilatation the elevated ICP is associated with the increased total blood flow. Similarly vasospasm which causes an initial reduction in ICP is associated with reduced cerebral perfusion. Thus the interpretation of data obtained through ICP monitoring must be weighed within the context of the clinical situation.

Maintaining an adequate perfusion pressure is important. It is generally recommended that the CPP needs to be maintained at a level of at least 50 mm Hg in older children; levels around 40 mm in toddlers and 25 mm in neonates are acceptable.<sup>5</sup> These values are however, debatable.

### Autoregulation

The brain has ability to autoregulate its blood supply in response to its perfusion pressure. The blood flow is affected by a number of metabolic and chemical factors.

The blood flow is coupled to the cerebral metabolic rate, and is increased in conditions with increased cerebral metabolic activity such as seizure, fever, etc.

*Metabolic:* The most critical metabolic mediator is the arterial carbon dioxide tension ( $\text{pCO}_2$ ). Hypercapnia causes marked cerebral vasodilatation increasing CBF up to 350 percent of normal.<sup>6</sup> Hypocapnia causes intense vasoconstriction capable of changing cerebral blood flow by 4 percent for every mm Hg change in  $\text{pCO}_2$  within a physiologic range.<sup>7</sup>  $\text{CO}_2$  readily crosses the blood-brain barrier and lowers the CSF pH *via* its reaction with carbonic anhydrase. Alterations in tissue pH produce changes in arteriolar diameter. Changes in  $\text{pO}_2$  also influence the blood flow but to a lesser degree than  $\text{pCO}_2$ . Hypoxemia with  $\text{pO}_2$  less than 50 mm Hg causes a rise in blood flow by vasodilatation;<sup>8</sup> increase in oxygen content produces vasoconstriction but to a lesser degree.

*Myogenic:* As blood pressure or CPP falls, cerebral vessels dilate, and conversely as the pressure rises, vessels constrict thereby altering resistance to maintain a uniform flow rate. Changes in blood pressure within the range of 60 to 160 mm Hg do not normally affect the blood flow. However, the ability to autoregulate may be lost in presence of infection, hypoxia, ischemia and a variety of cerebral injury.

It has been recently suggested that the myogenic mechanism plays a secondary role to other mechanisms and is mainly involved in dampening arterial pulsations.<sup>6</sup>

*Neurogenic:* The sympathetic nervous system has been shown to shift autoregulation towards higher pressures and sympathetic blockage to shift it down-wards.<sup>9</sup> The sympathetic nervous system also has an effect on the regulation of cerebral blood volume and CSF formation.<sup>10</sup>

*Endothelial cell dependent:* Nitric oxide (NO) produces relaxation of both cerebral arteries and arterioles and influences blood flow regulation under a variety of normal and pathological conditions, such as ischemia and hypoxia.<sup>11</sup>

### ICP: Normal Range and Pressure Volume Relationships

ICP gradually increases with age. Normal values for a neonate are less than 2 mm Hg, at 1 year 5 mm Hg,<sup>12</sup> 7 years 6-13 mm Hg and in older children up to 15 mm Hg.<sup>13</sup> At any age, pressures of 20 mm Hg or more are high, and 40 mm Hg very high. The ICP fluctuates during the day and is greater in the supine than erect position and during transition to deep sleep. Coughing, sneezing and Valsalva maneuver increase the

ICP dramatically. The normal brain is capable of dealing with these transient changes and ICP increase is significant primarily when brain homeostasis is disturbed.

The initial increase in volume of intracranial contents is compensated by displacement of CSF into the vertebral canal, a decrease in CSF production, increase in CSF reabsorption and displacement of blood into dural venous sinuses. But these compensatory mechanisms are soon exhausted and the ICP rises. In the early phase the rise in pressure in response to a given increase in volume is small. However, as the ICP rises, the brain becomes less compliant, autoregulation fails and small increases in volume lead to higher increases in ICP. Thus the pressure volume relationship of intracranial contents is not a straight line.<sup>14</sup> The increase in ICP is also influenced by the rate of rise in intracranial volume. If the rate is slow, as with many brain tumors, volume compensation may occur for sometime. On the other hand, acute increase in volume as with intracranial hemorrhage cannot be compensated and leads to immediate increase in ICP.

### Etiology of raised ICP

Raised ICP may emanate from various causes as listed in Table 21.1.

### Clinical Features of Intracranial Hypertension

Raised ICP *per se* does not cause signs until it reaches levels that preclude cerebral perfusion and cause global

ischemia. Clinical signs are due to secondary pressure effects and tissue shifts and are often determined by the rate of rise of ICP and the underlying condition. The following clinical features may be seen:

*Headache:* It may be bioccipital or bifrontal or generalized. It is generally maximum in early morning but may persist throughout the day or for a number of days. It is a consequence of stretching of dura, venous sinuses and sensory nerves.

*Vomiting:* It is most prominent in early morning, is often projectile and is not associated with nausea. It may provide relief from the associated headache.

*Altered mentation:* Irritability, lethargy, apathy, drowsiness, loss of memory with decline in school performance is often seen. Various levels of coma are seen depending on the rapidity and severity of increase in ICP.

*Visual changes:* Although vision may be entirely normal in the early stages, enlarged blind spots may be present. Later, the visual acuity decreases. Paresis of one or both sixth cranial nerves may lead to diplopia and convergent squint. The eyes may show the classic 'sunset' sign with impairment of upward gaze. Although papilledema is a reliable sign of intracranial hypertension, it may take time to develop. It is generally not seen in young infants with open fontanelle and sutures.

Headache, vomiting and papilledema have been considered hallmarks of raised ICP. It must, however, be remembered that raised ICP may exist even in the absence of these features.<sup>15</sup>

*Increase in head size:* An increase in head size with delay in closure of sutures occurs with chronically raised ICP. The fontanelle becomes full and tense and loses its normal pulsations. The Macewen or 'crack-pot' sign (resonant sound on percussion of the skull) is positive.

*Vital functions and brain herniation:* A sudden increase in ICP is a medical emergency. Compensatory mechanisms are triggered to maintain cerebral perfusion. The systemic blood pressure rises. This is achieved by an increase in peripheral vascular resistance and relative bradycardia which increases end-diastolic filling time and stroke volume. The Cushing reflex (hypertension and bradycardia) carries a bad prognosis. Some patients may have tachycardia. Hyperventilation occurs in an attempt to control the rise in ICP. However, if the ICP exceeds the compensatory mechanisms, herniation with secondary compression and infarction of brain tissue occurs. Pressure gradients may develop between, (i) right and

**Table 21.1: Etiology of intracranial hypertension**

#### Intracranial Causes (Primary)

CNS infections: meningitis, encephalitis, neurocysticercosis, cerebral malaria, brain abscesses  
 Status encephalitis  
 Trauma  
 Brain tumor  
 Intracranial hemorrhage (nontraumatic)  
 Benign intracranial hypertension  
 Multiple cortical thrombosis

#### Extracranial Causes (Secondary)

Airway obstruction  
 Hepatic failure  
 Hypertensive encephalopathy  
 Shock  
 Drugs- tetracycline, rofecoxib  
 Hyperpyrexia

#### Postoperative

Cerebral edema  
 Intracranial hematoma  
 Vasodilatation  
 CSF obstruction

**Table 21.2: Herniation syndromes**

Herniation syndrome	Anatomical description	Clinical findings
Uncal (lateral transtentorial)	Inferior displacement of medial temporal lobe (uncus) past free edge of tentorium cerebelli	Ipsilateral oculomotor nerve palsy Posterior cerebral artery infarction Kernohan's notch phenomenon
Central (transtentorial)	Progressive downward displacement of diencephalon and brainstem	Progressive brainstem dysfunction Medium sized fixed pupils Decorticate posturing Cheyne-Stokes respiration Diabetes insipidus
Ascending (transtentorial)	Infratentorial mass effect protruding upward compressing the midbrain	Nausea/vomiting Progressive stupor
Subfalcine	Cingulate gyrus forced under falx cerebri	Behavioral changes Contralateral lower limb monoparesis Anterior cerebral artery infarction
Tonsillar	Downward displacement of cerebellar tonsils through foramen magnum	Small reactive pupils Medullary dysfunction Cardiorespiratory arrest Bilateral arm dysesthesia

left supratentorial compartments across the falx, (ii) supratentorial compartments and the posterior fossa (upward shift and cone), (iii) posterior fossa and infratentorial fossa or (iv) posterior fossa and spinal cord across the foramen magnum.

The pressure gradient may only be a few mm Hg to cause a shift and cone. Signs of herniation syndromes are shown in Table 21.2. Immediate measures to reduce the ICP must be taken if any of these findings are noted, especially in combination.

#### ICP Waveform

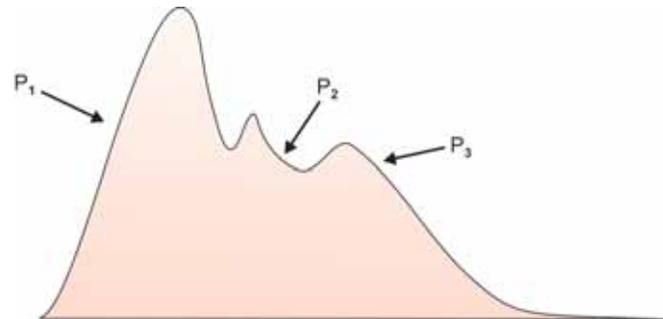
The ICP waveform resembles an arterial waveform. Respiratory excursions due to transmission of intrapleural pressure to the intracranial vault may be seen. The resting ICP, CPP and compliance may be interrupted by sudden rises in ICP termed 'plateau waves'. These are often precipitated by noxious maneuvers like suctioning or physiotherapy and pain. They last for 1-10 min, range from 25-60 mm Hg, and are most pronounced in patients with decreased intracranial compliance.<sup>16</sup>

The normal ICP waveform contains three phases (Fig. 21.1)

- P<sub>1</sub> (percussion wave) represents arterial pulsations.
- P<sub>2</sub> (rebound wave) reflects intracranial compliance.
- P<sub>3</sub> (dichrotic wave) represents venous pulsations.

#### Pathologic Waveforms

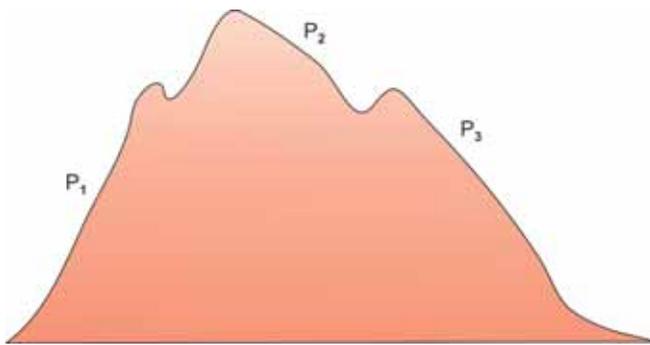
As the ICP increases, cerebral compliance decreases, arterial pulses become more pronounced, and venous

**Fig. 21.1: Normal ICP waveforms**

components disappear. Pathologic waveforms include Lundberg A, B, and C types. Lundberg A waves, or plateau waves, are ICP elevations to more than 50 mm Hg lasting 5 to 20 minutes. These waves are accompanied by a simultaneous increase in MAP, but it is not clearly understood if the change in MAP is a cause or effect. Lundberg B waves, or pressure pulses, have amplitude of 50 mm Hg and occur every 30 seconds to 2 minutes. Lundberg C waves have amplitude of 20 mm Hg and a frequency of 4 to 8 per minute; they are seen in the normal ICP waveform, but high-amplitude C waves may be superimposed on plateau waves<sup>17</sup> (Fig. 21.2).

#### Indications of ICP Monitoring

ICP monitoring, being an invasive procedure and not free from complications, merits specific indications for a favorable risk-to-benefit ratio and may be considered in following situations:



**Fig. 21.2:** High ICP waveforms

1. Patients with low GCS of 8 or less at admission.
2. Patients with traumatic brain injury with abnormal admission CT scan.
3. Patients with GCS more than 8 but requiring treatment like PEEP which may increase ICP.
4. Patients with multiple systemic injuries with altered level of consciousness.
5. Patients who undergo operative procedures like removal of intracranial mass lesions.
6. Patients with conditions like cerebral infarction which have a likelihood of expansion leading to progressive clinical deterioration.

ICP monitoring is generally carried for duration until 24-48 hours elapse with normal ICP recording in absence of anti-raised ICP measures.

### Methods of Measuring ICP

It is generally assumed that a steady pressure state exists within the cranium. This may not always be true, especially in the early stages of an illness. Pressure near an expanding lesion may be high even when intraventricular pressure is normal. Pressure gradients may also develop if there is obstruction in CSF pathways. Lumbar CSF pressure may be normal in patients with supratentorial lesions if there is a tentorial block. In such conditions, therefore, ICP is best measured from the supratentorial compartments. Also measurement of ICP by lumbar puncture may be complicated by prolonged leakage from the punctured spinal site and subsequent brain herniation. The curled up position for lumbar puncture often causes a rise in pressure due to jugular venous compression, particularly in small children where restraint is necessary.<sup>5</sup> Hence the lumbar site is not appropriate for ICP monitoring.

Numerous ICP monitoring devices have been designed which can be inserted at the bedside in an intensive care unit. These are summarized in Table 21.3. Intraventricular catheters are most suitable for those

children with severe intracranial hypertension who need precise ICP monitoring and reduction of ICP by withdrawal of CSF. Availability of intraparenchymal fiberoptic monitors and catheter tip strain gauge transducers has limited the use of previously popular subarachnoid and epidural monitors.<sup>4</sup>

Non-invasive monitoring by transcranial Doppler ultrasound has recently been reported to be of help in early detection of deterioration in cerebral hemodynamic trends.<sup>15</sup>

### Goals of Therapy

The goals of ICP treatment may be summarized as follows:

1. Maintain ICP at less than 20 to 25 mm Hg.
2. Maintain CPP at greater than 60 mm Hg by maintaining adequate MAP.
3. Avoid factors that aggravate or precipitate elevated ICP.
4. To maintain regional brain tissue O<sub>2</sub> saturation (PbtO<sub>2</sub>) more than 20 mm Hg.

### Complications of ICP Monitoring

The most common complication of ventriculostomy catheter placement is infection with an incidence of 5 to 14%; colonization of the device is more common than clinical infection.<sup>18</sup> Use of antibiotic-coated ventriculostomy catheters has been shown to reduce the risk of infection from 9.4 to 1.3%.<sup>19</sup> Other complications of ventriculostomy catheters are hemorrhage with an overall incidence of 1.4%, malfunction, obstruction, and malposition.

### MANAGEMENT OF RAISED INTRACRANIAL HYPERTENSION

ICP rise can be controlled by a number of measures. These are in general based upon the principle of reducing any of the components of the intracranial vault.

#### General Measures

These measures should be undertaken in all patients in whom intracranial hypertension is present or even anticipated.

**Head position:** It has been shown that moderate elevations of head (15-30°) optimize CPP.<sup>20,21</sup> The reduction in ICP afforded by 15 to 30° of head elevation is probably advantageous and safe for most patients. When head elevation is used, the pressure transducers

**Table 21.3: Intracranial pressure monitoring devices**

Device	Placement	Advantages	Disadvantages
<b>Intraventricular catheter</b>	Frontal horn of nondominant lateral ventricle	Most accurate (gold standard) Immediate reduction of ICP by CSF withdrawal possible CSF access available Can measure brain compliance Recalibration possible	Risk of intracerebral/intraventricular hemorrhage, infection and catheter obstruction Technically difficult
<b>Subarachnoid bolts</b>	Subarachnoid space	Simple insertion Brain substance not invaded Placement possible even in severe cerebral edema with obliterated ventricles	Less accurate especially at higher levels of ICP Risk of meningitis Inability to withdraw CSF Cannot be used in small infants with thin skulls Accuracy doubtful when anterior fontanelle open
<b>Epidural monitors</b>	Extradural space in direct contact with dura	Simple technique Low risk of serious infection No CSF access	Less accurate Cannot measure compliance
<b>External monitors (fontanometers)</b>	On the open anterior fontanelle	Non-invasive and simple Suitable for small infants, newborns and preterm babies	Accuracy questionable ICP readings affected by the precise positioning of the monitor and the force with which it is held No CSF access
<b>Intraparenchymal fiberoptic monitors</b>	Brain parenchyma 1 cm below subarchnoid space	Ease of insertion even with slit like ventricles and midline shift. Ability to accurately measure subdural intraventricular and intraparenchymal pressure	Inability to withdraw CSF Inability to recalibrate Potential for breakage or dislodgement

for blood pressure and ICP must be zeroed at the same level (at the level of the foramen of Monro) to assess CPP accurately. With lower elevations, ICP is elevated and with greater elevations the arterial pressure fails to maintain CPP. Also, the head should be kept in midline position to avoid distension of jugular veins which occurs easily when the head is turned. This distension impedes venous outflow from the cranium and leads to a rise in CBV and ICP with a decrease in CBF; jugular catheters should also be avoided for the same reason.

*Temperature control:* Fever increases cerebral metabolic demand and therefore blood flow and ICP increase. Thus the patient should be kept normothermic. Cooling may be achieved by using cooling mattresses, but shivering which can increase ICP, should be avoided by using phenothiazines or muscle relaxants.

*Prevention and control of seizures:* Seizures increase the metabolic rate, blood flow and oxygen consumption and can result in dangerous elevations of ICP if the brain is injured and has lost its autoregulatory capacity. Ongoing seizures should be treated immediately with intravenous benzodiazepines (lorazepam 0.1-0.2 mg/kg IV) followed by loading dose of dilantin (20 mg/kg). If a patient has sustained unexplained ICP elevations inspite of treatment, subclinical seizures must be suspected or EEG asked for. Also the use of muscle relaxants and paralytic agents may make the identification of seizures rather difficult. In such cases, ideally electrical monitoring should be used to exclude seizure activity.

*Respiratory care:* Endotracheal suctioning and intubation are associated with spikes in ICP apparently due to laryngeal stimulation,<sup>22,23</sup> and can be prevented by

using appropriate anesthetics and muscle relaxation.<sup>24</sup> A small dose of barbiturate should be given prior to such procedures.

High levels of positive end expiratory pressure lead to rise in intrathoracic pressure, thereby decreasing venous outflow from the brain and increasing ICP. These should be avoided as far as possible.

*Relief of pain:* Painful procedures increase ICP, and therefore appropriate analgesics and anxiolytics should be used. If child needs to be paralyzed intravenous infusion of pancuronium 0.1 mg/kg/h may be used.

*Fluids:* In the past, fluid restriction was advocated in brain-injured patients. However, it has now been shown that normovolemic patients fare just as well.<sup>25</sup> The type of intravenous fluids to use is debatable. In general hypotonic fluids should not be used. Ringer's lactate or half normal saline are appropriate fluids.

*Hypertension:* Elevated blood pressure is seen commonly in patients with intracranial hypertension, especially secondary to head injury, and is characterized by a systolic blood pressure increase greater than diastolic increase. It is associated with sympathetic hyperactivity.<sup>26</sup> It is unwise to reduce systemic blood pressure in patients with hypertension associated with untreated intracranial mass lesions because cerebral perfusion is being maintained by the higher blood pressure. In the absence of an intracranial mass lesion, the decision to treat systemic hypertension is more controversial and may need to be individualized for each patient. Systemic hypertension may resolve with sedation. If the decision is made to treat systemic hypertension, the choice of antihypertensive agent is important. Vasodilating drugs, such as nitroprusside, nitroglycerin, and nifedipine, can be expected to increase ICP and may reflexively increase plasma catecholamines, which may be deleterious to the marginally perfused injured brain. Sympathomimetic-blocking antihypertensive drugs, such as  $\beta$ -blocking drugs (labetalol, esmolol) or central acting  $\alpha$ -receptor agonists (clonidine) are preferred because they reduce blood pressure without affecting the ICP. Agents with a short half-life have an advantage when the blood pressure is labile.<sup>27</sup>

*Treatment of anemia:* The mechanism is thought to be related to the marked increase in CBF that is required to maintain cerebral oxygen delivery when anemia is severe. Although anemia has not been clearly shown to exacerbate ICP after TBI, a common practice is to maintain hemoglobin concentration at a minimum of 10 g/dL.

## Medical Measures

### *Heavy Sedation and Neuromuscular Blockage*

Intracranial hypertension caused by agitation, posturing, or coughing can be prevented by sedation and nondepolarizing muscle relaxants that do not alter cerebrovascular resistance. These should be used judiciously. Selection of shorter acting agents may have the advantage of allowing brief interruption of sedation to evaluate neurologic status. A commonly used regimen is morphine and lorazepam for analgesia/sedation and vecuronium as a muscle relaxant, with the dose titrated by twitch response to stimulation. Once control is achieved the sequence can be reversed. Intravenous propofol has also been used as a general anesthetic for sedation.<sup>28</sup> It has the advantage of rapid onset and emergence from sedation. However, it has been implicated in fatal metabolic acidosis in the ICU<sup>29</sup> and its use should be monitored closely.

Rapid reduction of ICP has been shown with use of lidocaine 1.5 mg/kg IV bolus. It is somewhat safer than thiopental in children with hemodynamic instability and is used for decreasing ICP before intubation.

### Hyperosmolar Therapy

Mannitol is most commonly used. Recently considerable new information is available regarding the chain of events produced by mannitol upon intravenous administration. Mannitol reduces blood viscosity and transiently increases cerebral blood flow and ICP.<sup>30,31</sup> Cerebral oxygen transport then improves<sup>32</sup> and adenosine levels decrease.<sup>30</sup> Cerebral vasoconstriction occurs in response to decreased adenosine if the autoregulatory system is intact and the cerebral blood flow is kept constant. As a result of lower blood volume, the ICP decreases. If autoregulation is impaired, less of an effect is seen. Intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes with a peak effect at 20 to 60 minutes. A slightly delayed effect, occurring within 15 to 30 minutes and lasting for up to 6 hours, results from a direct osmotic effect on neural cells with reduction in total brain water.<sup>33</sup> Additional possible mannitol effects include reduced CSF production,<sup>34</sup> free radical scavenging,<sup>35</sup> and inhibition of apoptosis.<sup>36</sup>

Mannitol is used at a dose of 0.25 g/kg. Two prospective clinical trials, one in patients with subdural hematoma and the other in patients who have herniated from diffuse brain swelling, have suggested that a higher dose of mannitol (1.4 g/kg) may give significantly better results in these extremely critical situations than lower doses of mannitol.<sup>37,38</sup> Rapid

administration of mannitol seems to be more effective in lowering ICP.<sup>39</sup> The osmolar gap correlates better with the mannitol level and is the preferred monitoring parameter to prevent mannitol-induced renal failure.<sup>40</sup> Attention should be paid to replacing fluid that is lost because of mannitol-induced diuresis, or else intravascular volume depletion results.

Increasingly, hypertonic saline solutions given in concentrations ranging from 3 to 23.4% are being used as an adjunct to mannitol in basic science research and clinical studies. In addition to its dehydrating effect, it promotes rapid CSF absorption,<sup>41</sup> increases cardiac output, and expands intravascular volume thereby augmenting the CPP with a positive inotropic effect,<sup>42</sup> diminishing the inflammatory response,<sup>43</sup> and inducing glutamate reuptake.<sup>42</sup> Hypertonic saline may prove advantageous over mannitol in hypovolemic and hypotensive patients with ICH as it augments blood pressure in addition to decreasing ICP. However, use of hypertonic saline as prehospital bolus to hypotensive patients with severe TBI was not associated with improved neurological outcome.<sup>44</sup>

Prolonged increase in osmolality induces the cerebral homeostatic mechanism to produce idiogenic osmoles to reduce the osmotic gradient.<sup>45</sup> Because of this phenomenon, osmotic therapy must be tapered after 24 hours of continued use to avoid rebound AIH.<sup>46</sup> Adverse effects of hypertonic saline administration include hematologic and electrolyte abnormalities, such as bleeding secondary to decreased platelet aggregation and prolonged coagulation times, hypokalemia, and hyperchloremic acidosis.<sup>47</sup> Hyponatremia should be excluded before administering hypertonic saline to reduce the risk of central pontine myelinolysis.<sup>48</sup> Relative contraindications to osmotic therapy include chronic or acute renal failure and symptomatic congestive heart failure.

*Loop diuretics:* Furosemide has been used either alone or in combination with osmotic diuretics. It interferes with CSF formation and sodium and water movement across the blood brain barrier and causes preferential excretion of water over solute in the renal tubule. The usual dose is 0.5-1 mg/kg but doses as high as 5-10 mg/kg have been used. Fluid and electrolyte status of the child should be carefully monitored while using diuretic therapy. Furosemide and mannitol work better together than either one used alone. Giving mannitol 15 min before furosemide has the largest effect on ICP control.<sup>39</sup>

*Carbonic anhydrase inhibitors:* Acetazolamide (Diamox) reduces CSF production and promotes diuresis but does not work quickly enough to have an acute effect. For long term use a dose of 8-30 mg/kg/d divided into

3-4 doses orally may be used. It is most often used as a temporizing measure for control of CSF production in patients with hydrocephalus.

### Steroids

Steroids have been shown to be highly effective in reducing vasogenic edema around brain tumors and their use is therefore advocated in such conditions.<sup>49,50</sup> It has been suggested that they stabilize the blood-brain barrier, enhance brain electrolyte metabolism and promote renal excretion of electrolytes and water. They may also facilitate CSF absorption impaired by inflammatory changes in the subarachnoid space or arachnoid villi. Dexamethasone at a loading dose of 1 mg/kg, then 0.25 mg/kg every 6 h is generally used. The onset of action is delayed for approximately 24 h. However, there is ample evidence that corticosteroids do not improve outcome in acute brain injury from trauma, ischemia, or hemorrhage and may actually be harmful due to increased adverse effects related to its use.<sup>51-55</sup>

### Hyperventilation

Hyperventilation is an effective measure in emergency situations with impending cerebral herniation, such as with cerebral hemorrhage or acute cerebral edema, where reduction in ICP must be achieved immediately at all costs. In patients with head trauma and severe intracranial infection, hyperventilation has been found to be very effective in reducing cerebral edema. However, it has not been found to have any beneficial effect in patients with hypoxic cerebral edema.<sup>56</sup>

Hypocapnia achieved through hyperventilation causes cerebral vasoconstriction with resultant decrease in cerebral blood volume and hence ICP. It also has the theoretical advantage of reversing brain and CSF acidosis. However, the disadvantages of hyperventilation are cerebral ischemia, hypoxia and local inverse steal caused by regional or global vasoconstriction.<sup>57-59</sup> In an experimental model it was found that the effects of hyperventilation lasted only up to about 6 hours and sudden discontinuation of hypocapnia caused a rebound increase in ICP.<sup>60</sup> As a general policy prolonged hyperventilation should not be used as hyperventilation beyond 6 hours loses its efficacy in reducing ICP due to rapid cerebral compensation.<sup>61</sup> During discontinuation pCO<sub>2</sub> should be allowed to rise slowly to avoid rebound rise in ICP.

Thus while aggressive hyperventilation (pCO<sub>2</sub> 25-30 mm Hg) is a useful tool for acute, short reduction of ICP, chronic hyperventilation to such levels is

harmful and should be avoided. If hyperventilation is to be used for a relatively longer period, levels of  $p\text{CO}_2$  should be kept in the 30 to 35 mm Hg range.<sup>62,63</sup>

### Barbiturates

Barbiturates have been used to reduce ICP. They reduce cerebral metabolism thereby reducing oxygen need and blood flow. They also cause a direct reduction in cerebral blood volume and flow. The cerebral vasoconstriction seen with barbiturates may either be secondary to reduction in metabolism or a direct effect. Several studies have now shown that barbiturate use provides no better outcome than routine management in coma,<sup>64,65</sup> and may in fact be associated with significant side effects such as hypotension.<sup>65</sup> Hypotension caused by barbiturates should first be treated with volume replacement and later with ionotropes, if indicated. Experimental studies suggest that dopamine infusion can offset the beneficial effects of barbiturates by increasing cerebral metabolic requirements.<sup>66</sup> The use of barbiturates is thus restricted to patients with ICP refractory to maximal medical and surgical therapy. Extensive hemodynamic monitoring is essential in case barbiturates are used.

Short-term use of barbiturates, before endotracheal intubation or suctioning in a child being treated for intracranial hypertension, is useful for blunting the rise in ICP associated with such procedures. The child must be hemodynamically stable. A test dose of thiopental 0.5 mg/kg is given. If blood pressure is stable, 1-3 mg/kg dose is given prior to the procedures.

### Hypothermia

This has been used since 1940s as an additional measure to reduce ICP. Induced hypothermia is effective in reducing ICP from multiple causes<sup>66-69</sup> by suppressing all cerebral metabolic activities, thereby reducing CBF. The degree of cooling used (30°C) caused significant side effects such as cardiac arrhythmias, coagulopathies, and fluid, electrolyte and acid-base disturbances. Multicenter randomized clinical trial and pilot randomized clinical trial of moderate hypothermia in severe TBI in children showed no improvement in neurological outcome even after reduction of ICP by hypothermia.<sup>70,71</sup> A significant number of issues remain unresolved, including the ideal target temperature (mild, moderate, or deep hypothermia), patient selection, mode of administration of cooling (surface vs. endovascular), timing of intervention (prophylactic, early vs. delayed or only with AIH), duration of

treatment (24 hours vs. prolonged-72 hours), duration and rapidity of rewarming, and control of shivering.

### Surgical Interventions

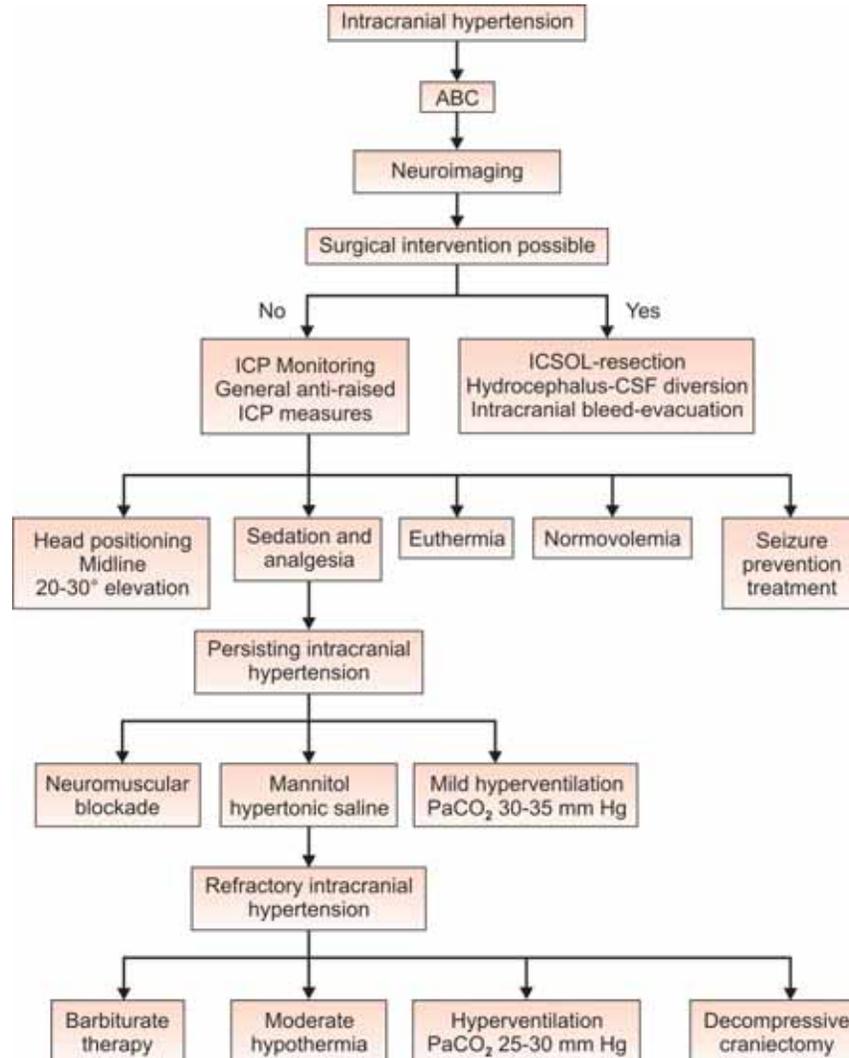
- Ventricular CSF drainage:* Drainage of CSF through an intraventricular catheter is one of the most rapid and effective ways of reducing ICP in an emergency setting particularly in conditions of obstruction to CSF flow or reduced absorption as in hydrocephalus and meningitis. It has also been used as a first line measure for reducing ICP in patients with head injury. However, if the brain is diffusely swollen, the ventricles may collapse, and then this modality has limited utility.
- Operative removal of mass lesions:* Operative removal of mass lesions such as hematomas, brain abscess, tumors and subdural collections is an essential factor in controlling raised ICP. Surgical management of spontaneous intracerebral hemorrhage is controversial.
- Decompressive craniectomy:* Cranial decompression with removal of portions of the bony calvarium and adjacent dura has been used in rare circumstances when all other measures fail to control intracranial hypertension. It relieves the raised intracranial pressure by allowing for herniation of swollen brain through artificially created bone window.

Despite several case series showing positive results, a large randomized controlled trial of decompressive craniectomy for spontaneous ICH failed to improve outcome compared with aggressive medical management.<sup>72</sup> However, minimally invasive surgical techniques employing stereotaxy with or without frame and endoscopy with or without clot thrombolysis consistently show benefit compared with medical management alone.<sup>73-75</sup> Decompressive craniectomy may be lifesaving for patients with refractory AIH.<sup>76,77</sup> However, long-term functional outcome is usually not very good. Reported complications include hydrocephalus, hemorrhagic swelling ipsilateral to the craniectomy site, subdural hygroma and even paradoxical herniation after lumbar puncture in a patient with decompressive craniectomy.<sup>78,79</sup>

### Experimental Therapies

Studies of the cascade of biochemical pathways responsible for delayed primary and secondary brain injury have prompted research on newer preventive agents.<sup>80,81</sup> These include free radical scavengers—lipid peroxidase antagonists, cyclo-oxygenase inhibitors, opioid antagonists, calcium channel blockers and neurotransmitter moderators.

Flow chart 21.1: Management of intracranial hypertension



In conclusion, intracranial hypertension is an emergency that requires prompt recognition and vigorous treatment. Applications of new insights into the monitoring and treatment of ICP and measurement of cerebral metabolic activity are expected to lead to better outcome of patients with raised ICP.

Flow chart 21.1 gives an algorithm for management of patients with intracranial hypertension.

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The term *acute-onset flaccid paralysis* (AFP) is used in public health programs to identify suspected patients with paralytic disease consistent with acute poliomyelitis. The syndrome of AFP can be used in the clinical context to define disorders characterized by rapid onset of weakness of limbs, and may be accompanied by weakness of respiratory muscles and difficulty in swallowing, progressing to maximum severity within 1 to 10 days.<sup>1,2</sup> The term “flaccid” denotes the absence of spasticity or other signs of corticospinal tract dysfunction such as hyperreflexia, clonus or extensor plantar response. AFP surveillance is a prime strategy for monitoring the progress of polio eradication and is a sensitive instrument for detecting potential poliomyelitis cases and poliovirus infection. Since the World Health Organization (WHO) launched its global polio eradication program, the number of countries where polio is endemic has declined from 125 to seven, and the estimated incidence of polio has decreased by more than 99%.<sup>3</sup> AFP is a complex clinical syndrome comprising a broad array of etiologies, early diagnosis of which is essential. A number of the disorders have the potential to progress and lead to respiratory muscle paralysis, increased morbidity and even death.

### CLINICAL APPROACH

Most cases of AFP with an intact sensorium result from disorders that affect the lower motor neuron, namely, the anterior horn cells, the axons, the neuromuscular junction, or the muscle. In cases where the bulbar muscles are spared, it is essential to consider acute lesions of the spinal cord due to myelitis, vascular or traumatic etiologies. The early stages of acute spinal cord injury may be characterized by spinal shock with flaccidity and areflexia making it challenging to differentiate it from neuromuscular disorders.

When quadriparesis develops over weeks or months the distinction between disorders of the cerebral hemispheres, brainstem, spinal cord or the lower motor

neuron is usually possible by clinical criteria. Onset over hours or few days may be due to upper motor neuron, lower motor neuron or myopathic processes. All three patterns are associated with hypotonia. If the acute quadriparesis is associated with alteration of sensorium or cranial nerve involvement, the evaluation should include an urgent contrast MRI scan of the brain. If the child is alert and upper motor neuron signs or bowel-bladder involvements exist, an MRI scan of the cervical and thoracic spine is the investigation of choice. GBS and myopathic illnesses are important diagnostic possibilities otherwise; and meticulous electro-diagnostic studies are indicated. The presence of a sensory level, spinal tenderness, bowel-bladder involvement, even though the tone and reflexes are reduced or absent, makes a spinal etiology likely (transverse myelitis, epidural abscess, metastasis, tuberculosis, spinal cord ischemia from a dural arteriovenous fistula or other vascular anomaly). A gadolinium enhanced MRI of the cervical and thoracic spine should be performed. It is important to remember that it may take up to 10-14 hours for ischemia to manifest as changes on the MRI.

Unlike adults where diagnosis of site of pathology of the lower motor neuron may be relatively easy, diagnosis in the child is an exercise in patience and clinical acumen. The history may not be forthcoming in a preverbal child, sensory symptoms may be unavailable, a sensory level may not be easy to elicit, and a formal muscle testing may not be possible. Clinical observation of the child including his posture, head control, breathing, speech, difficulty in swallowing, inability to turn in bed, reach for his favorite toys or bear weight on his legs afford clues to the state and stage of illness. Certain disorders may present in a “hyperacute” fashion with weakness developing over minutes or hours. The causes include familial potassium-associated periodic paralysis, psychogenic weakness, and various intoxications.<sup>4</sup> Spinal cord trauma and infarction may have an apoplectic onset.

**Table 22.1: Conditions to be considered in a patient with AFP**

1. Motor neuron
  - A. Poliovirus
  - B. Other neurotropic viruses
2. Peripheral nerves
  - A. Acute Guillain-Barre syndrome (GBS)
  - B. Porphyria
  - C. Toxic neuropathies
    - Arsenic
    - Nitrofurantoin
    - Heavy metals
    - Thallium
  - D. Diphtheria
  - E. Collagen disorders
3. Neuromuscular junction (NMJ) disorders
  - A. Myasthenia gravis
  - B. Drug-induced neuromuscular blockade
  - C. Organophosphorus poisoning
  - D. Botulism
  - E. Animal venoms and toxins (snake bite)
  - F. Hypermagnesemia
4. Muscle
  - A. Periodic paralysis
  - B. Hypokalemia
  - C. Rhabdomyolysis
  - D. Inflammatory myopathies
5. Critical illness neuropathy and myopathy
6. Acute myelopathy
  - A. Spinal cord infection
    - *Viruses and retroviruses*
      - Rabies
      - Herpes simplex virus-2
      - HIV
    - *Bacteria*
      - Tuberculosis
      - Brucellosis
      - Mycoplasma
      - Borellia
    - *Parasitic*
      - Neurocysticercosis
      - Hydatid disease
    - *Fungi*
  - B. Compressive myelopathy
    - Trauma
    - Epidural abscess
    - Hematomyelia
  - C. Spinal cord infarction
  - D. Tumors
  - E. Idiopathic transverse myelitis (post or para-infectious)
7. Others
  - Cerebral venous thrombosis
  - Acute stroke
  - Hypoxic-ischemic events
  - Brainstem/posterior fossa tumors
  - Mitochondrial disorders

### Clues to the Diagnosis

The following are important diagnostic clues:

1. *Pace*: Weakness from motor neuron or peripheral nerve disorders develops over days while the evolution of symptoms from neuromuscular junction disorders and periodic paralysis may be marked in minutes or days.
2. *Past or family history*: Previous episodes of weakness or a positive family history should suggest periodic paralysis, porphyria, rhabdomyolysis or a metabolic myopathy.<sup>3,4</sup> History of vaccination or immunization may precede Guillain-Barré syndrome (GBS), transverse myelitis or acute demyelinating encephalomyelitis (ADEM). A history of drug ingestion including drugs used in malignancies should be enquired into, to detect toxic neuropathies.
3. *Gastrointestinal symptoms*: These accompany porphyria, botulism, sea food poisoning, organophosphorus toxicity, and arsenic or thallium ingestion. Acute hypokalemic weakness may follow chronic vomiting or diarrhea.
4. *Pain*: The onset of weakness from GBS, polio, porphyria or dermatomyositis may be preceded by neck pain, back pain or myalgias. Spinal pain may result from a caries spine, metastasis or compressive myelopathy. Distal paresthesias or dysesthesias may occur with GBS or toxic neuropathies.
5. *Pattern of limb weakness*: Polio and occasionally porphyria are distinguished by asymmetric limb weakness. Distal weakness is a feature of peripheral neuropathies.
6. *Bulbar dysfunction*: This is prominent in neuromuscular junction disorders and may be seen in GBS, porphyria, polio and diphtheria.
7. *Ptosis or ophthalmoplegia*: Should suggest a neuromuscular junction disorder, though it may be seen in GBS, Miller Fisher variant or brainstem pathologies like infarction or central pontine myelinolysis, etc.
8. *Pupillary changes*: Pupillary paralysis is a classic feature of botulism but is not invariably present. Paralysis of accommodation occurs with diphtheria and miosis with organophosphorus poisoning.

### Patterns of Weakness

1. Flaccid symmetric weakness with areflexia (+/- bulbar and respiratory involvement), with sensory symptoms and minimal sensory loss: GBS without sensory symptoms or signs: periodic paralysis.

2. Symmetric proximal weakness with preserved reflexes:  
Acute myopathy (PM-DM); osteomalacic myopathy
3. Flaccid paraplegia or quadriplegia with sensory level, and bowel-bladder dysfunction:  
Spinal cord pathology
4. Ophthalmoplegia with motor weakness:  
GBS; Miller-Fisher variant;  
Locked-in-state;  
Myasthenia gravis;  
Tick paralysis
5. Fatigable muscle weakness with bulbar signs/  
ophthalmoplegia:  
Myasthenia gravis

Some disorders may mimic a paralytic illness and pose diagnostic dilemmas such as acute cerebellar ataxia. Arthralgias, arthritis and bony injuries may restrict movements and hamper examination of the crying and reluctant child.

### Management

The two most important goals in the management of a child with AFP are:

1. Stabilization of the patient and attending to ventilatory needs.
2. History and physical examination to diagnose the disease, order appropriate tests, and institute specific therapy.

Whether the child requires ICU admission will depend on the presence of: (i) vasomotor and respiratory insufficiency; (ii) rapid progression of disease; (iii) bulbar symptoms; (iv) suspected poisoning, and (v) acute severe systemic illness.

### Laboratory Investigations

The following investigations can prove useful for establishing a diagnosis:

- *Complete blood counts*: Anemia and leukocytosis as possible markers of systemic illness.
- *Eosinophil count*: May be elevated in vasculitic neuropathy, trichinosis and cysticercosis.
- *ESR*: Often elevated in infections and autoimmune disorders.
- *CPK, aldolase*: Elevated in primary muscle diseases.
- *BUN*: Elevated in myoglobinuria, rhabdomyolysis and renal insufficiency.
- *Electrolytes, calcium, phosphorus, and magnesium*: For myopathic disorders and periodic paralysis.
- *Thyroid hormone assay*: For thyroid related myopathy.
- *Collagen markers*: Vasculitic neuropathy, poly-myositis, myasthenia gravis.

- *Nerve conduction studies, EMG, repetitive stimulation*: To diagnose GBS, myopathic disorders, myasthenia gravis.
- *MRI/CT scans*: Brain, spinal cord.
- *Lumbar puncture*: Transverse myelitis, TB arachnoiditis, GBS.

### Spinal Cord Disorders

The following steps are useful in assessing the patient with a suspected spinal cord disorder:

1. Initial evaluation of a patient with an evolving myelopathy should determine whether a structural compressive cause can be identified, ideally by a gadolinium contrast MRI of the cervical and thoracic spine.
2. If no structural cause can be detected, then a lumbar puncture should be performed to exclude an inflammatory cause of the myelitis. The CSF should be examined for biochemistry, cytology, as well as for intrathecal antibody synthesis. A small volume can be stored in the refrigerator for future studies if needed.
3. If the MRI spine shows no gadolinium enhancement and there is no pleocytosis in the CSF, then a “non-inflammatory” cause is likely.
4. If an “inflammatory” myelopathy is identified, then a brain MRI and visual evoked potentials (VEP) should be obtained to determine the extent of the inflammation. The presence of demyelination on VEP but not in the brain, indicates neuromyelitis optica (Devic’s disease). If demyelination is detected on MRI brain then the diagnosis is ADEM or possible multiple sclerosis.
5. Patients with an inflammatory myelopathy and absence of demyelination in the brain or optic nerves are said to be having ATM. Further, evaluation should be done to decide whether ATM is “primary” or “disease-associated”.

#### Acute Transverse Myelitis (ATM)

The diagnosis of idiopathic ATM requires the following features:<sup>5</sup>

- a. Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord;
- b. Bilateral signs and symptoms;
- c. Exclusion of extra-axial compressive etiology by MRI;
- d. Inflammation within the spinal cord demonstrated by CSF pleocytosis, increased IgG index, or gadolinium enhancement of lesion on MRI;
- e. Progress to nadir between 4 hours to 21 days following onset.

Exclusion criteria include: the presence of radiation injury, spinal cord infarction, specific viral infections, multiple sclerosis, and optic neuritis.<sup>5</sup> The general term ATM should be reserved for those patients in whom no specific etiology is identified. When a specific etiology is known, this is best included in the designation, e.g. Epstein-Barr virus ATM.

The syndrome is characterized by a sudden onset of progressive weakness of legs. The earliest symptom is sensory loss or pain in the back, thighs or legs. Bowel-bladder involvement occurs in over 70% patients. The weakness may ascend leading to a flaccid quadriplegia. In the largest series of ATM reported in 45 children,<sup>6</sup> the illness was clustered between the age groups of children younger than 3 years, and those between 5 to 17 years. Twenty eight percent patients had a confirmed immunization or allergy shot within 30 days. The vaccines included oral polio, measles-mumps-rubella (MMR), hepatitis A, diphtheria-pertussis-tetanus (DPT), influenza, varicella, Japanese B encephalitis, and *Haemophilus influenzae*. Time for maximal weakness was 48 hr, and a sensory level could be determined in 85% patients. Elevated WBC's in the CSF were seen in 50% of cases, but only 5% demonstrated a high IgG index.

Treatment involves administering methylprednisolone (1 g/1.73 sq m daily × 3-5 days) intravenously, followed by oral prednisone tapered over 2-3 weeks. IVIG and other immunosuppressants can be used in non-responders. Residual disabilities of gait, numbness and bladder dysfunction may persist in 40 to 75% cases even after many years.<sup>6,7</sup>

Factors associated with better functional outcome include:

- a. Older age at onset
- b. Shorter time to diagnosis
- c. Lower anatomic level of spinal cord injury
- d. Absence of T1 hypointensity on spinal MRI
- e. Lack of leukocytes in the CSF
- f. Involvement of few spinal segments

### *Viral Myelitis*

Acute viral myelitis can be subdivided into gray matter syndromes causing AFP, resembling poliomyelitis due to anterior horn cell involvement, and partial or complete white matter syndromes with or without gray matter involvement causing an ATM-like deficit. Viral myelitis results from direct viral infection of the neural elements of the spinal cord. The presence of fever, rash, meningeal signs, herpes eruptions, zoster rash, genital ulcers and adenopathy should arouse suspicion of a viral etiology.

The herpes viruses can cause viral myelitis. Herpes simplex virus type 1 (HSV 1) commonly causes myelitis in children, while HSV 2 causes myelitis in adults. Both forms of disease can vary from mild involvement with full recovery to a severe necrotizing myelitis with severe residual deficits. Genital herpes may precede HSV 2 myelitis by several days. Decreased sensation to pain, touch, and temperature is common and tends to be severe in the sacral dermatomes. Typical CSF cell counts tend to range between 10 and 200 cells/cu mm; in necrotizing myelitis striking pleocytosis with up to 5000 cells with preponderance of neutrophils may be seen. The CSF protein is almost raised. Diagnosis depends on demonstration of HSV DNA in CSF by polymerase chain reaction (PCR) or evidence of intrathecal synthesis of HSV-specific antibodies by detecting the presence in CSF of immunoglobulin M (IgM) anti-HSV antibodies.<sup>8</sup>

Varicella-zoster virus (VZV) can cause zoster myelitis, with most cases occurring in immunocompromised hosts. Myelitis can occur as a complication of primary varicella or chickenpox. Spinal cord involvement follows the onset of zoster by 5 to 21 days, and patients present with a sub-acute onset of asymmetric leg weakness, progressing to a sensorimotor paraparesis. CSF shows a mononuclear pleocytosis in about 75% and raised proteins in 70% of patients. The spinal MRI demonstrates areas of high T2-weighted signals in patients with zoster and chicken pox myelitis. No controlled trials of treatment are available, but acyclovir is given in doses of 30 mg/kg/day for 21 to 35 days.<sup>8</sup>

Cytomegalovirus (CMV) involvement of the spinal cord is a disease primarily of HIV-infected patients, presenting as a pure ATM or a cord syndrome accompanied by radicular or peripheral nerve involvement. A distinguishing feature of this disorder is the common occurrence of a neutrophil-predominant pleocytosis in the CSF of up to 1000 cells/cmm. ATM as a manifestation of Epstein Barr virus (EBV) is rare but may occur 1 to 2 weeks after infectious mononucleosis.

### *Poliomyelitis*

Poliomyelitis can be distinguished from GBS in that the patients tend to present with an acute febrile viral meningitis syndrome with meningeal signs, malaise, headache and gastrointestinal symptoms. The lower motor neuron signs develop within 1 to 2 weeks, but may rarely develop along with other presenting symptoms. The motor signs are clearly maximal in 1 to 4 days and are usually asymmetric with lumbar involvement being more than cervical, and spinal cord

being more involved than brainstem. The proximal muscles are more involved. There is no sensory deficit but myalgias may be severe. A CSF neutrophilic pleocytosis may occur; these are replaced after a few days by moderate numbers of lymphocytes and monocytes. The protein content of CSF is slightly raised, but it rises gradually till the third week in paralytic cases, and returns to normal by the sixth week. Atrophy appears rapidly, usually within 5 to 7 days, and can progress over several weeks.

Electrophysiology studies will help to differentiate poliomyelitis due to poliovirus or other neurotropic viruses from a peripheral neuropathy such as GBS. In difficult situations MRI shows increased T2 weighted signal in the anterior horns and cord swelling. Isolation of the pathogen from the stools is a reliable mode of diagnosis. There is no specific treatment. General supportive measures and intensive care are the same as described for GBS.

#### *Polio-like illness due to non-polio Viruses*

Small epidemics have been caused by non-polio enteroviruses: Coxsackie A7 virus caused outbreaks of paralytic disease in former Soviet Union, South Africa and Scotland; and enterovirus 71 recently caused outbreaks in Southeast Asia in the late 1990s. Japanese B virus is reported to cause an AFP with clinical and pathological findings similar to poliomyelitis, and is considered to be the commonest cause of AFP in South Vietnam.<sup>9</sup> Other flaviviridae including West Nile virus, Murray Valley virus and tick-born encephalitis cause damage to the anterior horn cells resulting in AFP.

#### *Transverse Myelitis due to Systemic Inflammatory Diseases*

Transverse myelitis may result from systemic inflammatory diseases like Sjogren syndrome, systemic lupus

erythematosus (SLE), antiphospholipid antibody syndrome, mixed connective disorder, and sarcoidosis. These disorders should be suspected in the presence of: rash, oral or genital ulcers, arthritis, livedo reticularis, photosensitivity, erythema nodosum, keratitis, conjunctivitis, serositis, anemia, thrombocytopenia, elevated erythrocyte sedimentation rate (ESR), and history of venous or arterial thrombosis. Appropriate serological tests, tests for autoantibodies, coagulation parameters and complement levels need to be carried out.<sup>5</sup>

### Peripheral Neuropathies

Acutely presenting neuropathies are few, majority of neuropathies have a subacute or chronic course. Neuropathies manifesting in days include GBS, vasculitic neuropathies, diphtheria, acute intermittent porphyria, critical illness neuropathy and toxic neuropathies. Toxic and metabolic neuropathies present as distal symmetrical neuropathies, whilst proximal involvement may occur with GBS, porphyria and diabetes. Asymmetric presentation as in mononeuritis multiplex should alert the clinician to connective tissue disorders and vasculitic neuropathies.

#### *Guillain-Barré Syndrome (GBS)*

GBS has been considered synonymous with acute inflammatory demyelinating polyneuropathy (AIDP). However, it is now established that GBS can also present with two patterns of predominant axonal involvement. The severe form involves both motor and sensory axons and was called "axonal GBS" and more recently termed acute motor-sensory axonal neuropathy (AMSAN).<sup>10-12</sup> Second, a form limited to nearly pure motor involvement, termed "acute motor axonal neuropathy" (AMAN),<sup>13,14</sup> a pattern commonly seen in China and which represents the benign end of a single

**Table 24.2: Differentiating polio from Guillain-Barré syndrome (GBS)**

Features	Poliomyelitis	GBS
Age (years)	<5 years	>3 years
Fever	Fever, headache, meningeal signs	May occur 2-3 weeks prior
Progression	Rapid, 24-48 hr	Average 12 days for maximum weakness
Symmetry	Asymmetrical, monoplegia, para- or quadriplegia	Symmetrical, legs > arms
Atrophy	Rapid, starts in 5-7 days	Weeks
Sensory	Motor dominant	Sensory symptoms in 70%
Cranial nerves	In bulbar polio	Facial weakness in 53%, ophthalmoplegia, bulbar nerves
Electrophysiology	Acute denervation and reduced compound action potentials	Reduced conduction velocity, increased distal latency in demyelinating GBS; sensory nerves are involved

pathogenetic spectrum with the more severe cases producing the AMSAN variety.

GBS is rare during infancy. Reports are mainly in older literature, and it seems that most previously diagnosed cases were of infantile botulism. GBS is the most common paralytic disorder affecting children in countries with an established immunization program. Acute inflammatory demyelinating neuropathy (AIDP) was the erstwhile phenotypic presentation of GBS. Primary demyelination results from immune attack directed at the Schwann cells and myelin. Axonal injury occurs to some in many cases of AIDP, usually secondary to the pathological events of demyelination (e.g. "bystander" injury). Cases of GBS with primary demyelination and secondary axon loss should not be confused with acute axonal form of GBS. The axonal form represents 5 to 10% of cases of GBS in North America, but is more common in Japan and China. In India, 85% cases of GBS were AIDP, and 10% were the axonal variety.<sup>15</sup>

The mean age of presentation is 7 years with a slight male predominance. Cytomegaloviruses, Epstein-Barr virus, HIV, vaccinia virus, *Campylobacter jejuni* diarrhea and vaccinations are recognized prodromal illnesses preceding the polyradiculoneuropathy. An antecedent infectious disease is recognized in 65 percent of cases 3 days to 6 weeks before the onset of symptoms. The resultant neuropathy is predominantly motor and is typically accompanied by sensory symptoms and ataxia. Autonomic symptoms occur in up to 28 percent of children and include labile hypertension, bowel-bladder disturbances, GI motility disorders, pseudo-obstruction, cardiac arrhythmias and even cardiac arrest. Motor weakness is the most important complaint. A prominent feature is pain in the back, thighs and legs. About half the children will have difficulty with balance and up to 20 percent may complain of sensory symptoms. Neck stiffness may be present and pose diagnostic confusion.

Between 50 to 75 percent patients develop maximal weakness within 2 weeks. A fulminant course with maximum motor deficit and bulbar involvement within 24-48 hours is seen on occasions. The incidence of admission to the ICU ranges between 17 to 68 percent with the average length of stay about 11 days.<sup>16</sup> Up to 16 percent of 175 children with GBS required artificial ventilation.<sup>17</sup> The average duration of mechanical ventilation ranges from 17 to 22 days, although rare cases may require assisted ventilation for months. GBS is among the most gratifying neurologic emergencies to treat. The mortality has been reduced ten-fold by modern critical care.

Features that cast a doubt on diagnosis include a discrete sensory level, marked asymmetry in motor function and persistent bowel or bladder involvement. Criteria of exclusion include: history of hexacarbon abuse, evidence of porphyria, recent diphtheria, lead neuropathy, a pure sensory syndrome and definite diagnosis of an alternate paralytic disorder.

*Cerebrospinal fluid examination:* Albumino-cytological dissociation with elevated proteins in the absence of significant pleocytosis (>10 cells/cu mm) is characteristic. Significant pleocytosis is not seen in GBS and raises the question of infectious (HIV, CMV, Lyme, sarcoid), carcinomatous or lymphomatous polyradiculoneuropathy.

*Electrophysiology:* The typical findings of a demyelination may not appear for the first 7 to 10 days. However, changes will exist in the initial presentation to aid the diagnosis in majority of patients. The conduction studies will also identify children with the AMSAN form of GBS, which has a different prognostic implication in that these children are more severely affected, more often quadriplegic, require prolonged ventilation and hospital stay; and have a higher rate of residual deficits.

Differential diagnosis includes poliomyelitis, botulism, periodic paralysis, transverse myelitis, meningoencephalitis, brainstem encephalitis, stroke, porphyria, toxic neuropathies and posterior fossa tumors. Vasculitic mononeuritis multiplex may mimic GBS, and a history of disease evolution, systemic symptoms should be sought, and appropriate serological tests for a systemic vasculitis carried out.

All patients with GBS should be hospitalized due to the risk of respiratory failure and need for intubation and mechanical ventilation. There should be a low threshold for putting the child in an ICU.

*Indications for ICU admission:* These include: (a) Rapidly progressive weakness, (b) Oropharyngeal weakness, (c) Dysautonomia, (d) Respiratory insufficiency, and (e) Evidence of aspiration pneumonia.

The need for intubation should be determined. In general, one should err on the side of early intubation rather than late. Tracheostomy should be delayed at least 2 weeks, unless there is evidence of axonal type of GBS or significant bulbar weakness.

The proposed triage decisions are summarized in Table 22.4.

*Intravenous immunoglobulin (IVIg):* IVIG is a safe and convenient therapy in children with GBS. Side effects are few and mild (flu-like symptoms, nausea, headache, malaise). It should be avoided in children with

**Table 22.3: Differentiating myelopathy from neuropathy**

Findings	Transverse myelitis	GBS
Motor	Paraplegia/quadriplegia	Ascending in legs > arms weakness
Sensory	Usually can diagnose a sensory level	Ascending sensory loss from feet
Babinski sign	Present	Absent
Autonomic	Bowel-bladder involvement	Dysfunction of cardiovascular system
Cranial nerves	None	Facial nerve, extraocular nerves
Electrophysiology	Normal EMG and nerve conduction	Confined to peripheral nerves
MRI	Focal area of increased T2 signals in the cord	Normal
CSF	Pleocytosis, high Ig G index	Elevated proteins

**Table 22.4: Triage decisions in GBS<sup>18</sup>**

Clinical status	Triage/treatment
A. Very mild GBS Ambulatory, no ventilatory compromise	Admit to ward Monitor VC × 8 hourly Observation Consider IVIG/PE
B. Ambulatory with assistance No ventilatory compromise	Admit ICU Monitor VC Check ABG IVIG or PE
C. Not ambulatory Mild ventilatory compromise	Admit ICU Monitor VC and ABG IVIG/PE Intubate if: VC <12-15 ml/kg Falling VC over 6 hours Bulbar signs and aspiration Respiratory fatigue
D. Not ambulatory Requires ventilation	Admit ICU Ventilate IVIG/PE

VC = vital capacity; IVIG = intravenous immunoglobulins;  
ABG = arterial blood gases; PE = plasma exchange

IgA deficiency and in renal failure. We have treated over 40 children with IVIG in a dose of 2 g/kg administered over 2 days with good results. Shahar et al<sup>19</sup> found marked and rapid improvement in 25 of 26 children treated with IVIG. It is ideal if it can be instituted early in the disease (preferably within the first few days) so that the morbidity and severity of the disease is ameliorated, the need for assisted ventilation warded off or shortened; and the hospital stay reduced.

*Plasmapheresis:* This is equally effective as IVIG, but is limited to some degree by size constraints of the patients and availability of the equipment and staff. It may have limitations in children with autonomic and cardiovascular compromise.

*General and supportive care:* This includes the following:

1. Positioning and skin care.
2. Bladder and bowel care.
3. Eye and mouth care.
4. Fluid and nutrition: Adequate intake of calories and their proportionate increase in infected patients. Parenteral nutrition may be required, and the need for percutaneous gastrostomy considered.
5. Nosocomial infections may occur in up to 25 percent patients. Culture surveillance of urine and sputum once or twice a week may help to provide information should an infection arise.
6. *Physical therapy:* Passive motion of all joints is done twice daily for 2-3 weeks. In patients who are able, active motion and motion against resistance is attempted. There is clear indication that keeping the limbs flexible quickens the time to ambulation. Patients should spend 30 min sitting or reclining before standing to avoid dizziness. Exercise regimes should avoid overworking muscle groups.
7. *Pain:* A substantial number of patients have aching pain in the thighs, calves, buttocks and trapezii. The pain may be severe in the evenings and at night. Pain near the joints and burning sensations around the thighs, calves and feet may occur. Mild narcotics are effective at night and do not cause dependence. Non-steroidal analgesics are not consistently beneficial. Gabapentin, carbamazepine, and tricyclic antidepressant medications may also be helpful in the short-term and long-term management of neuropathic pain.
8. *Autonomic disturbances:* Hypotension may be treated with fluid replacement; vasopressors are rarely required. Hypertension should be treated with short acting alpha-adrenergic-blocking drugs, only if it is persistent and severe. Severe bradycardia may require temporary pacing.
9. Prevention of deep vein thrombosis.

*Outcome:* The prognosis is excellent with majority of patients making a good recovery over weeks or months. The factors that correlate with poor outcome are: rapid progression to severe weakness (7 days or less), need for ventilator support, mean distal compound muscle action potential amplitude less than 20 percent of normal and preceding *Campylobacter* infection.

### *Vasculitic Neuropathies*

Vasculitic neuropathies may follow primary or secondary systemic vasculitis. The typical clinical features of vasculitic neuropathy are acute to sub-acute onset of painful neuropathy. The most common presentations are of an asymmetric polyneuropathy or of mononeuritis multiplex. Commonly, the mononeuritis progresses rapidly so that on presentation the deficits appear confluent. Thus, it is important to obtain a detailed history of the clinical course of the initial and subsequent deficits. A distal symmetric neuropathy is uncommon, but vasculitic neuropathies can present in this manner. Accompanying constitutional symptoms may include myalgias, arthralgias, weight loss, fever, respiratory, abdominal pain, rash, or night sweats.

Electrodiagnostic studies help to reveal the acute-to-subacute axon loss of motor and sensory nerves, often in a patchy, multifocal distribution. Laboratory evaluation of suspected cases of vasculitic neuropathy should include a complete blood count (CBC), metabolic panel, ESR, C-reactive protein, antinuclear antibody, rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA), hepatitis B and C panel and cryoglobulins.

### **Diseases of the Muscle**

Weakness in muscular disorders is generally global involving upper and lower limbs with larger muscle groups being more affected. Acute myopathies may produce muscle pain and tenderness as in inflammatory myopathies (e.g. polymyositis, dermatomyositis). Muscle tenderness and swelling may indicate trichinosis, clostridial myositis or other bacterial myositis. An acute myopathy does not cause muscle atrophy and tendon reflexes are usually preserved. The presence of acute or rapid muscle atrophy and areflexia usually suggests a lower motor neuron (anterior horn cell or peripheral nerve) lesion. Acute painless myopathies may suggest periodic paralysis or toxic myopathies. Recurrent muscle weakness with myoglobinuria indicates a metabolic myopathy and appropriate genetic tests should be done.

### *Polymyositis/Dermatomyositis*

Dermatomyositis (DM) is more common than idiopathic polymyositis (PM) in children as compared to adults. It presents more acutely and is often associated with systemic manifestations. The diagnosis is not difficult as the disorder generally has an onset over weeks or months. An acute fulminant course can occur that may need differentiation from GBS. Selective muscle involvement of the neck flexors, hip and pelvic girdle muscles is an important clue as is the presence of deep tendon jerks, and absence of sensory signs and symptoms. Skin changes over the periungual region, knuckles and periorbital area often occur. A macular, erythematous rash may be present over the face, neck and anterior chest (V- sign) or on the shoulders and upper back (shawl-sign). A purplish scaly rash may be present over the dorsum of hands (Gottron's papules). Subcutaneous calcinosis is a significant problem in juvenile DM. Respiratory paralysis is not usual although interstitial lung disease may be observed in a group of patients. A small proportion of children will develop dysphagia, chewing and swallowing difficulty.<sup>20</sup>

The diagnosis requires the presence of typical muscle weakness and skin changes, raised CPK 10 to 50 times normal, EMG evidence of an inflammatory myopathy, and typical features on muscle biopsy. Corticosteroids (prednisolone 1-2 mg/kg/day in a single dose) are the first line of treatment. Methyl-prednisolone pulse therapy may be useful in severe and fulminant cases. Once the patient has stabilized or strength has returned to normal (usually 4-6 months), the dose can be reduced very gradually every 2-4 weeks. For steroid non-responders methotrexate, azathioprine, IVIG, cyclophosphamide and mycophenolate mofetil may be used.<sup>20</sup>

### *Acute Viral Myositis*

Although myositis can occur after many bacterial, parasitic, or viral infections, the viral myositides are the disorders most commonly seen by the clinician. A number of viruses like coxsackievirus, parainfluenza, mumps, measles, adenovirus etc. can cause myositis, but acute infection with influenza virus is commonly associated with muscle involvement.

As respiratory symptoms subside, pain, swelling, muscle tenderness signals the onset of myositis. The pain can be so severe so as to interfere with child's ability to walk or perform routine activities. Weakness can be profound, and myoglobinuria can result. The CPK can be elevated more than 10 times the normal upper limit. Treatment is conservative with bed rest,

hydration, and anti-inflammatory medications. Recovery takes place in 7 to 10 days.

### *Periodic Paralysis*

A simple classification of periodic paralysis is in relation to serum potassium: hypokalemic, hyperkalemic, and normokalemic. In addition, periodic paralysis may be primary (genetic) or secondary. The cause of secondary hypokalemic paralysis is gastrointestinal or urinary loss of potassium. Thyrotoxicosis is an important cause of hypokalemic periodic paralysis, especially in Asians.

### *Hypokalemic Paralysis*

In patients with hypokalemic periodic paralysis, there will be a family history of similar attacks, or previous episodes in the patient. Similar weakness can occur due to hypokalemia secondary to gastrointestinal losses or diuretic excess. There is no simple correlation between the severity of weakness and degree of hypokalemia. Quadriparesis may occur in patients with potassium levels  $<2$  mEq/L. Muscles of respiration and neck flexors may be involved. Although the deep tendon reflexes are often retained, areflexia may accompany severe hypokalemia. The response to potassium given parenterally is dramatic. Correction of hypokalemia may precipitate hypocalcemic tetany in undiagnosed coexistent hypocalcemia.

### *Barium Induced Periodic Paralysis*

The accidental ingestion of barium carbonate or chloride induces a hemorrhagic gastroenteritis with colic, vomiting, diarrhea, hypertension and cardiac arrhythmias. The hypokalemia is caused by an intracellular transfer of potassium.

### *Hyperkalemic Periodic Paralysis*

Generalized weakness is the only established neurological manifestation of hyperkalemia. The paralysis may occur in the background of familial periodic paralysis, or secondary to renal or adrenal insufficiency, exposure to spironolactone and during febrile episodes of malaria. There is no weakness unless the potassium is higher than 7 mEq/l, although the weakness may occur at levels  $>6$  mEq/l. Familial hyperkalemic periodic paralysis has an onset in children younger than 10 years. Patients complain of heaviness and stiffness in the muscles. Weakness starts in the thighs and calves, which then spreads proximally. Weakness occurs during rest after strenuous exercise or during fasting. It may also be provoked by cold, potassium, alcohol,

or stress. It may be relieved by mild prolonged exercise or a carbohydrate intake. In infants and small children, characteristic attacks are episodes of floppiness in which the child lies around and cannot move. In children, a myotonic lid lag of upper eyelid on downward gaze may be the earliest symptom. Clinically apparent myotonia is seen in less than 20% patients, but electrical myotonia may be found in 50 to 75%.

The weakness may be progressive or may occur intermittently with episodes lasting hours. Mild attacks last for less than 1 hour. Severe attacks can cause quadriplegia, with respiratory muscle involvement requiring ventilation. The tendon reflexes are absent and often hyperkalemic paralysis has been misdiagnosed as GBS.

### *Hypermagnesemia*

The paralysis is caused by the effect of high magnesium levels on acetylcholine release at the neuromuscular junction. It can occur in the setting of using magnesium-based antacids or cathartics in patients with renal insufficiency. The weakness is of the flaccid, areflexic type and respiratory muscles can be affected. Infants born to eclamptic mothers treated with magnesium sulfate may have generalized weakness, hypotonia and altered mental status.

### *Rhabdomyolysis, Myoglobinuria and Metabolic Myopathies*

Myoglobinuria is the presence of excessive amounts of the heme protein myoglobin in the urine that occurs when its serum levels exceeds the renal threshold, imparting a cola-like color to the urine following massive muscle necrosis known as rhabdomyolysis. It can be differentiated from hemoglobinuria by radioimmunoassay, and by the rise in CPK levels and absence of red cells in the urine. The attacks may be recurrent as in metabolic myopathies. The muscles are tender, swollen, and stiff and accompanied by weakness. There is leakage of phosphates, potassium, uric acid, creatine, carnitine, CPK and aldolase. Acute tubular obstruction and necrosis initiate renal failure. Causes of rhabdomyolysis include:

- a. *Infections*: Influenza, coxsackie, toxic shock, Gram-negative sepsis
- b. *Medications*: Chloroquine, amphotericin B, simvastatin
- c. *Drug abuse*: Alcohol, amphetamine, heroin, phencyclidine
- d. *Metabolic myopathies*: McArdle syndrome, carnitine deficiency, mitochondrial myopathy, debrancher enzyme deficiency

- e. *Electrolyte disturbance*: Hypokalemia, hypophosphatemia
- f. *Animal toxins*: Sea snake bite, spider bite
- g. Exercise, fever or trauma

Management consists in resting the patient with passive manipulation to prevent contractures and ischemia. Watch for compartment syndromes due to tight fascial compartments from swollen muscles. Renal failure should be prevented by maintaining fluid balance with appropriate use of diuretics (frusemide 1-2 mg/kg) and fluids (up to 150 ml/kg). A single dose of mannitol (1 g/kg) should be given. Blood levels of potassium, calcium and phosphate levels should be regularly monitored.

### Myoneural Junction Disorders

There are several disorders of the neuromuscular junction that affect children and infants:

1. Passively acquired autoimmune myasthenia gravis (MG) (transient neonatal MG)
2. Acquired autoimmune MG (Juvenile MG)
3. Non-autoimmune myasthenic syndromes (Congenital MG)
4. Botulism

Passively acquired MG is seen in approximately 15 percent of children born to mothers with MG. Only a small proportion of them are symptomatic. While most of them have a mild illness, some can be severely affected with a weak cry, hypotonia, swallowing and sucking difficulty, facial weakness, ophthalmoparesis and ptosis. Diagnosis is by the edrophonium test, and if symptomatic, the newborn can be given pyridostigmine (1-2 mg/kg every 4-6 hours) therapeutically till he is asymptomatic. The drug is tapered off 2 weeks after start of therapy. These children will not develop MG later.

Children with acquired autoimmune MG will present with fluctuating weakness and fatigability. Weakness of extraocular, facial, bulbar and or limb weakness will be variably present. A fulminant presentation may be encountered in some young children. The edrophonium test and electrophysiology will help to confirm the diagnosis. Acetylcholine receptor antibodies will be positive in most, but the mild cases. Treatment is with anticholinesterase drugs, and if needed, steroids and other immunosuppressants. Plasmapheresis, IVIG and IV methylprednisolone may be used in severe cases.

Patients with MG can become critically ill rapidly, and the severity of exacerbation may be misjudged. This state of myasthenic crisis may follow infection, surgery or use of corticosteroids. It is a medical

emergency and requires prompt treatment. The common reason for ICU admission is imminent respiratory failure. Measurement of vital capacity in the supine position is a useful measure. Patients with diaphragmatic weakness but no obvious respiratory failure have a significant decrease (up to 60 percent from the baseline value in the erect position) when tested lying.

Treatment of precipitating factors is frequently sufficient to restore adequate respiratory function. If this has not occurred within 24 to 48 hours, plasma exchange or IVIG should be considered. Endotracheal intubation may be avoided by measures such as nursing in the upright position, using incentive spirometry, and assisted coughing; and can almost be avoided if IVIG (400 mg/kg/day × 5 days) or plasmapheresis (5 plasma exchanges for 2 consecutive days) is started immediately.

Pyridostigmine is stopped temporarily during mechanical ventilation, to upgrade the acetylcholine receptors, and also to exclude the possibility of a cholinergic crisis. It can be restarted parenterally after 2-3 days, in doses smaller than were used before the crisis.

Supportive measures as in the case of GBS should be instituted. Care should be taken to avoid medications that affect the neuromuscular junction.

*Seasonal myasthenic syndrome*: This type of a neuro-paralytic syndrome has been seen in rural areas of India during the monsoon season. The mode of onset is acute, almost always overnight. The manifestations are bilateral ptosis, external ophthalmoplegia and bulbar, axial and proximal muscle weakness. This heterogeneous myasthenic syndrome seems to be due to a biologic toxin from snake bites.

### Botulism

Botulism occurs following ingestion of contaminated seafood (type E toxin) or improperly sterilized bottled or canned food (type A and B toxins). The disorder can be fatal, and the symptoms start 12 to 48 hours after ingestion of the contaminated food. Bulbar symptoms, including diplopia, ptosis, blurred vision, impaired speech, and difficulty in swallowing occur initially and are followed by weakness in the upper limbs, followed by the legs. In severe cases, respiratory failure requiring mechanical ventilation occurs. The descending paralysis may help to clinically differentiate it from GBS. One should remember that normal pupils do not exclude the diagnosis of botulism. In infants, this disorder occurs between 6 weeks and 9 months of age. Infants often have an antecedent history of constipation and poor

feeding, and a significantly large proportion has been fed honey.<sup>21</sup> Bulbar signs are common and include a poor cry, poor sucking, impaired pupillary responses and external ophthalmoplegia. With progress of the disease, a flaccid paralysis develops. The illness lasts 4-20 weeks and almost all infants recover. The diagnosis of botulism is difficult to establish as it may mimic viral encephalitis, GBS, sepsis and neonatal myasthenia. The presence of bulbar signs and pupillary abnormalities in an alert child is characteristic. An EMG will show the striking incremental response at 50 Hz repetitive stimulation. Whilst botulism in older children is due to ingestion of preformed toxins (A, B, or E), infant botulism results from colonization of the gut with type A or type B spores of *C. botulinum*.

In most cases, administration of antitoxin is ineffective by the time botulism is diagnosed. Treatment is supportive with mechanical ventilation, nasogastric feeding and care of the paralyzed patient.

#### *Organophosphorus Poisoning*

Organophosphorus compounds are irreversible inhibitors of acetylcholinesterase and cause accumulation of acetylcholine at the muscarinic and nicotinic synapses and in the CNS. While the compounds are absorbed by skin and inhalation, the acute poisoning follows accidental or suicidal ingestion of the insecticide. The time from exposure to the onset of toxicity is between 30 minutes and 2 hours. Nicotinic effects include twitching, fasciculations, weakness, hypertension, and tachycardia and in severe cases paralysis and respiratory failure. Muscarinic effects include nausea, vomiting, abdominal cramps, increased bronchial secretions, wheezing, dyspnea, sweating, miosis and lacrimation.<sup>22</sup> In severe poisoning, bradycardia, conduction block, hypotension and pulmonary edema may occur. An "intermediate syndrome" comprising paralysis and respiratory muscle weakness starts 1 to 4 days after exposures. The effects last less than 4 weeks with subsequent recovery.

Children with organophosphorus poisoning must be admitted to the ICU and the following measures adopted:

1. Gastric lavage.
2. Assess respiration and hemodynamic status and intubate if indicated.
3. Fluid and electrolyte management.
4. Treat seizures.
5. Control agitation.
6. *Antidote:* Atropine in a dose of 0.03 mg/kg for infants, and 0.1 mg/kg (max 0.4 mg) for older

children should be given every 10 to 30 min until the cholinergic signs are no longer present or the pupils become dilated. Pralidoxime (PAM) in a dose of 15-25 mg/kg should be given over 15-30 min. In children weighing more than 25 kg, PAM in a dose of 600 mg should be given at intervals till a maximum dose of 1800 mg has been administered. PAM reactivates the acetylcholinesterases and should be given 2-4 times a day for the first 2 days.

#### *Acute Neuromuscular Weakness in the Intensive Care Unit (ICU)*

Weakness acquired in the ICU due to neuromuscular disease is two to three times more common than primary neuromuscular disorders such as GBS, myopathies or motor neuron diseases.<sup>23</sup> Critical illness myopathy (CIM) and critical illness neuropathy (CIP) are being increasingly reported in adults, but in children the diagnosis is probably missed often and only the severe ones are reported. CIP and CIM maybe just another (neuromuscular) organ failure, developing in a parallel time course with other multiple organ failures in the critically ill patient.<sup>24</sup>

#### *Critical Illness Polyneuropathy and Myopathy*

It is a sensory motor neuropathy developing in critically ill patients affected by sepsis and multiorgan involvement. Sepsis and multiorgan failure occurs in up to 20-50 percent of patients in a medical intensive care unit<sup>25</sup> and 70 percent of such patients have critical illness neuropathy.<sup>26</sup> Sepsis, systemic inflammatory response syndrome (SIRS), and multiorgan failure are important in the development of these syndromes although additional factors such as use of NMJ blockers, corticosteroids, cytotoxic drugs, and status asthmaticus have been implicated in the development of CIP and CIM. The neuropathy may occur as early as 2 to 5 days in the presence of sepsis and SIRS.<sup>23</sup> The neuropathy may be severe enough to produce diaphragmatic weakness and up to 30 percent may have difficulty in being weaned off the respirator. The neuropathy may resemble GBS. However, the facial, bulbar and ocular muscles are not involved in critical illness neuropathy. CIM has been reported in children admitted to ICUs. They have persistent moderate or severe, flaccid, generalized weakness that becomes apparent when NMB is stopped. Distal and proximal muscles may be equally affected. The reflexes may be normal, reduced or absent. The most prominent problem in the ICU is weaning off the ventilator, due to diaphragmatic or intercostal weakness, and in a few patients ventilatory

failure is the presenting symptom. Most recover within 4 to 12 weeks. The laboratory fails to show hypokalemia, hypophosphatemia or hypermagnesemia. The CPK may be increased 2 to 3 times the normal very early in the course. Electrophysiological studies show a mixed axonal neuropathic and myopathic pattern.<sup>23,24</sup> Recovery occurs in a stereotyped manner, first in the upper and proximal lower limbs followed by successful weaning and then distal lower limbs. Treating infection, drainage of abscess, fluid resuscitation and physiotherapy all have a role in recovery. IVIG has not proven to be useful.

#### *Neuromuscular Blockade (NMB)*

Prolonged NMB occurs when synaptic transmission remains impaired and muscle weakness persists after NMB has been discontinued. It may be brief, lasting minutes or hours after a single dose of NMB. In the ICU, after repeated doses of pancuronium or vecuronium, a flaccid weakness of all 4 limbs with ptosis and ophthalmoplegia may persist lasting for days or weeks.<sup>27,28</sup> NMB used for mechanical ventilation for at least 2 days may produce prolonged muscular weakness, most likely from accumulation of the metabolites of pancuronium or vecuronium. In addition, the metabolism of these drugs may be affected by organ failure, resulting in accumulation of these agents or their metabolites. Such accumulation results in prolonged NMB lasting for days after the drug is stopped. Besides, these drugs being amino steroids may be myotoxic, especially when combined with steroids. The disorders can be recognized through repetitive nerve stimulation test and temporarily reversed by neostigmine.

#### *Neuromuscular Disease in the Newborn*

The question that needs to be addressed in the newborn ICU is whether the baby has central hypotonia or a neuromuscular disorder. The presence of weakness and areflexia helps to differentiate between the two entities. Seizures and encephalopathy point to a central cause. Microcephaly and other congenital anomalies may indicate a global disorder with cerebral dysgenesis as a cause of the problem. Assuming that oxygenation/perfusion is normal and that the newborn is not infected or suffering from an obvious systemic illness, the following screening tests may be helpful:

1. Blood gases, blood ammonia and urine metabolic analysis will help identify a number of metabolic disorders presenting in this period.
2. EEG to assess physiological maturity/activity and cranial ultrasound to exclude hemorrhage or dysgenesis.

3. Nerve conduction studies and EMG are extremely helpful in determining that hypotonia and weakness are due to a neuromuscular disorder and to determine the nature of disorder, i.e. peripheral neuropathy, anterior horn cell disease, etc.

If normal, causes of central hypotonia need to be looked into. If the nerve conduction studies are normal but EMG shows denervation, causes of motor neuron diseases (spinal muscular atrophy) need to be investigated. If the study shows a myopathic process, careful examination of the parents, especially the mother should be carried out. Congenital myotonic dystrophy is the most important specific congenital myopathy in newborns. If the parents are normal, a muscle biopsy is the next step in evaluating the newborn.

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# 23 Acute Bacterial Meningitis

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Acute bacterial meningitis (ABM) remains a common life-threatening condition in children. In a multicentric survey in India, ABM constituted 1.5 percent of admissions in pediatric wards and the mean case fatality was 16 percent.<sup>1</sup> Even though the mortality on account of this formidable disease has decreased over the years with the availability of potent antibiotics, a significant number of patients are left with neurological sequelae.<sup>2</sup>

## EPIDEMIOLOGY

Acute bacterial meningitis is essentially a disease of young children. Poor socioeconomic condition, overcrowding recent colonization with pathogenic bacteria, cerebrospinal fluid (CSF) communications (congenital or acquired) across the mucocutaneous barrier are some of the host factors which increase the risk of meningitis.<sup>3</sup> Exposure to cigarette smoke has been demonstrated to increase the risk of ABM.<sup>4</sup> The widespread use of conjugate vaccine against *Haemophilus influenzae* type b in many developed countries has led to marked decline in number of cases of meningitis. In countries with routine Hib vaccination, the median age of ABM has shown an increase with proportionately more cases occurring in adults.<sup>5</sup> This trend is likely to continue after initiation of routine immunization with conjugate pneumococcal vaccine in many developed countries.

Most cases of ABM are sporadic except meningococcal meningitis which often occurs in epidemic form specially in Sub-Saharan Africa and Indian sub-continent. Meningococcal meningitis occurs most frequently in young children with peak attack rates in 6-12 months infants. A second peak occurs in adolescence. Clusters of meningococcal disease among adolescents and young adults have been reported with increasing frequency in the last decade. Disease rates in adolescents are high because this group has highest rate of carriage of meningococcus.<sup>6</sup>

## ETIOLOGY

Any organism can potentially cause meningitis but the usual causative agents of ABM vary with age, immune system and immunization status of the patient. During the first 2 months of life, *Escherichia coli* K1 and other gram-negative enteric bacilli, *Streptococcus agalactiae* and *Listeria monocytogenes* are the usual offending organisms. In children between 2 months to 12 years, bacterial meningitis is primarily due to *H. influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis*. Meningitis in infants between the age of 1-3 months may be due to pathogens found both in neonates and older children.

In children with severe malnutrition, compromised immunity or anatomical defects, infection can occur with other microbes like *Staphylococcus*, *Salmonella*, *Pseudomonas*, etc. Reports from developing countries indicate that hemophilus and pneumococci accounts for most of the cases though a sizeable proportion of cases presumed to be bacterial in nature fail to demonstrate any pathogen.<sup>7</sup>

## PATHOGENESIS AND PATHOLOGY

The mucosal surfaces in the nasopharynx are the initial site of colonization for the common meningeal pathogens. The exact mechanism by which bacteria invade CNS is not clear. For some organisms. Specific surface components as K1 polysaccharide antigen of *E. coli* are essential for attachment to mucosal surface and specific virulence. Bacteria penetrate through or between mucosal epithelial cells and enter sub-epithelial blood vessels to enter bloodstream. The bacteria survive in bloodstream if it is able to counter the host defence mechanism. From the bloodstream the pathogen may cross blood-brain barrier to induce ABM. To get across the blood-brain barrier, pathogens attach to brain microvascular endothelial cells which is facilitated by receptors for meningeal pathogens found on endothelium in choroid plexus. After attaching itself to endothelial cell the pathogen gains entry to CSF

space either by transcellular or paracellular route.<sup>8</sup> Once inside the CSF space the bacteria multiply freely because of relative lack of host defense mechanism in this space. The release of bacterial components during this process of replication stimulates the release of pro-inflammatory cytokines. With induction of inflammation, neutrophils migrate into CSF, there is release of reactive oxygen species and nitric oxide and all this adds to the deleterious effect of inflammation on the brain.

The fundamental pathological change in ABM is inflammation of leptomeninges with meningeal exudates of varying thickness encasing the brain. The exudates extend into Virchow-Robin spaces along with penetrating vessels. Involvement of vessels leads to phlebitis or arteritis and softening or necrosis of corresponding vascular territory. Cerebral edema develops early in the course of ABM and together with acute hydrocephalus may be responsible for intracranial hypertension. Intracranial pressure (ICP) is maximally increased within the first 48 hours. This in turn impedes cerebral perfusion resulting in neuronal injury. Nearly 30 percent of infants and children with ABM have decreased cerebral blood flow ranging from 30-70 percent.<sup>9</sup> Transcranial Doppler studies on patients with meningitis show disease related arterial narrowing in approx 50 percent of cases and this correlates with neurologic impairment.<sup>10</sup>

### CLINICAL FEATURES

Early symptoms of meningitis in young children are often vague and ill defined. In general, younger the infant the more non-specific are the symptoms. History suggestive of upper respiratory infection may be noted in nearly 75 percent of patients. Intercurrent viral infection play a key role in invasive pneumococcal infections by generating local inflammatory factors that upregulate platelet activating factor receptor. Pneumococci adhere strongly to activated cells expressing PAF receptor.<sup>11</sup> The main symptoms which are highly suggestive of a diagnosis of ABM in infants are fever (with or without vomiting), alteration of behavior (infant becomes lethargic or drowsy, irritable, feeds poorly), a high pitched cry, seizures and a full or tense anterior fontanelle. Specific signs of meningeal irritation are hardly ever present in infants below the age of 2 years. In older children, classical signs and symptoms of meningitis like fever, headache, vomiting, photophobia, neck stiffness and the meningeal signs are likely to be present. Neck stiffness is the most important of all meningeal signs and earliest to appear.

It becomes more marked if tested while the patient sits up with knees extended. Kernig's sign and Brudzinski's sign are other meningeal signs. The meningeal signs are due to reflex muscle spasm in reaction to pain on stretching of contents of spinal cord. These signs may be absent in comatose patients.

The second mode of presentation is acute and fulminant in which manifestations of sepsis and meningitis develop rapidly associated with severe brain edema and raised ICP. This type of presentation is seen most often with *N. meningitidis*. Petechial hemorrhages appearing on the skin which rapidly coalesce producing areas of purpura are considered hallmark of this disease, although they may be seen in meningitis due to other organisms also. Profound hypotension and fatal shock has been reported.<sup>12</sup>

Seizures occur in about 30-40 percent cases of ABM. A high concentration of tumor necrosis factor (TNF) has been associated with occurrence of seizures.<sup>13</sup> Alterations of mental status and reduced level of consciousness is common and may be due to increased ICP, cerebritis or hypotension. Papilledema is uncommon in uncomplicated acute meningitis and when present suggests a more chronic process such as presence of intracranial abscess, or subdural empyema. Focal neurologic signs may be due to vascular occlusion, subdural collection or cortical infarction. Overall 14 percent of children of bacterial meningitis have focal neurological signs.<sup>2</sup>

Reactive thrombocytosis is common during recovery from meningitis and implies favorable prognosis for survival.<sup>14</sup>

### COMPLICATIONS

Complications of ABM can develop early in the course of illness or later after several days of therapy or may be noticed on follow-up (Table 23.1).

#### *Systemic Complications*

*Peripheral circulatory failure* is a life-threatening complication of meningitis. It occurs most commonly with meningococcal infection but can accompany other types of infection. About 15 percent children with pneumococcal meningitis have been reported to present with shock.<sup>15</sup> Antibiotic therapy may initially aggravate hypotension, hence intensive monitoring is required in the initial period.<sup>16</sup> Other manifestations of acute bacterial sepsis may be seen as coagulopathy, acidosis and hypoglycemia. Pneumonia, pericarditis and arthritis occur occasionally. Prolonged fever (>10 days) is seen in some cases due to intercurrent viral infection, secondary bacterial infection, thrombophlebitis or a drug

**Table 23.1: Complications and sequelae of ABM****Complication***Neurological*

- Increased intracranial pressure
- Seizures
- Subdural effusion/empyema
- Ventriculitis
- Cranial nerve palsies
- Hemi/quadruparesis
- Hearing loss
- Hydrocephalus

*Systemic*

- Peripheral circulatory failure
- Disseminated intravascular coagulation
- Syndrome of inappropriate antidiuretic hormone secretion
- Arthritis

**Sequelae**

- Epilepsy
- Sensorineural hearing loss
- Visual impairment
- Behavioral problems
- Motor deficits
- Hydrocephalus
- Learning disabilities

reaction. Secondary fever that is seen after an initial afebrile period is usually due to nosocomial infection. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported to occur in 28 percent of cases of ABM.<sup>17</sup> It leads to cerebral edema and hyponatremic seizures.

*Neurological Complications*

Increased ICP is present in almost all cases of ABM initially though only 1-3 percent of cases have persistent hydrocephalus.<sup>18</sup> Raised ICP as a complication of ABM should be anticipated and treated promptly. When ICP is very high, herniation of brain tissue may occur at the incisura or at foramen magnum and may lead to sudden respiratory arrest, sudden death or persistent vegetative state. Cerebral herniation following LP is an important contributor to overall mortality.<sup>19</sup> Lumbar puncture should therefore not be done in children with clinical evidence of raised ICP.

*Seizures* occur in about 30-40 percent of children with meningitis. Generalized seizures occurring within first four days are of no prognostic significance. Seizures that present after 4th day and those that are difficult to treat and those that appear late in the course of meningitis are associated with poor prognosis. Children with focal convulsions are more likely to have neurologic sequelae of meningitis. Causes of late onset

seizures include cerebritis, subdural effusion, vascular thrombosis and abscess formation.

*Subdural effusion* develops in 10-30 percent of patients with meningitis and are more common in *H. influenzae* meningitis. These effusions are mostly asymptomatic. Effusions usually resolve spontaneously and aspiration is required only in case of increased ICP or a depressed consciousness. Subdural empyema requires more aggressive treatment in form of aspiration.

*Transient cranial nerve dysfunction*, and motor deficits may be seen during acute phase of illness. *Hearing loss* is the most common sequel of ABM. Nearly 10-25 percent of survivors are left with permanent sensorineural loss.<sup>2,20,21</sup> All patients of ABM should have audiologic evaluation after recovery.

**Diagnosis**

The diagnosis of ABM is based on documenting inflammatory response of meninges (e.g. CSF cell count, protein, sugar) and on tests that demonstrate the specific causative bacterial agent in CSF (Gram's stain, culture, tests for bacterial antigen/ DNA). Since the clinical features of ABM are non-specific especially in infants, LP should be performed whenever there is suspicion of meningitis. Occasionally, LP may have to be postponed due to cardiorespiratory compromise, signs of increased ICP and infection at the LP site. Clinical signs of raised ICP is a more reliable indicator to withhold a lumbar puncture since even a normal CT scan does not exclude the imminent risk of coning. In case LP is deferred, empirical treatment should be started after taking blood culture.

*LP in Children with Febrile Seizures*

A seizure associated at onset of meningitis may not be distinguishable from simple febrile convulsion. It is therefore advocated that LP be routinely done in all infants/young children after an initial febrile seizure to exclude cases of occult meningitis. Lethargy, irritability, vomiting and presence of complex febrile seizures are strong indicators of meningitis in febrile infants with seizures.<sup>22</sup> LP in infants with seizures with fever should only be withheld if the patient is well and alert on examination and can be observed for the next few hours. In patients who have been pretreated with antibiotics or anticonvulsants, the signs are masked and hence they must be subjected to LP.

*CSF Examination*

CSF examination includes a naked eye examination, pressure, microscopy—total and differential leukocyte

count, gram-stain, estimation of proteins and glucose and CSF culture. The CSF should be examined immediately after doing the LP since the cell count tends to fall over a period of time and may be falsely low after 30-60 min. The normal CSF of children contains less than 6 WBCs/mm<sup>3</sup> and in 95 percent of cases there are no polymorphonuclear (PMN) leukocytes.<sup>23</sup> Hence, presence of even a single polymorphonuclear leukocyte in a child 6 weeks of age is suggestive of ABM. However, CSF lymphocytosis may be a predominant feature in 10-13 percent of cases.<sup>24</sup> CSF lymphocytosis is believed to represent an early phase of infection and repeat CSF examination in these cases will show a PMN predominance. Prior antibiotic therapy also results in lymphocytosis.

Proteins in CSF are elevated (normal 20-40 mg/dl); CSF sugar is decreased (normal > 50 mg/dl); and ratio of CSF to blood sugar is decreased (< 60%) in acute bacterial meningitis.

Gram-stain of the smear is one of the most simple, cheap and rapid diagnostic bedside tool useful for detection of etiological organism. In a series of patients with pneumococcal meningitis, Gram stains of CSF were positive in 90 percent cases.<sup>14</sup> Centrifugation of CSF increases the positivity. Fluorescent staining of bacterial DNA with acridine orange may show the bacterial morphology in cases where Gram stain is negative. Acridine orange staining is superior to Gram stain in pretreated patients.<sup>25</sup> CSF culture provides a confirmatory evidence of ABM and is essential for selecting appropriate antibiotic for the etiological organisms. The rate of bacterial isolation is affected by antibiotic use prior to lumbar puncture, further rate of isolation is increased if direct plating of CSF is done at bedside.

In case LP is traumatic it is recommended to do the cell count and then lyse RBCs with acetic acid and repeat cell count. The ratio of WBCs to RBCs (normal 1:500 to 1:750) can give some indication of the total cell count though it is rather cumbersome. Besides, the biochemical parameters and the Gram stain and culture are not affected by blood in CSF. CSF from a traumatic LP should therefore be interpreted on a combination of factors.

#### Rapid Diagnostic Tests

Various rapid diagnostic tests including counter immunoelectrophoresis (CIE), latex particle agglutination (LPA), and enzyme-linked immunosorbent assay (ELISA) are used to detect bacterial antigen. Of these the results of CIE and LPA can be available within-1-2 hours but ELISA takes a longer time. LPA is more

sensitive than CIE. The sensitivity of CIE can be improved by screening multiple body fluids. LPA kits are commercially available for detecting antigen of hemophilus, pneumococci and meningococci. Ultrasound enhanced LPA has been developed which is more sensitive than conventional LPA.<sup>26</sup> A negative test for bacterial antigen cannot exclude bacterial meningitis, since these tests are limited to a few specific pathogens. Due to high cost these tests should be reserved for patients who have received antibiotics if Gram stain is negative.<sup>27</sup> PCR of CSF has been employed to detect microbial DNA in patients with ABM. Primers are available for simultaneous detection of the common organisms. PCR based detection of meningococcal antigen in CSF has been found to be useful in patients who have been pretreated with antibiotics as bacterial DNA remains in CSF 2-3 days after treatment.<sup>28</sup> A combined PCR based assay for rapid diagnosis of meningitis due to *Haemophilus spp*, pneumococci and meningococci has been developed.<sup>29</sup> However, PCR cannot be used routinely because of high cost and need for special laboratories.

Various non-specific markers of inflammation such as C-reactive proteins, CSF lactate, CSF CPK, TNF  $\alpha$  and interleukins have been investigated to differentiate bacterial meningitis from aseptic meningitis and as marker of severity of ABM with relation to outcome.<sup>30</sup> Leukocyte aggregation score-which is based on percentage of cells aggregated is a rapid and cheap test to distinguish bacterial from viral meningitis. Further studies are required for confirmation of this simple test.<sup>31</sup> However, these tests do not help in confirming the diagnosis and are of no value in choice of therapy.

Despite advancements in laboratory techniques, routine culture of CSF, blood, and Gram stain of CSF remain the standard methods of establishing the etiological agent of ABM. LPA and PCR based tests are useful in patients pretreated with antibiotics. These tests can also be helpful in identifying the serotype of meningococci in outbreak situation.

*Blood culture:* Blood culture is positive in two-third cases of ABM and should be done in all cases. It is specially useful in cases in whom LP cannot be done or is traumatic.

*Smear of petechiae:* Smear of petechial lesion (if present) after puncture with a lancet should be made and subjected to Gram stain for meningococci.

#### Indications for Repeat Lumbar Puncture

If lumbar puncture is deferred on admission it should be performed after the patient is stable and an attempt

made to demonstrate organism on gram-stain or by LPA. A repeat spinal tap is not indicated in most of the cases of ABM. It should be done in case of poor clinical response to therapy of 48-72 hours, persistent fever, unusual etiological organism or suspicion of bacterial resistance. Similarly end of therapy LP is not routinely required if the patient is well and afebrile for the preceding 5 days.<sup>32</sup>

#### Radiological Evaluation

Cranial sonography is the investigation of choice in infants and neonates and can detect early structural changes. Sonography should be done in all neonates and infants less than 2 months since the risk of complications are higher. Contrast enhanced CT is the preferred modality if subdural empyema or parenchymal damage is suspected. However, in uncomplicated meningitis radiological evaluation by CT is not necessary.<sup>33</sup> These investigations should be considered in patients with (i) signs of raised ICP, (ii) focal neurologic deficits, (iii) persistent fever, (iv) recurrent/focal seizures, (v) prolonged coma and (vi) increasing head circumference.

### DIFFERENTIAL DIAGNOSIS

Several diseases, particularly aseptic meningitis, tuberculous meningitis, cerebral malaria, brain abscess and lead encephalopathy present with signs and symptoms similar to ABM. A careful examination of CSF, which shows pleocytosis with polymorphonuclear predominance with reduced CSF sugar is highly suggestive of ABM. Gram-stain and culture confirm the diagnosis. Pre-treatment of meningitis with oral or systemic antibiotics often poses a diagnostic problem since CSF is rapidly sterilized though cell count, and CSF biochemical abnormalities persist. In any case of clinically suspected ABM, empiric therapy for ABM should be immediately started.

### TREATMENT

Treatment can be broadly categorized into: (1) antibiotic therapy; (2) supportive care and (3) adjuvant therapy.

#### ANTIBIOTIC THERAPY

##### Selection of Initial Antibiotic Therapy

The antibiotic regimen should be such that it covers all the likely pathogens according to the age of the child, combination should not be antagonistic and it

should achieve bactericidal concentration in the CSF. Later the treatment can be modified depending upon the result of Gram stain and CSF culture. Various antibiotics used in initial therapy and subsequent treatment are shown in Table 23.2.

Third generation cephalosporins cefotaxime and ceftriaxone are the preferred initial antibiotics for meningitis as they are effective against most bacteria causing meningitis including resistant *H. influenzae* type b and penicillin resistant strains of *S. pneumoniae*.<sup>3,34</sup> Cefepime an extended spectrum cephalosporin has been used as monotherapy in empiric treatment of ABM with favorable results.<sup>35</sup> Cefuroxime, cefoperazone, and cefoxitin are not effective in ABM and should not be used. Due to the high cost of other antibiotics, a combination of penicillin and chloramphenicol is often used as initial therapy. Reports of increase in frequency of resistant pneumococci are emerging throughout the world.<sup>36</sup> In India, the exact incidence of resistant pneumococci varies from 3.3 to 8 percent.<sup>37</sup> Penicillin can no longer be recommended as empiric therapy when pneumococci is a likely pathogen since this therapy may not be effective for meningitis caused by penicillin resistant strains. Meropenem has been reported to be as efficacious and safe as cefotaxime as initial therapy for meningitis in a prospective study and can be considered as an alternative treatment.<sup>38</sup>

Subsequent therapy depends on the organism isolated and its antibiotic sensitivity. For penicillin resistant pneumococci, combination of ceftriaxone and vancomycin should be used. Addition of rifampicin should be considered in highly resistant strains. There are anecdotal reports of cefotaxime or ceftriaxone failure in the management of pneumococcal meningitis.<sup>39</sup> Meropenem has been used for treatment of penicillin resistant pneumococci and multi-drug resistant *Pseudomonas meningitis*.<sup>40</sup> Newer fluoroquinolones—levofloxacin and sparfloxacin have been shown to be effective against invasive *S. pneumoniae* isolates, though their routine use in ABM has not been studied well.<sup>41</sup>

Fortunately resistance to 3rd generation cephalosporins among *Haemophilus spp.* has not emerged. There are reports of meningococcal resistance to penicillin.<sup>41</sup> Chloramphenicol resistance in meningococci has been reported from Vietnam and France.<sup>42</sup> For multiple drug resistant staphylococci, vancomycin remains the drug of choice.

##### Duration of Therapy

The duration of antimicrobial therapy is based on the causative agent, and clinical response (Table 23.2). In

**Table 23.2: Initial and subsequent therapy in cases of bacterial meningitis**

<b>Initial Empiric Therapy</b>			
Age	Suspected pathogen	Drug of choice	Alternative choice
0-2 months	<ul style="list-style-type: none"> <li>Gram-negative enteric bacilli</li> <li><i>L. monocytogenes</i></li> <li><i>Streptococcus agalactiae</i></li> </ul>	Amikacin +	Ampicillin +
2 months to 12 years	<ul style="list-style-type: none"> <li><i>H. influenzae</i></li> <li><i>S. pneumoniae</i></li> <li><i>N. meningitidis</i></li> </ul>	Ceftriaxone or Cefotaxime	Ampicillin + Chloramphenicol
<b>Subsequent antibiotic therapy in children 2-12 months</b>			
Pathogen	Drugs of choice	Alternative choice	Duration of therapy (days)
Pathogen unknown	Ceftriaxone	Ampicillin +	14
<i>H. influenzae</i> type b	Ceftriaxone	Chloramphenicol Chloramphenicol +	10
<i>S. pneumoniae</i>		Ampicillin	
<ul style="list-style-type: none"> <li>Penicillin sensitive</li> <li>Penicillin resistant</li> </ul>	Crystalline penicillin	Chloramphenicol	14
	Ceftriaxone +	Meropenem	14
<i>N. meningitidis</i>	Vancomycin Crystalline penicillin	Ceftriaxone Chloramphenicol	7-10
<i>Staphylococci</i>	Nafcillin	Vancomycin	2-3 weeks
<i>Pseudomonas</i>	Ceftazidime + Amikacin	Meropenem	3 weeks
* Dosage Schedule (All drugs to be given IV)			
Ampicillin	300 mg/kg/24 hours, in 4 divided doses		
Ceftriaxone	100 mg/kg/24 hours, in 2 divided doses		
Cefotaxime	200 mg/kg/24 hours, in 4 divided doses		
Chloramphenicol	100 mg/kg/24 hours, in 4 divided doses		
C. Penicillin	300,000 units/kg/24 hours, in 4-6 divided doses		
Vancomycin	60 mg/kg/24 hours, in 3-4 divided doses		
Nafcillin	200 mg/kg/24 hours, in 4-6 divided doses		
Meropenem	120 mg/kg/24 hours, in 3 divided doses		
Amikacin	45-60 mg/kg/24 hours, in 3 divided doses		

children with rapid initial recovery, 4 days of ceftriaxone was found to be adequate.<sup>43</sup> However, this cannot be recommended as a standard duration of therapy. Longer duration of treatment is required in cases of complications such as subdural empyema, prolonged fever, persistence of meningeal signs or development of nosocomial infections. In such cases discontinuation of antimicrobial therapy is individualized.

### 3

#### Supportive Therapy

The first 3-4 days of treatment are critical because life-threatening complications of meningitis occur most

frequently during this period. It is advisable to manage infants and children with meningitis in hospitals that has staff with expertise in caring for infants and children who are critically ill. Vital signs of patients should be monitored regularly during the first 24-28 hours of treatment. The patient should be kept nil orally to prevent aspiration. Neurological examination should be performed initially and daily throughout hospitalization. Blood urea, sugar, gases, serum electrolytes, urine osmolality, and urine output, and body weight should be monitored closely.

Hypovolemia and hypotension should be aggressively treated with normal saline and inotropic support. Maintenance of systemic blood pressure is critical to

maintain cerebral blood flow. Concurrence of shock and cerebral edema is a therapeutic challenge. The treatment of shock with fluids and inotropes takes priority in such cases. Hyponatremia is a frequent finding in patients with meningitis most often due to SIADH.<sup>44</sup> However it may be due to volume contraction rather than water retention.<sup>45</sup> While optimizing the fluid therapy, it is important to recognize that hyponatremia may be due to dehydration or water retention as in SIADH. The circulatory compromise caused by hypovolemia is as dangerous as cerebral edema caused by water retention. Therefore the cause of hyponatremia should be assessed along with clinical signs of volume depletion and biochemical parameters, i.e., serum and urine osmolality.

In normovolemic patients fluids are conventionally restricted to two-third of maintenance initially until raised ICP and SIADH are excluded. Fluid administration may be returned to normal when serum sodium level has normalized. Recent evidence supports administration of maintenance fluids rather than restricted fluids in first 48 hours, in settings with higher mortality and where patients present late.<sup>46</sup>

Intracranial pressure can be reduced by elevating the head end of the bed by 30° to maximize venous drainage. Osmotic diuretics such as mannitol (0.5-1 g/kg) and oral glycerol can be used to reduce ICP. Hyperventilation to maintain the arterial pCO<sub>2</sub> between 27-30 mm of Hg may also be used to reduce ICP. Aggressive hyperventilation may be counter productive as it causes reduction of already compromised CBF with resultant ischemic damage.

Seizures are common during the course of bacterial meningitis. Metabolic complications like hyponatremia, hypocalcemia and hypoglycemia must be excluded and specific therapy instituted, if present. Immediate management of seizures include intravenous diazepam (0.1-0.2 mg/kg/dose) or lorazepam (0.05 mg/kg/dose). This is followed by a loading dose of phenytoin (15 mg/kg) and the maintenance dose of 5 mg/kg/24h for further control of seizures. Phenytoin is preferred over phenobarbitone because it causes less CNS depression and allows assessment of sensorium. Anticonvulsants can be discontinued after a few days unless there is evidence of persistent seizure activity.

### Adjunct Therapy

Improvement in our understanding of the pathophysiology of ABM has led to the development of therapeutic approaches to modulate the inflammatory cascade to reduce the incidence of sequelae and death. Adjunctive anti-inflammatory agents which may be of

benefit in treatment of bacterial meningitis include corticosteroids and newer anti-inflammatory drugs which are still in experimental stage.<sup>9</sup>

Corticosteroids have been used with objective of blocking secondary release of cytokines and toxic intermediaries from the brain cells and are also presumed to stabilize altered vascular permeability. A number of trials were conducted in the last 2 decades to evaluate the role of dexamethasone (0.15 mg/kg every 6 hours for 2-4 days). The benefit of dexamethasone use in these studies was only moderate and limited to decrease in frequency of audiologic sequelae in *haemophilus* meningitis.<sup>47,48</sup> According to a recent Cochrane review in all cause meningitis, use of corticosteroids decreases the incidence of severe hearing loss and reduces short-term neurological sequelae in high income countries.<sup>49</sup> In adults, dexamethasone has shown to be beneficial.<sup>49</sup> Comparison of oral glycerol with or without dexamethasone has shown that addition of oral glycerol prevents neurological sequelae but does not prevent hearing impairment in children.<sup>50</sup> The effect of dexamethasone in treatment of neonatal meningitis has not been evaluated. Dexamethasone should not be used if aseptic or non-bacterial meningitis is suspected; and if it is started before the diagnosis is established, it should be discontinued immediately. Dexamethasone should not be used in partially treated meningitis. The maximum benefit of dexamethasone is obtained when it is given along with the first dose antibiotics.

Anti-endotoxin antibodies have been produced by monoclonal antibody technology and appear to have beneficial role in ABM caused by Gram-negative organisms. Monoclonal antibodies against TNF, IL-1B and against CD 18 cells may help in reducing inflammation as shown in experimental studies. Non-steroidal anti-inflammatory agent, e.g. indomethacin inhibit synthesis of prostaglandins from arachidonic acid via cyclooxygenase pathway and can thereby reduce brain edema. Preliminary results of pentoxifylline, a methylxanthine phosphodiesterase inhibitor indicate that it reduces some of the inflammatory indices of ABM in animal model. Role of all these is still at experimental stage and further trials are required to define their use in meningitis in humans.<sup>51</sup>

### PROGNOSIS

The prognosis of a patient with pyogenic meningitis depends on many factors including age, causative microorganism, bacterial density, intensity of host's inflammatory response and time taken to sterilize the CSF. Case fatality is reported to be 3-6 percent in developed countries but higher mortality (16%) is

reported from developing countries.<sup>1</sup> Most deaths occur within first 48-72 hours. Early fatality is most often due to septic shock. Close monitoring for signs of septic shock and brain herniation should be done in first 2-3 days of hospitalization.

Neurodevelopment sequelae are seen in 10-20 percent of patients.<sup>3,16</sup> Baraff *et al* in a meta-analysis of 19 reports estimated that 83.6 percent patients had no sequelae. The common sequelae reported were deafness (10.5%), mental retardation (4.2%), epilepsy (4.2%) and motor deficits (3.5%). The sequelae of bacterial meningitis may improve with time and even resolve completely. The potential for recovery is attributed to the plasticity of brain. Focal neurological signs at admission have been found to be reliable predictors of permanent sequelae especially later epilepsy.<sup>52</sup> Persistence of fever, neck rigidity and reluctance to leave the supine position beyond the first week was associated with risk of neurologic complication or sequelae.<sup>53</sup> Prognosis is poorest among infants less than 6 months, in those with delayed sterilization of the CSF, seizures beyond 4th day of hospital stay, coma, (Glasgow Coma Scale <8), focal neurological signs on presentation and infection with pneumococci, and other organisms like *Salmonella* or *Pseudomonas*.

## PREVENTION

Prevention of ABM is possible with (i) Prevention of secondary cases with antibiotic chemoprophylaxis of index case and close contacts, and (ii) Vaccination of susceptible population with specific vaccines. Vaccination is not a substitute for chemoprophylaxis because secondary cases develop within 2-7 days of presentation of index case and vaccination is not effective in that stage.

## Chemoprophylaxis

Rifampicin prophylaxis for *H. influenzae* is recommended (20 mg/kg daily for 4 days) for all household contacts, if there is an infant (<12 months) in the household or when a child 1-3 years who is inadequately immunized resides in the household.<sup>54</sup> Prophylaxis for index case is not required for those treated with cefotaxime or ceftriaxone. Ampicillin and chloramphenicol do not eradicate *H. influenzae*, therefore patients treated with these antibiotics should be given rifampicin before discharge from hospital.

For *N. meningitidis*, chemoprophylaxis is recommended for all close contacts (household contacts, day care contacts and any one exposed to oral secretions) regardless of age and immunization status. If the

organism is sensitive to sulfonamides, chemoprophylaxis can be given with sulfisoxazole (500 mg every 12 hours for children 1-12 years, and 1 g every 12 hours for contacts over 12 years for 2 days). Alternatively rifampicin (10 mg/kg every 12 hours for 2 days) can be given. There is concern about emergence of resistance to rifampicin among strains of meningococci.<sup>55</sup> This has to be monitored closely with obvious implication for prophylaxis. Ceftriaxone (250 mg intramuscularly as a single dose) and ciprofloxacin (single dose 500 mg) are other effective chemoprophylactic agents. No prophylaxis for *S. pneumoniae* is required for normal hosts.

## Vaccination

Immunization with *H. influenzae* type b vaccines-HIB OC (3 doses IM at 2, 4, 6 months and a booster at 15 months) or PRP-OMP (2 doses IM at 2, 4 months and booster at 12 months) are routinely given in most developed countries with impressive decline in meningitis. However, *Haemophilus* conjugate vaccines are too costly for many developing countries. Annual mean number of cases of *H. influenzae* meningitis decreased from 10.7 to 3.8 following introduction of Hib vaccination in private health sector in India.<sup>56</sup>

Mass immunization with a quadrivalent meningococcal vaccine against serogroup A, C, Y and W135 has been used to control epidemics. Immunogenicity of quadrivalent vaccine is well established but it provides limited protection of short duration in young children in whom the risk of disease is greatest. The quadrivalent meningococcal vaccine is still given to high-risk children, e.g. those with asplenia (anatomic or functional) and to people travelling to areas with high endemicity and to control outbreaks. This vaccine is not approved for use in children younger than 2 years. Group B polysaccharide is poorly immunogenic and no efficacious vaccine is available for control of serogroup B outbreaks. Conjugate C meningococcal vaccine has been introduced in UK where the rate of meningococcal disease was estimated to be 2/100,000 and 40 percent of cases were due to serogroup C. It has been incorporated in the routine childhood immunization schedule with infants given 3 doses at 2, 3 and 4 months concurrently with DPT and *Haemophilus* vaccine.<sup>57,58</sup> Early recognition and treatment of meningococcal infection is the another way to reduce morbidity and deaths due to this disease. Preadmission treatment with benzylpenicillin reduces mortality in most patients with meningococcal disease and is recommended to be given in any one suspected to have meningococcal infection.<sup>59</sup>

An urgent need for vaccination against pneumococci is being felt because of increasing antibiotic resistance. The main problem with fight against pneumococci is the prevalence of 90 different serotypes, which vary across different geographic regions. This creates difficulty in vaccine production. Impressive results with use of pneumococcal 7 valent conjugate vaccine (PCV7) which contains common prevalent serotypes have been reported.<sup>60</sup> Subsequently PCV7 has been incorporated in immunization schedule of USA. Three doses of PCV7 are recommended to be given at 2,4 and 6 months of age and a fourth dose at 12-15 months.<sup>61</sup> Efficacy of this vaccine has not been proved in the older children; therefore the high risk group > 5 years should get 23 valent polysaccharide pneumococcal vaccine. The vaccine is licensed for use in a number of countries in Europe. Besides giving immunity to the individual patient, vaccination can interrupt the transmission of antibiotic resistant organisms belonging to the serotypes included in the vaccine and thus hold the promise of reducing the frequency of ABM caused by antibiotic resistant strains.<sup>62</sup>

Universal immunization with PCV7 is likely to bring down the incidence of invasive pneumococcal disease particularly meningitis. The implication of this strategy will be seen after a couple of years but definitely it will reduce the burden of ABM in some countries. Unfortunately this will not have much impact on the global burden of ABM, since the vast majority of children in the developing world will not be able to benefit from this strategy. The overall incidence of ABM will fall only if the cost of vaccination is brought down so that it can be given to children all over the world. In the meantime development of new and effective antimicrobial drugs against the ever increasing resistant pathogens is urgently needed.<sup>63</sup>

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Encephalitis is an inflammatory process that affects brain tissue. Encephalopathy implies cerebral dysfunction due to circulating toxins, poisons, abnormal metabolites or intrinsic biochemical disorders affecting neurons but without inflammatory response. Encephalitis is almost always accompanied by inflammation of the adjacent meninges, thus the term meningo-encephalitis. Both entities may be caused by a wide variety of agents.<sup>1</sup> Some of the causes are self-limiting, while others may rapidly lead to death or severe neurological damage.

Diagnosis of encephalitis with absolute certainty is only possible by microscopic examination of brain tissue. Practically, the diagnosis is made based on neurological manifestations, recovery of infectious agent, serologic evidence of infection and relevant epidemiological findings.

Acute encephalitis is more common in children (more than 16 cases per 100,000 patient years) than in adults (between 3.5 and 7.4 cases per 100,000 patient years). In the United States, about 1000-2000 cases of viral encephalitis are reported to the Center for Disease Control, Atlanta annually.<sup>2</sup> Its incidence in India is not known.

### ETIOLOGY

Common etiologic agents of acute encephalitis and acute meningoencephalitis are detailed in Table 24.1. Infectious causes of encephalitis in immunocompromised patients are also mentioned in Table 24.1. Although evidence of an infectious etiology is presumed in most cases, often no causative agent can be identified. Of 412 patients with encephalitis under 16 years of age (1968-1987), the chief causes included measles, mumps and rubella in 30.4 percent, herpes group in 24.1 percent, respiratory viruses (adenovirus, parainfluenza virus, respiratory syncytial virus and influenza A and B viruses) in 18.3 percent, enteroviruses in 9.7 percent, *Mycoplasma pneumoniae* in 13.1 percent, more than one virus in 2.9 percent, post-vaccination encephalitis (measles-mumps-rubella, polio) in 1.0 percent.<sup>3</sup> No agents were identified in 32 percent.

In India, Japanese B encephalitis (JE) is probably the commonest form of viral encephalitis and occurs in epidemics over large parts of the country. Rabies also poses a public health problem in this country. There is paucity of data from our country on the etiologic importance of other agents.

### EPIDEMIOLOGY

Several factors such as age, geographical location, season, climate and host immunocompetence affect the epidemiology of viral encephalitis. The incidence of encephalitis differs greatly in different countries and in different seasons of the year. This is due to the seasonal variation in the incidence of common viral infections such as enteroviruses and mumps, as well as the geographical restriction of arboviral infections influenced by the activity of their insect vectors. JE is transmitted in our country by female mosquitoes *Culex tritaeniorhynchus* and *Culex vishnui*. Herpes tends to occur worldwide with little seasonal variation.<sup>4</sup> Mumps, measles and rabies encephalitides have been eradicated from many developed countries.<sup>2</sup>

### PATHOGENESIS

Acute encephalitis may; be (i) primary—direct invasion and replication of the virus leading to tissue necrosis, e.g. encephalitis due to herpes simplex, arboviruses and rabies; (ii) parainfectious—a postinfectious inflammatory response characterized by immune mediated central nervous system (CNS) damage, demyelination with preservation of neurons and their axons. Clinical manifestations in such a type of injury are variable and recovery is likely. Distinction between primary infection and parainfectious is however, difficult.<sup>5</sup> The reactions of brain tissue to viral invasion are similar in all forms of encephalitis. Many viruses cause widespread inflammation, cerebral edema and necrosis. Some such as herpes and rabies have a predisposition to involve specific areas of the brain namely temporal lobes and basal structures, respectively.<sup>2,4</sup> Most neuronal

**Table 24.1: Common etiologic agents in acute encephalitis and acute meningoencephalitis**

<i>Viruses</i>	<i>Bacteria*</i>
<b>Spread person to person only</b>	<i>H. influenzae, N. meningitidis, S. pneumoniae, M. tuberculosis</i>
Herpes simplex 1 and 2+	<b>Spirochetes.</b> <i>Borrelia, Leptospira, Treponema pallidum</i>
Varicella zoster virus+	
Mumps virus	
Measles virus+	<b>Others</b>
Variola	<i>Chlamydia</i>
Epstein-Barr virus	<i>Rickettsia</i>
Cytomegalovirus	
Influenza virus	<i>Mycoplasma</i>
Enteroviruses+	
Rubella virus+	
Rotavirus	<b>Fungi</b>
Adenovirus	<i>Cryptococcus neoformans+</i> , <i>Coccidioidomycosis+</i> , <i>Blastomycosis+</i> ,
Human herpesvirus 6+	<i>Histoplasmosis+</i> , <i>Aspergillus+</i> , <i>Candida+</i>
<b>Spread to people by mosquitoes or ticks</b>	
Japanese B encephalitis virus	<b>Protozoal</b>
Kyasanur forest disease	<i>Plasmodium falciparum</i> , <i>Trypanosomes</i> ,
Dengue virus	<i>Naegleria+</i> , <i>Acanthamoeba+</i> ,
West Nile virus	<i>Toxoplasma+</i>
Equine encephalitis viruses	<b>Helminths</b>
St Louis encephalitis virus	<i>Schistosoma</i>
<b>Spread by warm blooded mammals</b>	
Rabies	
Lymphocytic choriomeningitis virus	
Others	
Human immunodeficiency virus	
Slow virus infections, prion diseases	

\*Often have an encephalitic component

+Infectious causes of encephalitis in immunocompromised patients; JC (polyoma) virus produces progressive multifocal leukoencephalopathy in patients with HIV infection.

destruction is probably due to direct viral invasion, whereas the hosts tissue response induces demyelination and vascular and perivascular destruction.

### Clinical Features

The clinical findings in encephalitis are determined by: (i) The severity of involvement and anatomic localization of the affected portions of the nervous system; (ii) The inherent pathogenecity of the offending agent; (iii) The immune and other reactive mechanisms of the patient. A wide variety of clinical manifestations may occur ranging from inapparent, mild abortive type of illness, or aseptic meningitis syndrome to severe encephalomyelitis with or without radiculitis.

The onset of encephalitis usually is acute, but signs and symptoms of CNS involvement often are preceded by a non-specific, acute febrile illness. Presenting symptoms in older children are headache and malaise; infants typically are irritable and lethargic. Fever, nausea,

vomiting, neck pain, and photophobia are common. Alteration of level of consciousness ranges from mild lethargy and confusion to coma. Evidence of brain parenchymal involvement is the hallmark of encephalitis.<sup>1</sup> Children with encephalitis may demonstrate evidence of diffuse disease such as behavioral or personality changes; decreased consciousness; and generalized seizures or localized changes, such as focal seizures, hemiparesis, movement disorders, cranial nerve deficits and ataxia.<sup>6</sup> The most common cause of focal encephalopathic findings is *Herpes simplex* virus. Nuchal rigidity is often not as pronounced as in purely meningitic illness. Neurological abnormalities may be stationary, progressive or fluctuating. Unprovoked emotional bursts and loss of bowel and bladder control may occur.

Sudden severe rise of intracranial pressure may result in decerebration, cardiorespiratory insufficiency, hyperventilation and autonomic dysfunction. Uncontrolled cerebral edema may lead to herniation at

tentorial hiatus, compression of the midbrain causing deterioration in consciousness, pupillary abnormalities, ptosis, sixth nerve palsy, ophthalmoplegia, paralysis of upward gaze, Cheyne-Stoke breathing, hyperventilation and bradycardia. Herniation of cerebellum through the foramen magnum causes distortion and compression of the medulla oblongata with severe disturbances of vital centers leading to respiratory or cardiac arrest. The course of encephalitis varies from that of the fulminating type, ending in death in 2 to 4 days, to that of a mild form in which the illness subsides in 1 or 2 weeks with complete recovery. Typically this stage lasts for 7-10 days after which there is gradual recovery with or without sequelae.

There is tropism of a variety of viruses for different CNS cell types (e.g. polioviruses for motor neurons; rabies virus for neurons of the limbic system; mumps virus for ependymal cells of newborn). Demyelination follows the destruction of oligodendroglia, whereas the involvement of ependymal cells can result in hydranencephaly. Certain specific clinical features of viral encephalitis are shown in Table 24.2.

## Diagnosis

The diagnosis of viral encephalitis is usually made on the clinical presentation of a nonspecific prodrome

**Table 24.2: Clinical features of viral encephalitis**

Agent	Typical findings/history
Enterovirus	Herpangina, myocarditis, pleurodynia, rhombencephalitis*
<i>Herpes simplex</i> type I	Symptoms due to focal necrosis of orbital or temporal regions <sup>#</sup> , focal neurological symptoms
Japanese B encephalitis	Extrapyramidal signs, respiratory difficulties, vasomotor instability
<i>Varicella zoster</i>	Characteristic rash, cerebellar ataxia, hemiparesis
Rabies	History of animal bite, autonomic dysfunction, hydrophobia
Mumps	Parotitis
Lymphocytic choriomeningitis virus	History of exposure to rodents
Adenovirus	Acute respiratory disease, conjunctivitis, keratoconjunctivitis
Influenza	Acute respiratory disease, opisthotonus, ataxia, transverse myelopathy
Epstein-Barr virus	Encephalomyelitis, meningoencephalitis

\*Myoclonic jerks, ataxia, brainstem signs

<sup>#</sup>Anosmia, aphasia temporal lobe seizures, memory loss, disordered behavior, olfactory or gustatory hallucinations

followed by progressive CNS symptoms. The immediate goals are to identify focal features that may imply herpes simplex encephalitis (HSE) and to detect other disorders that may mimic encephalitis.<sup>2</sup> History is taken for prior viral infections, exanthem (e.g. echovirus, coxsackievirus, *Varicella zoster* virus, measles, rubella) or recent vaccination. History of a bite from a potentially rabid animal, travel history, exposure to mosquitoes, rodents and ticks, the season in which illness occurs, and the diseases prevalent in the community may provide clues to the diagnosis.

Patients with fever and altered neurological function require a prompt neurodiagnostic evaluation that typically includes an electroencephalogram (EEG), a neuroimaging study computed tomography (CT) or magnetic resonance imaging (MRI), and a lumbar puncture. Patients with suspected viral encephalitis require a detailed microbiological evaluation. In the acute stage, blood counts usually show a polymorphonuclear leukocytosis.

Positive identification of viral infection in the CNS helps to curtail investigations, rationalize treatment, and improve the reliability of prognosis. Though the identification of etiology is difficult, a rational use of various diagnostic studies may result in etiological diagnosis in approximately 60 percent patients.<sup>6</sup>

## Cerebrospinal Fluid

The CSF pressure is normal or slightly elevated. There is usually lymphocytic pleocytosis (5-500 cells/mm<sup>3</sup>); rarely more than 1,000 cells/mm<sup>3</sup> may be seen in conditions like eastern equine encephalitis and lymphocytic choriomeningitis. Early in the disease, the cells might be polymorphonuclear; later mononuclear cells predominate. This change in cellular type is often demonstrated in CSF samples obtained as little as 8-12 hours apart. However, CSF pleocytosis is found in only half of patients with clinically suspected encephalitis.<sup>7</sup> Some patients with HSE may show a xanthochromic or bloody CSF, usually with less than 500 red blood cells/mm<sup>3</sup>.

The protein content is mildly elevated (50-200 mg/dl). The concentration of proteins may be high in some patients with HSE and extensive brain destruction. The CSF glucose content is normal or slightly decreased. Neonates with HSE tend to have mild hypoglycorrhachia. A small proportion of patients with mumps encephalitis may have CSF sugar lower than 40 mg/dl.

## Microbiological Evaluation

The CSF should be cultured for viruses, bacteria, fungi and mycobacteria; in some instances when suspected,

special examinations are indicated for protozoa, mycoplasma and other pathogens.

Various laboratory methods involved in diagnosing viral infections of the CNS include isolation of virus, detection of viral antigen or its nucleic acids and serology. Workup includes viral culture of respiratory secretions, throat swab, CSF, blood, urine, stool, swab from skin rash and brain tissue taken as early as possible in the illness.<sup>7</sup> Appropriate transport media should be used. These specimens should, if possible, be taken within four days of the onset of the illness and sent quickly to the laboratory on ice, but should not be frozen. Detection of viral antigen can be done in brain tissue or CSF (leukocytes or soluble antigen). Detection of antibodies in CSF and the CSF to blood ratio of specific IgG can be helpful in diagnosing HSV infection. Single serum IgM value or paired sera (acute and convalescent phase) to show rising titers of IgG are also useful. Polymerase chain reaction to detect viral nucleic acids in CSF is promising and is likely to provide a rapid, accurate diagnosis in future.

Measurement of interferon  $\alpha$  in CSF provides evidence of active viral infection in the CNS but this test is not widely available. IgG index, which is derived by calculating the ratios of IgG and albumin in CSF and serum is another indicator of intrathecal synthesis of antibodies. A raised IgG index and the presence of oligoclonal bands in CSF suggest intrathecal synthesis of IgG.<sup>7</sup> Various virologic and serologic tests are detailed in Table 24.3.

### Electroencephalogram (EEG)

EEG may be useful in patients with (i) Markedly altered neurological function, where EEG helps in detecting seizures and monitoring the efficacy of anticonvulsant therapy; (ii) Suspected HSV infection where characteristic periodic sharp waves repeating every 0.5 to 4 seconds are found. Such EEG abnormalities may be diffuse or temporofrontal, unilateral or bilateral, and are always accompanied by diffuse or temporally accentuated excess delta activity.<sup>8</sup>

### Neuroimaging

It can help to separate viral encephalitis from metabolic or toxic disorders and acute disseminated encephalomyelitis (ADEM). Early viral encephalitis is characterized by low density lesions on CT, and prolonged T1 and T2 relaxation times on MRI. MRI appears to be significantly more sensitive.<sup>9</sup>



**Fig. 24.1:** Axial MRI on T2-weighted sequence through midbrain showing bilaterally symmetrical hyperintensity signals in midbrain typically sparing substantia nigra and red nucleus (Panda's eye sign) in a child with Japanese B encephalitis

### Japanese B Encephalitis

In JE, CT shows non-enhancing low-density areas in the thalamus, basal ganglia, midbrain, pons and medulla. MRI show extensive involvement of the thalamus, midbrain, cerebrum and cerebellum (Fig. 24.1). Classically, the lesions are hyperintense on T2-weighted images and hypointense on T1-weighted images. In 70 percent patients they are hemorrhagic. Bilateral hemorrhagic thalamic involvement is characteristic of JE in endemic areas.<sup>10</sup>

### Herpes Simplex Encephalitis

CT abnormalities are usually not found before the fifth day of illness. MRI and single photon emission CT (SPECT) studies are more sensitive early in the course of the disease. MRI with greater spatial resolution than SPECT is the modality of choice. The characteristic CT findings in HSE are poorly defined areas of low density in the anteromedial portion of the temporal lobe with extension to the insular cortex but sparing of the lentiform nucleus. A gyral pattern of contrast enhancement is frequently seen. MRI shows prolonged T1 and T2 relaxation times in the medial temporal lobe, the insular cortex, and the orbital surface of the frontal lobe, particularly the cingulate gyrus (Figs 24.2 and 24.3).<sup>11</sup>

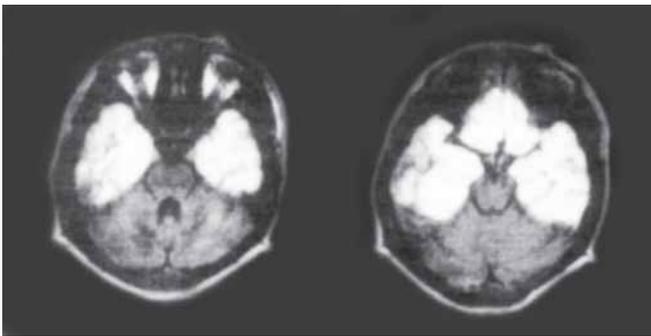
### Acute Disseminated Encephalomyelitis (ADEM)

CT and MRI show moderate to large areas of demyelination, characterized by low density lesions on

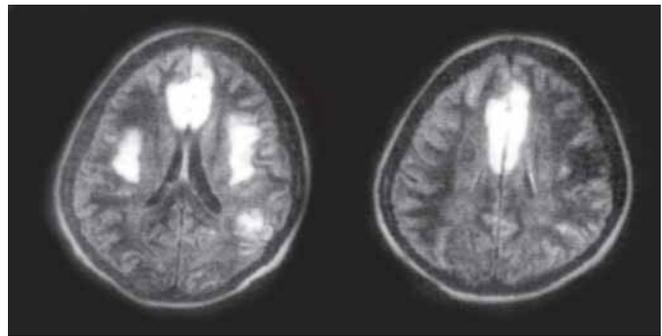
**Table 24.3: Virologic and serologic studies in viral encephalitis**

Agent	Virologic studies	Serologic studies
HSV	Culture- CSF, brain biopsy; Antigen detection-brain biopsy (IFA)*; PCR-CSF (method of choice)	Acute, convalescent sera; CSF antibody detection (less useful); CSF: serum antibody ratio
Arboviruses	Culture-CSF, brain; Antigen detection-brain, CSF (IFA)	IgM (isotype antibody capture immunoassay)# CSF, serum (very useful); Acute, convalescent sera-IgG
Cytomegalovirus	Culture-CSF, brain; PCR-CSF	Acute, convalescent sera (little diagnostic value)
Epstein-Barr virus	Rarely cultured; PCR-CSF	Acute sera for antibody profile (serology most useful)
Varicella zoster virus	Culture-skin vesicles, CFS; DFA**"-skin, brain; PCR-CSF	Acute, convalescent sera; Antibody in CSF (IgA, IgG)
Rabies	Fluorescence microscopy or culture- corneal smear, skin biopsy, muscle biopsy (nape of neck), saliva, CSF; Antigen detection/culture-brain	Serology (possible); CSF antibody detection
Adenovirus	Culture-CSF, brain, urine, nasal or conjunctival swab	Acute, convalescent sera-IgG
Enteroviruses	Culture-stool, CSF, urine, blood, brain biopsy; PCR-CSF	Acute, convalescent sera (not useful)
Influenza	Culture-respiratory secretions	Acute, convalescent sera-HAI* antibody
Paramyxoviruses	Culture-CSF;PCR-CSF	Acute, convalescent sera; elevated CSF globulin
Rubella		Serology-IgM
Human immunodeficiency virus	Culture/PCR-CSF, brain biopsy;p24 antigen-blood	Serology-ELISA, western blot (>18 months age)
Lymphocytic Choriomeningitis virus	Culture-CSF, blood, urine, pharyngeal secretions; RT-PCR <sup>o</sup> -CSF	Serology; IgM CSF

\*IFA indirect immunofluorescent antibody; #Also known as MAC-ELISA (enzyme-linked immunosorbent assay) or IgM capture test; \*\*DFA Direct fluorescent antibody; •HAI Hemagglutination inhibition; <sup>o</sup>RT-PCR reverse transcriptase PCR



**Fig. 24.2:** Axial FLAIR MRI sequence showing bilaterally symmetrical hyperintensity signals in basifrontal and temporal lobes characteristic of herpes simplex encephalitis



**Fig. 24.3:** Axial FLAIR MRI sequence (at a level higher than Fig. 24.2) showing extension of signal abnormalities in bilateral medial frontal lobes and insular cortex, which are pathognomonic of herpes simplex encephalitis

CT and prolonged T1 and T2 relaxation times on MRI. The MRI findings in this condition are more extensive, appear to be of the same age, are frequently bilateral and reveal abnormalities of the deep cerebral nuclei in 50 percent children.<sup>12</sup> The white matter lesions are asymmetrical and predominantly involve subcortical areas.

### Differential Diagnosis

Viral encephalitis should be considered in a patient with acute onset of fever and altered consciousness. A wide range of CNS disorders would need careful exclusion. The sequence of tests are dictated by the clinical features. A wide differential diagnosis is illustrated in a case series, in which 50 percent patients with presumed viral encephalitis were found to have other disorders.<sup>13</sup>

In India, viral encephalitis should be distinguished from other CNS infections such as bacterial or tuberculous meningitis, cerebral malaria, encephalitis or meningoencephalitis due to *Leptospira spp.*, *Mycoplasma pneumoniae* or *Acanthamoeba* and brain abscess. Patients with bacterial infection of the CNS usually appear more acutely ill than those with viral infection. However, meningitis caused by *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b may be insidious in onset. CNS infection caused by less virulent bacteria, such as *Mycobacterium tuberculosis*, *Treponema pallidum* may also be clinically indolent. If CSF shows pleocytosis, acute bacterial meningitis should be carefully excluded. If CSF is normal, then disorders like cerebral malaria, Reye syndrome and enteric encephalopathy need to be differentiated. Clinical findings distinguish patients with encephalitis from viral meningitis; the latter usually have nuchal rigidity, headache, photophobia, irritability, fever and the sensorial loss is usually not severe.<sup>4</sup> Cerebral venous thrombosis, electrolyte and metabolic encephalopathies, drug ingestion, post-infectious disease including Guillain-Barré syndrome and acute cerebellar ataxia, brain tumors, and cerebral vascular disorders should be excluded.

#### Acute Disseminated Encephalomyelitis (ADEM)

A distinction should be made between acute viral encephalitis and ADEM or postinfectious encephalomyelitis, since the outcomes are quite different.<sup>12</sup> ADEM involves autoimmune responses that are directed, at least in part, against myelin antigens. Before widespread vaccination, postinfectious encephalomyelitis most commonly occurred after smallpox and measles

infections. In recent years, the disease has been associated with various viral and bacterial infections. Patients may have a history of an exanthem or a non-specific respiratory or gastrointestinal illness 1 to 3 weeks before onset of neurological symptoms. Neurologic findings vary and reflect the areas of the brain involved. The clinical features include multifocal neurological signs, lethargy, coma and seizures, which often implicate widespread areas of the brain, spinal cord, and optic nerves.<sup>12</sup> Acute cerebellar ataxia is a form of acute postinfectious encephalomyelitis following varicella infection.

CSF pressure may be slightly elevated and white cells are mild to moderately increased to 15 to 250 cells/mm<sup>3</sup> with lymphocytes predominating. CSF protein is normal or slightly elevated (35 to 150 mg/dl) and glucose levels are normal. Oligoclonal bands are usually negative and Myelin basic protein level is usually increased in the CSF. EEG is abnormal in most cases, with high voltage slow frequency waves. The EEG abnormalities may persist for several weeks after apparent clinical recovery. Neuroimaging findings have been described above.

### Treatment

Until a bacterial cause is excluded by culture of blood and CSF, parenteral antibiotic therapy should be given. Patients with presumed virus encephalitis require treatment strategies that are tailored to the severity of the illness and the availability of specific antiviral therapy. Such patients require frequent assessment of their level of consciousness and anticipatory care for the potential complications of encephalitis like seizures, increased intracranial pressure, hyperpyrexia, inadequate respiratory exchange, disturbed fluid and electrolyte balance, aspiration and asphyxia, and cardiac or respiratory arrest of central origin.

The three immediate steps are to give intravenous acyclovir promptly if focal features suggest HSE, to search for other treatable causes of an acute encephalopathy and to protect the child's brain against further insult.

### Principles of Treatment

The main objectives of treatment of a child with viral encephalitis are to reduce intracranial pressure (ICP), to optimize systemic arterial pressure to maintain adequate cerebral perfusion pressure and prevention of secondary complications. Increased ICP contributes greatly to the morbidity and mortality. Dangerous elevations in ICP are manifested by rapid deterioration

in clinical status as detailed earlier and by radiographic changes such as obliteration of the lateral ventricles or basal cisterns on CT. The most important step is early identification. Most therapeutic measures fail if they are instituted late, as irreversible cerebral damage has already occurred. The control of raised ICP involves:

- (i) Avoiding situations that increase the ICP; and
- (ii) Therapeutic measures to decrease ICP.

In patients with evidence of increased ICP, placement of a pressure transducer in the epidural space may be indicated for monitoring of ICP. Although the ICP can be monitored from the ventricle, brain parenchyma, subarachnoid space, subdural space and epidural space, it is important to realize that the pressure is not equal throughout the intracranial space.

### Control of Factors Aggravating Intracranial Pressure

*Positioning and general care of patient:* A 15°-30° head up tilt with head kept in the midline position facilitates venous return from the head, decreases ICP and improves cerebral perfusion pressure.<sup>14</sup> Hyperflexion, hyperextension or turning the neck which can elevate ICP, as can inordinately tight tracheostomy ties, should be avoided. Increase in ICP with suctioning can be minimized with gentle suctioning and intravenous lidocaine. Elevations in ICP from indirect transmission of elevated intrathoracic pressure to the intracranial vessels can be avoided by sedation and decreasing the inspiratory phase of the respirator.

*Temperature control:* Aggressive treatment of fever is essential as increased temperature increases ICP by increasing cerebral metabolism, cerebral blood flow and cerebral edema. Temperature control may be accomplished with cooling mattresses and the administration of paracetamol.

*Role of sedation:* Pain and arousal cause elevated ICP by increasing cerebral blood flow. Sedatives play an important role in the prevention of worsening of ICP by this mechanism. Conventionally, sedatives were avoided (except for seizure control), due to the fear of clouding the neurological examination. Midazolam may be tried initially as a first step. Inadequate sedation in the ventilated patient is clearly detrimental. The ideal sedative should have a rapid and smooth onset, decrease ICP, preserve autoregulation and vasoreactivity to carbon dioxide and allow easy titration of effect during neurological assessment. Propofol causes a decrease in cerebral blood flow and ICP, and maintains a degree of autoregulation. Barbiturates are no longer

used as long-term sedatives because of their prolonged effects.

*Seizures control:* Normal blood levels of glucose, magnesium and calcium should be maintained to minimize the threat of seizures. Seizures increase ICP by increasing cerebral metabolism and cerebral blood flow. Midazolam or diazepam is effective for emergency use. Phenytoin, which does not have the depressant effects of barbiturates, should be considered for acute treatment. Management of seizures is discussed elsewhere.

### Fluid and Electrolyte Management

The patient should be kept nil orally for first 24 hours. Thereafter the decision to start oral feeds depends upon the sensorium. The patient should receive intravenous fluids as N/5 in 5 percent dextrose in normal maintenance requirements, except in shock when a fluid bolus with normal saline or Ringer's lactate is required. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is quite common in acute CNS disorders. If there is clinical or laboratory evidence that the patient is suffering from SIADH, two-thirds of maintenance fluids are started and symptomatic management for hyponatremia instituted. Full maintenance requirements of sodium should be given as hyponatremia impairs cerebrovascular reactivity. There may be cerebral salt wasting with a combination of hypovolemia, hyponatremia, excessive renal sodium losses and marked elevation of plasma atrial natriuretic hormone. Treatment includes volume-for-volume replacement of urinary sodium losses and oral sodium supplementation after discharge from the hospital to correct and maintain normal fluid balance.

### Measures to Decrease Intracranial Pressure

*Hyperventilation:* Hyperventilation after endotracheal intubation with maintenance of PaCO<sub>2</sub> between 25-30 mm Hg effectively reduces ICP by causing cerebral vasoconstriction. The drop in ICP occurs within 1 to 5 minutes of initiation of hyperventilation. ICP can be satisfactorily controlled in two-thirds of patients using a combination of a hyperosmolar agent and hyperventilation. Hyperventilation should not be prolonged beyond 1-2 days, following which it is gradually discontinued. Failure to reduce ICP with hyperventilation is a grave prognostic sign.

The potential deleterious effects of hyperventilation include an elevation of mean airway pressure and diminished cardiac filling pressures, resulting in

barotrauma and hypotension. Although hyperventilation is useful in acutely decreasing ICP, prolonged hyperventilation, in fact, worsens the outcome. Chronic aggressive hyperventilation might result in areas of oligemia in marginally perfused brain tissue.

### Mannitol

Mannitol is the most commonly used agent for control of raised ICP. Mannitol acts by two different mechanisms. While vascular mechanism is the explanation for the rapid (acute) effect of mannitol, diuresis explains the more prolonged effect of mannitol. On intravenous administration, it leads to an abrupt increase in intravascular osmolality relative to the brain compartment. This osmotic gradient facilitates a fluid shift from the brain into the vascular space. The dose is 0.25 to 1.0 g/kg body weight every 4 to 6 hours, or 20 percent mannitol 5 ml/kg over 5-10 minutes followed by 3 ml/kg 6 hourly till 48 hours, beyond which mannitol loses its efficacy. The onset of action is within 1-5 minutes and duration 2-3 hours. Complications include dehydration and electrolyte imbalance especially hyponatremia.

### Other Medications

Acetazolamide in dose of 20-50 mg/kg/day in 3 to 4 doses, oral glycerol 1 ml/kg/dose 8 hourly may be used if ICP is elevated beyond 48 hours. Furosemide can be given in a dose of 1 mg/kg intravenously every 12 hours. It may be added if response to mannitol is poor. Furosemide has a synergistic effect with mannitol in terms of reducing the ICP by virtue of decreasing free water. Barbiturates, e.g. pentobarbital and thiopentone reduce cerebral metabolism which leads to reduction in cerebral blood flow and intracranial volume and the ICP. Barbiturates are generally used only when standard therapy consisting of osmotic agents, hyperventilation and head position has failed to control the ICP. They should be used only in intensive care setting. Complications include hypotension in 50 percent, pneumonia and hyponatremia. The use of corticosteroids to reduce ICP or decrease toxic effects of inflammatory cytokines is controversial. They probably should not be used in acute viral diseases because of risk of potentiation of the viral infection.

*CSF removal by an external ventricular drain:* It has a therapeutic potential by allowing CSF removal once the ICP has reached dangerous levels.<sup>15</sup> After all medical measures for ICP control have been exhausted and barbiturate coma therapy is being considered, CSF removal may produce dramatic reduction in ICP. It

may also provide temporary relief for elevated ICP in patients with acute hydrocephalus.

### Supportive Management

*Maintenance of cerebral perfusion:* It is essential to prevent secondary cerebral ischemia. In conditions where cerebral autoregulation is impaired, cerebral perfusion depends exclusively on the cerebral perfusion pressure. The normal cerebral perfusion pressure in infants is in the range of 30 mm Hg. Hence, it is important that the cerebral perfusion pressure should be maintained above 30 mm Hg in infants less than 6 months age, above 40 mm Hg in older children and above 60 mm Hg in adolescents. Considering the fact that the clinical signs appear when ICP is usually above 15-20 mm Hg, it is imperative to maintain a mean arterial pressure above 75 mm Hg in mild and moderate grade coma and more than 85 mm Hg in severe grade coma.

*Feeding:* Feeding should be started once the sensorium improves.

*Monitoring:* The patient should be managed in an intensive care unit. The aim is to evaluate cardio-respiratory stability and detect acute life-threatening neurological complications at the earliest. Vitals including temperature, pulse, respiratory rate, blood pressure, neurological status, head size, body weight and urine output are recorded carefully.

### Antiviral Therapy

Despite intensive clinical and laboratory investigations, relatively few viruses can be treated with specific antiviral chemotherapy (Table 24.4). Specific therapy is recommended in encephalitis due to herpes group of viruses.

### Herpes Simplex Encephalitis

In some centers in the west, acyclovir treatment is started as soon as viral encephalitis is suspected even without evidence of localization. We recommend that specific therapy for HSE should be given early, if the diagnosis is suspected, e.g. in patients with localizing clinical signs, focal EEG changes, neuroimaging showing focal involvement of temporal lobes, or CSF examination showing red cells. Early therapy is mandatory, even before virological confirmation is obtained. Patients with suspected or confirmed HSE should receive acyclovir as detailed in Table 24.4. Because HSV- induced thymidine kinases effectively phosphorylate the drug to its more active form, acyclovir which has a relatively specific action on virus-infected cells and few side effects. Relapse after

**Table 24.4: Antiviral chemotherapy for viral encephalitis**

Virus	Drug	Dose	Toxicity
HSV	Acyclovir	10 mg/kg (500 mg/m <sup>2</sup> of body surface area for children < 12 years) every 8 hours intravenously for 14 to 21 days+	Local-bullous inflammatory reaction, nephrotoxicity (renal tubular crystalluria with elevation of serum creatine), leukopenia, tremor, confusion, rarely, seizures, encephalopathy
Varicella zoster virus	Acyclovir	10 to 15 mg/kg (500 mg/m <sup>2</sup> ) every 8 hours intravenously for 7-10 days	As above
Cytomegalovirus	Ganciclovir	7.5 mg/kg/day in 3 divided doses* for 14 to 20 days	Myelosuppression, nausea, vomiting, CNS irritability, liver dysfunction
Influenza <sup>18</sup>	Amantadine	100 mg twice daily orally (<40 kg, 1-10 years: 5 mg/kg/d orally in 2 divided doses; maximum 150 mg/d) for 5 to 7 days	Depression, congestive heart failure, vomiting, CNS irritability, confusion
	Rimantadine	<14 years not recommended, ≥14 years 100 mg orally twice daily	

+ In the form of a 20 mg/ml solution, administered over an hour. A higher dose, such as 15 mg/kg every 8 hours, or a longer duration of therapy may occasionally be required.<sup>4</sup>

\*Alternative regimens using ganciclovir and CMV immune globulin have been proposed : Ganciclovir (7.5 mg/kg/24 hr I/V in three divided doses for 14 days) and CMV immune globulin 400 mg/kg on days 1,2,7 and 200 mg/kg on day 14 or Ganciclovir (7.5 mg/kg/24hr I/V in three divided doses for 20 days) and CMV immune globulin 500 mg/kg every other day for 10 doses.<sup>17</sup>

acyclovir therapy has been described in a small proportion of cases. Strains of HSV resistant to acyclovir have been isolated from immunocompromised patients who have received several courses of the drug. Should acyclovir therapy fail to arrest the disease, a trial of intravenous foscarnet is recommended at a dosage of 60 mg/kg every 8 hours intravenously for 14 days.<sup>16</sup>

#### *Varicella Zoster Encephalitis*

Although controlled studies have not been conducted, current data indicates that acyclovir can be used in dose regimens similar to those for HSE.<sup>16</sup>

#### *Japanese B Encephalitis*

No effective treatment exists for JE. Treatment with oral or parenteral corticosteroids is not indicated. Interferon  $\alpha$  has been used in a small number of patients and larger trials are awaited.<sup>19</sup>

#### *Therapy for ADEM*

Many agents have been used, including corticosteroids, adrenocorticotropic hormone, intravenous immunoglobulin (IVIG) and cyclosporine. Most patients respond

to corticosteroid treatment. The clinical response is observed within hours of initiation of treatment with intravenous corticosteroids (15-20 mg/kg methylprednisolone or 5 mg/kg dexamethasone for 7 days). There are however, no clear guidelines regarding the appropriate steroid dosage and length of therapy. Corticosteroid dependency may occur during tapering necessitating a slower taper. In cases resistant to high doses of corticosteroids, IVIG or cyclosporine may be used. Patients in coma from ADEM have been successfully treated with plasma exchange or plasmapheresis.

#### **Outcome and Prognosis**

The prognosis in all encephalitides is guarded with respect to immediate outcome and sequelae. Sequelae involving the CNS include intellectual, motor, psychiatric, epileptic, visual or auditory.

Clinical features are helpful in predicting the outcome. Young age, lower Glasgow coma score, abnormal oculocephalic responses, focal neurological signs, reduction in cerebral perfusion pressure (difference between systolic blood pressure and ICP), abnormal neuroimaging study and unilateral hyperperfusion on SPECT suggest a poor prognosis.<sup>6,7,20</sup>

Case fatality rate of 34 percent was reported among 338 children under 3 years of age with acute encephalopathies in a study by Madge *et al* which was similar whether or not encephalitis was diagnosed.<sup>21</sup> At 10 years follow-up, almost half the survivors had motor dysfunction and educational problems, one-third had neurological dysfunction and one-fifth had behavioral abnormalities.<sup>21</sup> In a study of 462 children under 17 years of age the mortality and serious morbidity of encephalitis were 2.8 percent and 6.7 percent, respectively. An increased risk of adverse outcomes was observed after *Mycoplasma pneumoniae* encephalitis and HSE.<sup>6</sup>

Mortality rate has been reported between 10 to 50 percent. High mortality has been reported in some recent outbreaks of encephalitis.<sup>22</sup> Major sequelae including mental retardation, neurological deficits and/or epilepsy have been reported in 45 percent and minor motor deficits, behavioral problems and/or scholastic backwardness in 25 percent.<sup>23</sup>

Overall the prognosis is good in ADEM with early diagnosis and appropriate treatment. In 90 percent of survivors there is complete recovery. The exception is measles, in which sequelae may occur in 20 to 50 percent of patients.

Supportive and rehabilitative efforts are important after patients recover. Motor incoordination, seizure disorders, deafness, visual and behavioral disturbances may appear only after an interval of time. Neuro-developmental and audiologic evaluation should be a part of routine follow-up of such children.

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Diarrheal diseases continue to be one of the major public health problems world over. Oral rehydration therapy (ORT), one of the greatest scientific achievements in the last century, has revolutionized management of diarrheal dehydration and led to a significant reduction of diarrhea related mortality from 5 million deaths in 1978 to 1.4 millions deaths annually.<sup>1</sup> However, diarrheal diseases still contribute 13 percent of under five deaths.<sup>2</sup> In India, prevalence of diarrheal episodes in children less than 3 years continues to be as high as 12.7 percent.<sup>3</sup> Frequent episodes of diarrhea in young children and high mortality related to these episodes accord a high priority to diarrhea case management in the Integrated Management of Childhood Illness (IMCI) strategy.<sup>4</sup>

Dehydration, the immediate consequence of diarrheal diseases, remains the primary focus in case management. Dehydration is a frequent and a serious consequence of acute watery diarrhea (acute episode of diarrhea lasting < 2 weeks) including cholera, but some cases of dysentery (clinical syndrome characterized by the presence of blood and mucus in the stools, abdominal cramps and fever)<sup>5</sup> and persistent diarrhea (an episode that lasts for 14 or more days, a proportion of these episodes are associated with growth failure)<sup>5</sup> may also present with variable degree of dehydration. Prolonged and recurrent episodes of diarrhea adversely affect the nutritional status of a child and thereby significantly contribute to vicious cycle of malnutrition and infection.<sup>6</sup>

### DIARRHEAL DEHYDRATION

Young children are more susceptible to develop dehydration due to limited urinary concentration capacity of the kidneys, more insensible losses of water through skin and lungs owing to large surface area and rapid breathing, and their dependence on adults to replace their fluid losses. Loss of water and electrolytes in the diarrheal stool results in depletion of the extracellular fluid volume (ECFV), electrolyte imbalance and clinical manifestation of dehydration. Even though

intracellular and extracellular fluid compartments are equally depleted in diarrhea, the measurement of ECFV show mostly a depletion of this compartment.<sup>7</sup> The reason is that ECFV contracts in “two directions”- out in the stools and into the cell, so that the net measured loss of volume appears to come chiefly from the ECFV. Continued ECFV contraction is at the root of all the physiological changes taking place in dehydration<sup>8</sup> and reversion to normal is more readily accomplished by solutions more nearly approximating that of the extracellular fluid.

In the past, higher mortality which was reported soon after admission, was mostly due to uncorrected volume depletion or electrolyte imbalance.<sup>9</sup> These observations highlight the importance of the “first day” in the fluid therapy of severe dehydration and the need for prompt replacement of losses particularly in severe secretory diarrhea like cholera which results in rapidly progressing dehydration, metabolic acidosis and other electrolyte imbalances. The first symptom of dehydration appears after fluid loss of about 5 percent of body weight. When fluid loss reaches 10 percent, shock often sets in and the cascade of events that follows can culminate in death unless there is immediate intervention. Without treatment, severe episodes literally wring out body fluids from the victim faster than they can be replaced. Rehydration, whether given orally or intravenously, is the only effective therapy.

### COMPENSATORY MECHANISMS

Contraction of the ECFV consequent upon loss of water and electrolytes in diarrheal stools, leads to increase in renin, angiotensin, aldosterone and antidiuretic hormone (ADH), and fall of GFR. All these changes lead to compensatory retention of salt and water but proportionately more of the latter. The first response to ECFV contraction is thirst and if water is administered, it will be mostly retained due to the effect of ADH. In addition, water may also be generated internally by steroids and catecholamines. Therefore, retention of water by these mechanisms results in

isotonic or hypotonic dehydration. Pre-existing or uncorrected potassium deficiency can also perpetuate hypotonicity.<sup>10-12</sup>

Comparison of various intravenous regimens containing high or low sodium have shown that rational treatment should reverse all the compensatory events by restoring volume quickly, correcting acidosis and reducing potassium deficit with solutions approximating the composition of the extracellular fluid. The more hypotonic the fluid is with respect to sodium, the less well it can quickly correct the ECFV contraction.

### CLINICAL FEATURES

Most enteropathogens can cause diarrhea by more than one mechanism. Hence the clinical presentation depends upon the underlying pathophysiological changes taking place in the gastrointestinal tract. Three clinical types of diarrhea have been defined, each reflecting a different mechanism.

- i. *Secretory diarrhea*: It is characterized by acute watery diarrhea with profound losses of water and electrolytes due to sodium pump failure as a result of the action of identified toxins (e.g. cholera, ETEC). This group is at risk of rapid development of dehydration and electrolyte imbalance.
- ii. *Invasive diarrhea (Dysentery)*: Intestinal mucosal cells are actually invaded by the microorganisms which sets up an inflammatory reaction clinically presenting with blood and mucus in the stools (*Shigella*, *Salmonella*, enteroinvasive *Escherichia coli* (EIEC), *Campylobacter jejuni*, rotavirus, *E. histolytica*). This group is also prone to develop other complications like intestinal perforation, toxic megacolon, rectal prolapse, convulsions, septicemia and hemolytic uremic syndrome.
- iii. *Osmotic diarrhea*: Injury to enterocytes may result in brush border damage (*Giardia lamblia*, EPEC, *Y.*

*enterocolitica*) and destruction leading to decreased mucosal disaccharidase activity (*Y. enterocolitica*). Clinical presentation in these cases is characterized by passing of large, frothy, explosive and acidic stools. High osmolar solutions given orally (e.g., carbonated soft drinks and ORS with high sugar content) can also result in osmotic diarrhea. Besides worsening in the hydration status of the child there is also a serious danger of developing hypernatremia in these cases.

### CASE MANAGEMENT

In order to institute an appropriate treatment plan, a patient with acute diarrhea should be assessed to determine:

- Nature and pattern of diarrhea
- General assessment of the child
- Assessment of hydration status. A number of clinical signs and symptoms can help in detecting dehydration. However, a simple assessment chart can be referred for quick assessment of dehydration (Table 25.1) and administration of appropriate fluids for prevention and treatment of dehydration
- Correction of electrolyte and acid-base imbalance
- Proper feeding to provide normal nutritional requirements
- Zinc supplementation
- Treatment of associated problems like dysentery, nutritional rehabilitation
- Health education for prevention of diarrhea.

### ASSESSMENT OF DEHYDRATION

Loss of water electrolytes in the stools can produce varying degree of dehydration. Thirst and irritability are the earliest symptoms which appear by the time an infant has already lost almost 4-5 percent of body

**Table 25.1: Assessment of dehydration in a patient with diarrhea<sup>4,5</sup>**

Clinical Signs			
General condition	Well, alert	Restless, irritable	Lethargic or unconscious
Eyes	Normal	Sunken	Sunken
Thirst	Drinks normally, not thirsty	Drinks eagerly, thirsty	Drinks poorly, not able to drink
Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly
<b>Decide hydration status</b>	The patient has <i>No signs of Dehydration</i>	If the patient has two or more signs, there is <i>Some Dehydration</i>	If the patient has two or more signs, there is <i>Severe Dehydration</i>
<b>Treatment plan</b>	Plan A	Plan B	Plan C

weight. Extreme degree of dehydration presents with alteration in consciousness, shock, acidosis and renal failure. A number of clinical signs and symptoms can help in detecting dehydration. However, a simple assessment chart, developed by World Health Organization as a part of IMCI strategy<sup>4</sup> and adapted by its Indian version named Integrated Management of Neonatal and Childhood Illness (IMNCI)<sup>5</sup> can be referred for quick assessment of dehydration (Table 25.1). According to the assessment chart, a patient may be grouped as 'no dehydration' (when there are no signs of dehydration), 'some dehydration' identified by

the presence of at least two of the signs in this category in the chart) and 'severe dehydration' (cases with two or more signs suggestive of severe losses of fluid and electrolytes). Depending upon the state of hydration, patients with 'no dehydration' (Plan A) or 'some' dehydration (Plan B) can be successfully treated with oral rehydration therapy (ORT) and the ones with 'severe dehydration' should be initially rehydrated by intravenous therapy (Plan C) and supplemented by/changed over to ORT as soon as the child is able to take orally (Table 25.2). ORT alone may not be successful to rehydrate a child with 'some dehydration'

**Table 25.2: Rehydration therapy in acute diarrhea**

Treatment Plan	Plan A	Plan B	Plan C
State of hydration	No dehydration	Some dehydration	Severe dehydration
Percentage of body weight loss	< 5	5-10	> 10
Estimated fluid deficit (ml/kg)	< 50	50-100	> 100
Goals of management	Replacement of ongoing losses of fluid and electrolytes	Correction of existing deficits of fluid and electrolytes	Urgent replacement of existing deficits of fluid and electrolytes
Fluid therapy	Maintenance (oral)	Rehydration (oral)	Rehydration (IV)
Treatment facility	Home	Health facility	Health facility
Rehydration fluid	Home made solutions/ORS	ORS	Ringer's lactate*
Amount of rehydrating fluid	For every loose Stool: 10 ml/kg body wt or <i>Children &lt; 2 years:</i> (50-100 ml) <i>Children 2-10 years:</i> (100-200 ml) Older children and adults: as much as desired  <b>plus</b> Free access to drinking water	50-100 ml/kg body wt (average 75 ml/kg) over 4 hours**  <b>plus</b> <i>Non-breastfeed infants less than 6 months:</i> 100-200 ml of clean drinking water <i>Older children and adults:</i> Free access to plain water in addition to ORS	Intravenous fluids <i>Infants:</i> 30 ml/kg over 1 hour followed by 70 ml/kg over 5 hours <i>Older children and adults</i> 30 ml/kg over ½ hour followed by 70 ml/kg over 2 ½ hours  <b>plus</b> ORS (5 ml/kg/hour) to be started orally as soon as the child is able to drink
Monitoring	Watch for vomiting, early signs of dehydration, blood in the stools, etc. Reassess after 2 days or earlier	Monitor every hour and reassess after 4 hours: — If still in Plan B, repeat as above — If rehydrated shift to Plan A on ORS	Monitor ½ hourly and reassess after 6 h (infants)/3 h: (older children) — If still in Plan C, repeat as above — If rehydrated shift to Plan B or A as per hydration status

\*Normal saline (0.9 percent NaCl) or half strength Darrow's solution may be used if Ringer's lactate is not available

\*\* Severely malnourished children should be rehydrated slowly over 6-12 hours

in certain situations like high rates of purging (watery stools >15 ml/kg/hour), persistent vomiting (4 or more episodes of vomiting/hour), inability to drink (due to severe stomatitis, fatigue, central nervous system depression induced by antiemetics or antimotility drugs) and glucose malabsorption. Such cases need to be rehydrated with intravenous therapy as per Plan C.

### ORAL REHYDRATION THERAPY

Oral rehydration therapy (ORT) has radically changed the treatment of diarrheal diseases. The term ORT includes (a) ORS solution of WHO recommended composition, (b) Solution made from sugar and salt (if prepared correctly), (c) Food based solutions (with appropriate concentration of salt) given, and (d) Along with continued feeding.<sup>4,5</sup>

The use of oral rehydration salts (ORS) to treat diarrhea stems from the discovery during 1960s of coupled active transport of glucose and sodium in the small bowel resulting in the passive absorption of water and other electrolytes even during copious diarrhea. Results of several studies have shown that optimum absorption of glucose takes place from the intestines between a glucose concentration of 111-165 mmol/l<sup>13</sup> and the sodium: glucose ratio between 1:1 to 1:14. The standard WHO/UNICEF ORS formula containing sodium chloride 3.5 g, sodium bicarbonate 2.5 g or trisodium citrate 2.9 g, potassium chloride 1.5 g and glucose 20 g to be dissolved in 1 liter of clean drinking water (Na<sup>+</sup> 90 mEq/L, K<sup>+</sup> 20 mEq/L, Cl<sup>-</sup> 80 mEq/L, HCO<sub>3</sub> 30 mEq/L or citrate 10 mEq/L, and glucose 111 mmol/l) has been effectively used for rapid rehydration of dehydrated patients. The standard WHO/UNICEF formulation has saved millions of lives during the last three decades but did not decrease diarrheal duration or stool output. Additionally, there was a concern among pediatricians that there was a risk of hypernatremia with standard WHO-ORS when given to children with non-cholera diarrhea.

Reduced osmolarity of ORS achieved by reducing the glucose and salt concentrations of the solution, to avoid possible adverse effects of hypertonicity on net fluid absorption, has been found to be safe and efficacious in treating children with diarrhea. Because of the improved effectiveness of reduced osmolarity ORS solution, WHO and Indian Academy of Pediatrics now recommend use of low osmolarity ORS (Table 25.3) as the universal solution for treatment and prevention of dehydration for all causes of diarrhea and at all ages.<sup>14-16</sup>

If low osmolarity ORS is not available, it is recommended that standard WHO ORS with 90 mmol/l of

**Table 25.3: Low osmolarity ORS formulation recommended by WHO/UNICEF<sup>15</sup>**

Reduced osmolarity ORS	g/liter		mEq/liter
Sodium chloride	2.6	Sodium	75
Glucose, anhydrous	13.5	Chloride	65
Potassium chloride	1.5	Glucose, anhydrous	75
Trisodium citrate, dehydrate	2.9	Potassium Citrate	20
Total osmolarity	245 mOsm/kg		10

sodium can be safely given to treat dehydration. After dehydration has been corrected, offering breastfeeding and plain water is the most important single step to prevent hypernatremia.

### ORS IN NEONATES

Neonatal diarrhea with dehydration has been successfully treated with standard WHO/UNICEF ORS.<sup>17</sup> Even low birth weight babies can be successfully rehydrated with standard WHO ORS.<sup>18,19</sup> Even though some reports have indicated a risk of excessive sodium retention, slow correction of acidosis, periorbital edema, mild pedal edema and excessive irritability,<sup>20</sup> and even higher incidence of hypernatremia<sup>21</sup> with the use of standard WHO ORS in neonates, availability of low sodium low osmolarity ORS can overcome some of these problems. If low osmolarity ORS is not available, it is recommended that standard WHO ORS with 90 mmol/l of sodium can be safely given to treat dehydration if they are able to drink oral fluids, and if given in amounts appropriate for the degree of dehydration, under proper supervision along with breastfeeding or by offering plain water to non-breastfed babies in a 2:1 ratio of ORS and water. Offering breastfeeding and plain water is the most important single step to prevent hypernatremia. During maintenance therapy too, breastfeeding or plain water should always be offered in the same ratio.<sup>4,5</sup>

### INTRAVENOUS FLUID THERAPY

Ringer's lactate given rapidly as 30 ml/kg followed by 70 ml/kg for deficit therapy is considered the treatment of choice for severe dehydration (Table 25.2). However, in order to encourage oral feeding, the child should be offered ORS (5 ml/kg/h) along with intravenous infusion as soon as he is able to drink orally. It is imperative to closely watch the child for passage of urine after plasma expansion has been achieved by rapid intravenous therapy. If the child fails to pass

urine even after 2 hours of giving Ringer's lactate, he should be considered to have developed acute renal failure and managed accordingly.

### REHYDRATION OF SEVERELY MALNOURISHED CHILDREN

Rehydration of severely malnourished children deserves special attention owing to certain pathophysiological changes in water and electrolyte balance peculiar to protein energy malnutrition (PEM). Children with severe PEM have an increase in total body water and sodium while potassium stores in the body are depleted. The renal concentrating capacity is poor and thus they cannot conserve water efficiently. Moreover they cannot handle excessive fluid and salt load and can develop fluid retention. Hence malnourished children are more prone to diarrheal dehydration, and if given excessive fluids run a risk of developing cardiac failure. This risk is further increased by the fact that it is often difficult to judge the extent of dehydration in these children owing to absence of subcutaneous fat. Assessment of hydration status is also difficult because a number of signs that are normally used are unreliable. Marasmic children normally have sunken eyes, and the diminished skin turgor may be masked by edema in children with kwashiorkor. In both types of patients, irritability or apathy makes assessment of mental state difficult. Signs that remain useful for assessing hydration status in severe PEM include: eagerness to drink (sign of some dehydration); very dry mouth and tongue, cool and moist extremities and weak or absent radial pulse (signs of severe dehydration). It is often difficult to distinguish between some and severe dehydration in severely malnourished children and it is best to assume at least some dehydration if they have acute watery diarrhea.<sup>5</sup>

Several workers have reported a high incidence of hyponatremic dehydration in malnourished children<sup>22,23</sup> but satisfactory results have been reported by others who used ORS containing 90 mmol/l of sodium.<sup>24</sup> Low osmolarity ORS is safer in these children. However, it is recommended that rehydration of severely malnourished children should be carefully monitored and preferably take place in a hospital. Rehydration with ORS solution should be preferred because IV fluids can easily cause overhydration and heart failure. Rehydration should take place slowly in children with severe malnutrition giving 70-100 ml of ORS solution per kg body weight over 6-12 hours (5 ml/kg every 30 minutes for first 2 hours, then 5-10 ml/kg/hour for the next 4-10 hours).<sup>13,25</sup> The exact amount depends on how much the child wants, volume of stool loss and whether the child is vomiting.

Feeding should begin as soon as possible and supplemental potassium should be given with food for 2 weeks.

### ELECTROLYTE DISTURBANCES

#### Hypernatremia

Some children with diarrhea, especially young infants, develop hypernatremic dehydration which usually follows use of hypertonic drinks (canned fruit juices, carbonated cold drink, incorrectly prepared salt and sugar solutions, ORS with high glucose content). Children with hypernatremic dehydration (serum sodium  $>150$  mEq/L osmolality  $> 295$  mOsm/kg) are extremely thirsty, out of proportion to the other signs of dehydration and sometimes have convulsions. Patients with hypernatremic dehydration have a total body deficit of sodium, even though the concentration of this cation in serum and extracellular fluid is abnormally high.<sup>3</sup> Therefore infants with overt diarrheal dehydration of the hypernatremic variety can be successfully treated with an oral rehydration regimen that uses a glucose electrolyte solution containing 90 mmol/l of sodium alternating with plain water.<sup>26</sup> Rapid absorption of this solution during the rehydration phase leads to expansion of intravascular compartment and increases renal perfusion, while administration of plain water provides free water for the infant's renal physiologic mechanism to carry out further homeostasis. However, if the child is unable to drink orally, Ringer's lactate can be initially given to treat shock and later switch over to ORT with ORS alternating with plain water.

#### Hyponatremia

Patients who ingest only large amount of water or watery drinks that contain very little salt, may present with hyponatremia (serum sodium 130 mEq/L, osmolality  $< 275$  mOsm/kg), which may be clinically associated with lethargy and seizures. ORS is safe and effective therapy for hyponatremia as well. However, in the treatment of hyponatremia, administration of standard ORS alone without extra water has been observed to be superior because of higher sodium intake.<sup>22</sup> For children who are unable to drink orally, intravenous infusion of Ringer's lactate can effectively treat hyponatremia.

#### Hypokalemia

Inadequate replacement of potassium losses during diarrhea can lead to potassium depletion and hypokalemia (serum potassium  $< 3$  mEq/L), which may result in muscle weakness,<sup>27</sup> paralytic ileus, renal

impairment and cardiac arrhythmias. Severe potassium depletion particularly in malnourished children may lead to acute onset flaccid paralysis ranging from neck flop to quadriplegia and even respiratory paralysis.<sup>28</sup> The potassium deficit can be corrected by using ORS solution for rehydration therapy and by feeding potassium rich foods (e.g. banana, fresh fruit juices) during and after diarrhea. Oral potassium supplementation (2 mEq/kg/day) is indicated in malnourished children. In transient flaccid paralysis due to hypokalemia, potassium can be administered parenterally by using 15 percent solution of potassium chloride (1 ml = 2 mEq of potassium) but not exceeding 40 mEq/L of IV fluids after ensuring adequate renal functions.<sup>29</sup>

### Metabolic Acidosis

During acute diarrhea, large amounts of bicarbonate may be lost in the stool. If the kidneys continue to function normally, most of the lost bicarbonate is replaced and a serious base deficit does not develop. Metabolic acidosis tends to correct spontaneously in most of the cases as the child is properly rehydrated. WHO/UNICEF ORS solution contains adequate bicarbonate/citrate to counter acidosis in less severe cases. However, in severe dehydration, compromised renal function leads to rapid development of base deficit and metabolic acidosis. Hypovolemic shock as a consequence of rapid loss of water and electrolytes in severe diarrhea results in excessive production of lactic acid, which may further contribute to metabolic acidosis. Rapid intravenous infusion of Ringer's lactate, which contains 28 mEq/L of lactate (metabolized to bicarbonate), is recommended in severe dehydration. However, in the presence of circulatory failure bicarbonate precursors (e.g., citrate, lactate) may not be readily metabolized in the body.

If the patient presents with severe metabolic acidosis (pH < 7.20, serum  $\text{HCO}_3^- < 8$  mEq/L), sodium bicarbonate in a bolus dose of 2-3 mEq/kg can be given to correct acidosis. If facilities for blood gas estimation are available accurate dose of bicarbonate can be calculated by the formula: bicarbonate dose (mEq) = (desired  $\text{HCO}_3^-$  - observed  $\text{HCO}_3^-$ )  $\times$  0.6  $\times$  body weight in kg. It is preferable to increase the bicarbonate level only up to 12 mEq/L to prevent overshoot metabolic alkalosis.<sup>29</sup> Attention should be paid to serum potassium concentration as correction of acidosis in a patient with low potassium can lead to life-threatening severe hypokalemia.

### Zinc Supplementation

Zinc deficiency is common in children from developing countries because of intake of predominant vegetarian

diets and the high content of dietary phytates. Increased fecal losses during many episodes of diarrhea aggravate pre-existing zinc deficiency. WHO and Indian Academy of Pediatrics recommends zinc supplementation as an adjunct to ORS in the treatment of diarrhea. The National IAP Task Force recommended that all children older than 6 months suffering from diarrhea should receive a uniform dose of 20 mg of elemental zinc as soon as diarrhea starts and continued for a total of 14 days. Children aged 2 to 6 months should be advised 10 mg per day of elemental zinc for a total period of 14 days.<sup>16</sup>

### Indications for Use of Antibiotics

Diarrhea in young children is often infective in origin. The organisms most frequently associated with acute diarrhea in young children in developing countries include rotavirus, enterotoxigenic *E. coli* (ETEC), *Shigella*, *Campylobacter jejuni*, *Cryptosporidium*, *Vibrio cholerae*, non-typhoidal *Salmonella* and Enteropathogenic *E. coli* (EPEC). However, it is important to remember that most of these infections are self limiting and antibiotic therapy does not significantly alter the clinical course. Antibiotic therapy in most of these cases, therefore, is not only unnecessary but may lead to undesired side effects and consequences. Antibiotic therapy should be reserved for cases of dysentery and suspected cholera only. Therefore every case of diarrhea needs to be carefully evaluated for presence of blood in the stools, which indicates dysentery and to identify cases of suspected cholera (high purge rate with severe dehydration in a child above 2 years in an area where cholera is known to be present). For the management of dysentery it is assumed that the cause is shigellosis and therefore an oral antibiotic to which *Shigella* are sensitive should be prescribed. Earlier, trimethoprim (TMP)-sulfamethoxazole (SMX) at a dose of TMP 5 mg/kg and SMX 25 mg/kg twice a day or nalidixic acid 15 mg/kg/dose 4 times a day was recommended for 5 days. In view of widespread resistance to cotrimoxazole, Indian Academy of Pediatrics Task Force now recommends ciproflox (15 mg/kg per dose twice a day  $\times$  3 days) as first line drug in areas where resistance rates to cotrimoxazole exceeds 30%. Switch to oral cefixime, if there is no response in 48 hours. This may be continued for 5 days. However, the stool microscopy for ameba/giardia needs to be done, if the child does not respond to 48 h of cefixime. For proven as well as suspected cases of cholera single dose doxycycline (5 mg/kg) is recommended in children > 2 years.<sup>5</sup> Other alternatives include single dose administration of ciprofloxacin or azithromycin.

### Antibiotics in Severely Malnourished Children

In severe malnutrition, the usual signs of infection such as fever are often absent, yet multiple infections are common. Hypoglycemia and hypothermia are often signs of severe infection.<sup>25</sup> Therefore, it is assumed that all malnourished children have an infection on their arrival in the health facility and should be treated with broad spectrum parenteral antibiotics like ampicillin with gentamicin.<sup>5,25</sup>

### Risk Factors for Diarrheal Morbidity and Mortality

Early home therapy with ORT at the onset of a diarrheal episode remains the treatment of choice in almost all cases of diarrhea. However, it may be necessary to identify on the first day of an episode of diarrhea, signs and symptoms which indicate an increased likelihood of developing dehydration. Alteration in thirst (increased in a normal child and decreased in a dehydrated child as his hydration worsens), 6 or more loose stools, presence of fever, vomiting and a reduction in appetite<sup>30</sup> are some of the clinical features, which help to recognize potentially severe cases who should be kept under close surveillance. Associated major infections (pneumonia, septicemia or meningitis), severe wasting and severe stunting have been reported as risk factors for fatal diarrhea<sup>31</sup> and hence such children need to be identified and targeted for intensive intervention.

### Nutritional Management during and after Diarrheal Episode

Diarrhea is a major cause of malnutrition owing to low food intake during the illness, reduced nutrient absorption in the intestine, and increased nutrient requirements as a result of the infection. Poor appetite, vomiting and the common practice of withholding or diluting food are some of the reasons for poor intake during an episode of diarrhea. Therefore, food intake should never be restricted during or following diarrhea. Rather, the goal should be to maintain the intake of energy and other nutrients at as high a level as possible. When this is done, even with only 80-95 percent carbohydrates, 70 percent fat and 75 percent nitrogen being actually absorbed during acute diarrhea<sup>32</sup> sufficient nutrients can be absorbed to support continued growth and weight gain. Continued feeding also speeds the recovery of normal intestinal function, including the ability to digest and absorb various nutrients. In contrast, children whose food is restricted or diluted

usually lose weight, have diarrhea of longer duration, and recover intestinal function more slowly.<sup>33</sup>

During an episode of diarrhea, specific recommendations for feeding are determined by the child's age and feeding pattern before the illness and the state of hydration. If the child is dehydrated, *during the dehydration phase* breastfeeding should be continued and normal feeding resumed after dehydration is completed. However, in severely malnourished children some food should also be offered as soon as possible during the rehydration period.<sup>34</sup> *After the dehydration phase* the dietary management during an episode of diarrhea include: (i) Breastfeeding should be continued, as often as the child wishes; (ii) Young infants who take animal milk should continue to take undiluted milk as before; (iii) Children 6 months of age and older should receive energy rich mixture of soft weaning foods in addition to breast milk or animal milk; (iv) Energy rich food (thick preparations of staple food with extra vegetable oil or animal fats), potassium rich foods (legumes, banana) and carotene containing foods (dark green leafy vegetables, red palm oil, carrots, pumpkins) should be given to the child in sufficient quantity. In young children these foods should be particularly well cooked and soft or mashed to aid digestion. Owing to loss of appetite or vomiting, children may need considerable encouragement to eat. It is helpful to give food frequently in small amounts, i.e. 6 times per day or more.

After an episode of diarrhea, a child should receive more food than usual for at least two weeks after diarrhea stops. During this period, the child may consume up to 150 cal/kg of body weight per day. A practical approach is to give the child at least one extra meal each day with energy rich foods.<sup>34</sup>

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## INTRODUCTION

Acute liver failure (ALF) or fulminant hepatic failure (FHF) is the sudden acute deterioration of liver functions and is the final common pathway of a variety of insults of the liver. ALF is a medical emergency and carries a very high mortality of around 85% without liver transplantation.<sup>1,2</sup> Mortality in ALF is related to multiorgan dysfunction, cerebral edema, sepsis, coagulopathy and bleeds.<sup>3</sup> Orthotopic liver transplantation (OLT) is a substantial advancement in the management of ALF and provides definite treatment. Intensive care unit (ICU) intervention opens a “window of opportunity” for patients with ALF and enables successful liver transplantation in patients who are too ill at presentation. Newer liver support devices like molecular adsorbent recirculating system (MARS) and extracorporeal liver assist device (ELAD) also help buy time for transplantation once the patient is waitlisted for OLT. Newer ideas like hepatocyte transplantation may be beneficial in the future.

## DEFINITIONS

There are several definitions proposed to define ALF or FHF. Trey and Davidson defined FHF in 1970 as a potentially reversible condition as a consequence of severe liver injury in which encephalopathy develops within eight weeks of the onset of first symptoms in the absence of pre-existing liver disease.<sup>4</sup>

O’Grady et al used the terms hyperacute liver failure, acute liver failure and subacute liver failure for patients presenting with encephalopathy within 7 days, 8-28 days and 5-12 weeks of onset of jaundice, respectively.<sup>5</sup>

The International Association of Study of Liver Disease (IASL) accepts the definition of acute liver failure as onset of encephalopathy within 4 weeks of jaundice and subacute hepatic failure from 4 weeks to 6 months.<sup>6</sup>

The above-mentioned definitions are designed for adults and have various shortcomings for applicability

in children. Early stages of encephalopathy are difficult to assess in small children, and encephalopathy may not be apparent until terminal stages of ALF in infants. Also, duration of illness can be difficult to assess, particularly in infants, who present with ALF in the first few weeks of life. The Pediatric Acute Liver Failure Study Group (PALFSG), after analyzing data from 24 pediatric liver centers, has defined ALF as biochemical evidence of liver injury with no known history of chronic liver disease, coagulopathy uncorrected by vitamin K administration and prothrombin time, international normalized ration (INR) greater than 1.5 if the patient had encephalopathy, or greater than 2 if the patient does not have encephalopathy.<sup>7,8</sup>

## ETIOLOGY

The etiologies of ALF in children differ from that of adults. Also, etiologies are different in various age groups and different geographical regions of world (Tables 26.1 and 26.2).<sup>1,7,9</sup> The largest pediatric data on ALF in the literature is from pediatric acute liver failure study group (PALFSG) from 24 pediatric hepatology centers. This data reveals that in the developed world, majority (49%) of ALF cases are indeterminate in etiology, whereas infections are responsible in just 6%. Drug induced ALF (both acetaminophen and non-acetaminophen) are seen mainly in older children above 3 years of age. Metabolic causes of ALF, on the other hand, are seen mainly in less than 3 years age group, except for Wilson’s disease, which is seen in older children.<sup>7</sup> Contrary to this, data from developing world reveals infectious hepatitis (viral hepatitis A, E, B or mixed type) to be the commonest etiology (94-96%) of ALF in children. Viral hepatitis A is the commonest cause, followed by hepatitis E, combined A and E, and hepatitis B<sup>9</sup> (Tables 26.1 and 26.2). Etiologies of ALF in neonates are entirely different and constitute conditions like neonatal hemochromatosis, galactosemia, tyrosinemia, sepsis, perinatal herpes simplex virus infection and hemophagocytic lymphohistiocytosis.<sup>1</sup>

**Table 26.1: Causes of acute liver failure<sup>1,7</sup>**

Etiology	Disease
<i>Neonates</i>	
Infections	Hepatitis-B, herpes viruses, echovirus, adenovirus, sepsis
Metabolic	Galactosemia, tyrosinemia, neonatal hemochromatosis, mitochondrial hepatopathies
Ischemic	Congenital heart disease, cardiac surgery, myocarditis, severe perinatal asphyxia
Vascular	HVOTO, hemangioma, hemangioendothelioma
Others	Congenital leukemia, neuroblastoma, hemophagocytic histiocytosis
<i>Older Children</i>	
Drugs	Paracetamol, valproate, isoniazid, halothane, phenytoin, tetracycline, methotrexate, phenytoin, iron, minocycline, pravastatin
Infection	HAV, HBV, HEV, HCV, HSV, EBV, CMV, Adenovirus, sepsis
Toxins	<i>Amanita phalloides</i> , carbon tetrachloride, phosphorus
Metabolic	Wilson's disease, hereditary fructose intolerance, alpha-1 antitrypsin deficiency, FAO defects, urea cycle defects, Reye's syndrome
Autoimmune	Types 1, 2 and 3
Ischemic	Congenital heart disease, cardiac surgery, myocarditis, shock
Vascular	HVOTO
Malignancy	Lymphoma, Leukemia, hemophagocytosis

**Abbreviations:** HVOTO-Hepatic venous outflow tract obstruction, also known as Budd-Chiari syndrome, HAV-Hepatitis A virus, HBV-Hepatitis B virus, HEV-Hepatitis E virus, HCV-Hepatitis C virus, HSV-Herpes simplex virus, EBV- Epstein-Barr virus, CMV-Cytomegalovirus, FAO-Fatty acid oxidation.

**Table 26.2: Etiology of ALF (Comparison of data from developed and developing world)**

	PALFSG (24 centers from USA, Canada, UK) (n = 348) <sup>6</sup>	Poddar et al PGI Chandigarh, India (n=67) <sup>8</sup>	Sir Ganga Ram Hospital, New Delhi, India (n=94) <sup>^</sup>
	<3 years (n – 127)	>3 years (n=221)	
Infectious	7%	5%	94%
Drugs	3%	28%	-
Autoimmune	5%	7%	-
Metabolic*	18%	6%	-
Others <sup>#</sup>	15%	8%	-
Indeterminate	54%	46%	6%
			60**
			8
			4
			11
			20

\* Metabolic group includes Wilson's disease, alpha – 1 antitrypsin deficiency, tyrosinemia, galactosemia, hereditary fructose intolerance, respiratory chain and fatty acid oxidation defects, mitochondrial disorders, urea cycle defects, Reye's syndrome, Niemann-Pick disease.

<sup>#</sup> Other conditions include shock, Budd-Chiari syndrome, hemophagocytic syndrome, leukemias, neonatal iron storage disorder, veno-occlusive disease.

<sup>^</sup> Unpublished data

\*\* 9 of the patients with infectious etiology have overlapping other disorder.

## CLINICAL FEATURES

The clinical presentation varies with etiology but essentially there is hepatic dysfunction with hypoglycemia, coagulopathy and encephalopathy. A detailed CNS examination will identify various grades of encephalopathy (Table 26.3).

Jaundice may be a late feature, particularly in metabolic disease. The clinical onset may be within

hours or weeks. ALF eventually represents a multiple organ dysfunction syndrome (MODS) involving the kidneys, lungs, bone marrow, circulatory system besides the brain. Therefore, the initial examination and biochemical investigations must establish hepatic, cerebral, cardiovascular, respiratory, renal and acid base status. The signs that predict the development of ALF are depicted in Table 26.4.

**Table 26.3: Grades of hepatic encephalopathy**

I	Reversal of sleep rhythm, personality and intellectual changes, euphoria, lack of concentration
II	Confusion, drowsiness, inappropriate behaviour, asterixis (flapping tremors)
III	Stupor, incoherence, unresponsive to verbal commands, hyperreflexia, positive Babinski's sign (extensor plantars)
IV	Comatose, gradually more unresponsive, decerebrate posturing, seizures

**Table 26.4: Warning signs of progressive disease**

- Decreasing liver size (shrunken liver) along with decline in transaminases and increase of bilirubin
- Prolonged prothrombin time, which is unresponsive to vitamin K
- Features of encephalopathy
- Persistent jaundice with a rapid increase in bilirubin / bilirubin >17.5 mg%
- Hypoglycemia, hypoalbuminemia, lactic acidosis

### Diagnosis

Diagnosis is established by a combination of clinical and biochemical features and specific diagnostic tests (Table 26.4). Biochemical features demonstrate marked conjugated hyperbilirubinemia, elevated aminotransferases, raised plasma ammonia and coagulopathy. Liver histology is usually impossible to obtain because of the abnormal coagulation.

The common differential diagnosis of ALF includes complicated malaria, enteric fever, leptospirosis, dengue hemorrhagic fever and Reye's syndrome.

### Management

There is no specific therapy for fulminant hepatic failure except hepatic replacement. Management therefore is directed towards supportive care, prevention and treatment of complications, early consideration for liver transplantation and hepatic support.

### General Measures

Management should be in a pediatric intensive care unit in an institution with an active transplant program. Priorities of intensive care management should include airway breathing and circulation. In patients with worsening encephalopathy (grade III, IV) and cerebral edema, increasing oxygen requirement, early acute respiratory distress syndrome (ARDS), or shock with or without multi-organ failure, endotracheal intubation and mechanical ventilation should be considered. For sedation, propofol/benzodiazepenes are used, propofol has the added benefit of decreasing cerebral blood flow and lowering intracranial pressure.<sup>10</sup> Muscle relaxant of choice for endotracheal intubation is atracurium since it is metabolized by Hoffman non-enzymatic hydrolysis

independent of liver or kidney dysfunction. Norcuron should be avoided for muscle relaxation since it is metabolized by liver. Fentanyl could be used for analgesia. Morphine and meperidine are not recommended because of active metabolites. A central venous catheter will be required for assessment of central venous pressure and volume status. Use of a double lumen or preferably triple lumen catheter enables simultaneous administration of blood products, intravenous fluids and drugs, and also makes blood sampling easy. An indwelling arterial line for measurement of blood pressure and for biochemical and acid-base monitoring is essential. A nasogastric tube is put in with regular gentle saline lavage to detect upper gastrointestinal bleed and to prevent aspiration. The urinary bladder is catheterized and strict output record maintained. Care should be taken for prevention of bed-sores. Baseline biochemical and other investigations are performed (Table 26.4). Frequency of monitoring will depend on the severity of illness ranging from daily in mild cases to 4-6 hourly in patients with stage III and IV coma and include complete blood count, blood gases, electrolytes, aminotransferases and prothrombin time, plus daily monitoring of plasma creatinine, bilirubin and ammonia and chest X-ray to follow the ARDS and heart size. An abdominal ultrasound may indicate liver size and patency of hepatic and portal veins, particularly if liver transplantation is being considered. Vitamin K is given to all patients though may be avoided in G6PD deficient cases due to risk of hemolysis. The nursing of the patient should be in a quiet environment and one must avoid excessive stimulation and pain. Sedation should also be avoided. If the patient needs sedation he/she should be electively intubated for assisted ventilation.<sup>11,12</sup>

### Fluid Balance

Maintenance fluid consists of 10 percent dextrose in 0.25 N saline and intake should be 75 percent of normal maintenance or in cases of cerebral edema fluid management should be based on central venous pressure (CVP) monitoring. Usually the sodium is maintained between 145-155 mEq/L especially in patients with hepatic encephalopathy. Potassium should be maintained between 3.5-5 mEq/L as hypokalemia may worsen encephalopathy. If urine output is low, despite use of loop diuretics, dopamine, colloid/fresh frozen plasma (FFP), hemofiltration or dialysis should be considered. Hemoglobin concentration should be maintained above 10 g/dl to provide maximum oxygen delivery to tissues. While managing coagulopathy care should be taken that massive doses of FFP could lead to fluid overload.

### Gastrointestinal Bleed

Gastrointestinal bleeding is a frequent complication and can be prevented and treated by using H<sub>2</sub> antagonists (ranitidine) or proton pump inhibitors (omeprazole or pantoprazole) and sucralfate. Packed RBC and FFPs should be arranged and transfused accordingly.<sup>13</sup>

### Infection

Infection is a common early complication of ALF, and a significant cause of death in these patients.<sup>14</sup> Management is aimed at prevention and prompt treatment of infection. Because infections can strike early in the course of ALF, and because they have a high associated mortality, there should be a low threshold for beginning empirical broad-spectrum antibiotics. There is growing evidence that the use of prophylactic antibiotics leads to a decrease in bacterial infections, decrease risk of progression to higher grades of encephalopathy increase the potential for successful transplants and shortened hospital stay with fewer deaths. Catheterized patients are at a high-risk of fungal superinfection; early treatment of fungal infection is also mandatory.<sup>11</sup>

### Hepatic Encephalopathy and Cerebral Edema

Hepatic encephalopathy (HE) and cerebral edema represent two different neurological complications of acute liver failure. Careful observation is necessary to detect the onset and progression of HE (Table 26.5).

Hepatic encephalopathy results from failure of bio-transformation and excretion of toxins normally processed by the liver. Raised plasma ammonia levels have been implicated; however, other chemicals

involved include mercaptans, fatty acids, aromatic chain amino acids, benzodiazepine like substance,  $\gamma$ -aminobutyric acid, glutamate and toxic metals (zinc, copper, manganese). Complex changes in blood-brain barrier permeability may also contribute. Hepatic encephalopathy is classified as grades I-IV, describing the progressions from normal mentation to hepatic coma.<sup>15-17</sup>

Grade I/II HE has a better prognosis than those progressing to grades III/IV in whom development of cerebral edema is more frequent. Elective intubation and ventilation is undertaken when patients progress to grades II-III and become unmanageable. Hypoxemia, hypoglycemia, sepsis, hypokalemia and gastrointestinal bleeding exacerbate HE and should be identified and treated. Lactulose may be administered in a dose of 1 ml/kg body weight, *via* nasogastric tube 3 to 6 times per day, to maintain loose, acid stool and regular stool output, though there is no randomized study on the effects of lactulose in ALF.<sup>18</sup>

More than 75-80% of patients, especially in stage IV encephalopathy develop cerebral edema and raised intracranial pressure (ICP), the primary cause of death.<sup>1,3</sup> Clinical signs of raised ICP include systemic hypertension, bradycardia, pupillary abnormalities, decerebrate posturing, epileptic form activity and brain stem respiratory patterns. However, most of these clinical signs are nonspecific and may develop in patients in hepatic grade IV encephalopathy without intracranial hypertension. Computerized tomography/Magnetic resonance imaging/Positron emission tomography are unreliable in diagnosis of intracranial hypertension in ALF patients. The most accurate method of diagnosis of intracranial hypertension is ICP monitoring.<sup>19</sup>

### Intracranial Pressure Monitoring and Significance:

Direct monitoring of ICP helps to diagnose and manage cerebral edema in ALF.<sup>19</sup> Epidural devices have a lower complication rate (3.8%) than both subdural (20%) or parenchymal monitoring (22%). The goal in the medical management of ALF patients with intracranial hypertension is to maintain ICP below 20 mm Hg and CPP above 70 mm Hg. Cerebral ischemia occurs if CPP is less than 40-50 mm Hg and liver transplantation should be contraindicated if CPP remains below 40 mm Hg for two hours.<sup>19,20</sup>

**Treatment:** Patients at risk of cerebral edema (AHF grade III/IV) are electively sedated, intubated and mechanically ventilated, in order to reduce cerebral irritation and ICP. Davenport et al suggested that a midline position with 30° head elevation provides

**Table 26.5: Investigations in acute liver failure***Baseline Essential Investigations**Biochemistry*

- Bilirubin, transaminases (AST/ALT)
- Alkaline phosphatase
- Albumin
- Urea and electrolytes
- Creatinine
- Calcium, phosphate
- Ammonia
- Arterial blood gas and lactate
- Glucose

*Hematology*

- Full blood count, platelets
- PT (Prothrombin time), PTTK (Partial thromboplastin time), FDP (fibrin degradation products), D-dimer
- +/- Factors V or VII, reticulocyte count, G6PD (glucose 6 phosphate dehydrogenase) estimation\*, peripheral smear for malarial parasite\*
- Blood group, cross-match

*Septic screen*

- Blood, urine, central line cultures, C-reactive protein

*Radiology*

- Chest X-ray
- Abdominal ultrasound
- +/- CT Scan or MRI\*

*Neurophysiology*

Electroencephalography (EEG)

*Diagnostic Investigations**Serum*

- Serology for viral hepatitis – IgM Hepatitis A, IgM Hepatitis E, HBsAg, IgM Anti-HBc, Anti-HCV antibodies
- Other viral serologies\*: CMV-PCR, EBV-PCR, IgM HSV
- Paracetamol levels\*
- Serum copper, ceruloplasmin, 24-hour urinary copper, slit-lamp examination for presence of Kayser Fleischer (K-F) ring<sup>#</sup>
- Autoantibodies: Antinuclear (ANA), anti-smooth muscle (SMA), anti-liver kidney microsomal (LKM) antibodies

*Urine*

- Toxic metabolites\*
- Aminoacidogram, succinylacetone\*
- Organic acids\*
- Reducing sugar\*

\* as per the clinical situation

<sup>#</sup> indicators for Wilson disease in a child with ALF are AST>>>ALT, evidence of Coomb's negative hemolytic anemia, Bilirubin : Alkaline phosphatase ratio > 2:1. Testing recommended in children older than 3 years.

optimal cerebral perfusion pressure.<sup>21</sup> Elevations to 40° and 60° may paradoxically increase ICP. Patient with cerebral edema benefit from minimal intervention (physiotherapy, suction through endotracheal tube) and a quiet environment. Positive end-expiratory pressure (PEEP) may increase ICP and should be used carefully. Mannitol, an osmotic diuretic that reduces brain water, is used to reduce ICP in patients with cerebral edema.

Clinical trails on ALF patients with intracranial hypertension have demonstrated mortality reduction.<sup>22</sup> It is used in doses of 0.25 g/kg to 0.5 g/kg and may be used several times to treat repeated surges. Its use is limited by the need to keep serum osmolality below 320 mOsm/L which should be assessed 6 hourly. Mannitol is contraindicated in cases of renal failure or pulmonary edema, but it may be used in anuric

patients when adequate renal replacement therapy has been initiated.<sup>22,23</sup> There are insufficient data to recommend a standard therapy of intracranial hypertension refractory to mannitol. However thiopentone, a barbiturate, can be considered. Thiopentone is used as an anticonvulsant in the treatment of status epilepticus and has been used in a dose of 3-5 mg/kg IV loading bolus followed by 1-3/mg/kg/hr in mannitol-resistant cases in which cerebral blood flow remains satisfactory. It is thought to cause cerebral vasoconstriction, reducing brain hyperemia and cerebral metabolic rate for oxygen (CMRO<sub>2</sub>). It may also act as an antioxidant and an anticonvulsant. Side effects include precipitous hypotension that may require fluid resuscitation and inotropic support besides hypothermia, hypokalemia and prolonged coma.<sup>22</sup>

*Role of hyperventilation:* Hyperventilation induces hypocapnea which leads to cerebral vasoconstriction, and thus decreases ICP and improves cerebral vascular autoregulation. Spontaneous hyperventilation which is usual in patients with ALF should not be treated. However, prophylactic hyperventilation is not recommended in patients with ALF because vasoconstriction can reduce cerebral oxygen utilization. Consequent maintenance of a PCO<sub>2</sub> between 30-40 mm Hg is a reasonable goal. Acute hyperventilation is however recommended as an emergency rescue therapy of patients with evidence of diencephalic herniation.<sup>11,12,17</sup>

*Role of hypothermia:* Induced moderate hypothermia (32°-33°) may decrease ICP in ALF patients with intracranial hypertension refractory to mannitol and stabilize ICP as a bridge to transplantation.<sup>17</sup>

*Role of hypertonic saline:* Hypertonic saline boluses have been used increasingly in neurocritical care patient with efficacy similar or superior to mannitol. Serum sodium should be monitored at frequent intervals with a goal to maintain levels between 145-155 mEq/L. Hypertonic saline in various concentrations (3%, 7.5%, 30%) administered prophylactically to adults with ALF with high grade encephalopathy as a constant infusion rates of 5-20 ml/hr to achieve a serum sodium of 145 to 155 mmol/L has been found to be beneficial.<sup>12,17</sup>

*Role of indomethacin:* Indomethacin has been shown to acutely decrease ICP and increase CPP by causing cerebral vasoconstriction (Ref 116 USALFs study group) and may be considered as salvage therapy.<sup>12</sup>

### Coagulopathy

Prothrombin time (PT) is an important prognostic indicator in patients with ALF, therefore correction by

administration of fresh frozen plasma is discouraged unless patients are hemodynamically unstable or actively bleeding. The most frequent of the hemorrhagic complications in ALF is GI bleed related to stress gastritis and ulcers. The use of H<sub>2</sub> antagonists, omeprazole or pantoprazole reduces the risk of this complication.<sup>13</sup> FFP and platelets should be given as and when needed. In the early stages of assessment, prolongation of PT is a sensitive guide to prognosis and need for liver transplantation. It is not necessary to maintain coagulation parameters (PT) in the normal range. In general mild to moderate coagulopathy (PT<30 sec) requires no therapy except support for procedures. Marked coagulopathy (INR > 7) should be corrected (10 ml/kg of FFP 6 hourly) to prevent the risk of bleeding particularly intracranial hemorrhage.<sup>3,24</sup> Occasionally, large amounts of FFP are required and to prevent volume overload, sometimes hemofiltration may be necessary. Exchange plasmapheresis has been shown in some studies to rapidly and effectively correct severe coagulopathy, but is not a recommended therapy.<sup>25</sup>

### Respiratory Complications

There are many respiratory problems that can complicate ALF. These include respiratory depression, hypoventilation, aspiration, pneumonia, ARDS, intrapulmonary hemorrhage, and intrapulmonary shunts. Oxygen supplementation, treatment of infections, endotracheal intubation and mechanical ventilation are important. Under these circumstances, the addition of PEEP may have deleterious effects on cerebral edema, hemodynamic stability, and hepatocyte regeneration.<sup>11</sup>

### Cardiac Support

A high cardiac output state with low systemic vascular resistance is seen in ALF. The clinical picture is similar to sepsis. After adequate fluid replacement and invasive cardiac monitoring, the cautious use of inotropes and vasoconstrictors may be helpful.<sup>11</sup>

### Renal Failure

Renal failure develops in more than 50 percent of patients with acute liver failure. Typically the renal failure is secondary to hepatorenal syndrome. Renal failure is sometimes due to acute tubular necrosis or drug toxicity. Management requires correction of hypovolemia and hypotension with fluid and albumin. Nephrotoxic agents such as aminoglycosides and contrast dyes should also be avoided.<sup>11,12</sup>

Hemodialysis or continuous arteriovenous hemofiltration may be indicated for the management of severe

metabolic acidosis, hyperkalemia, or fluid overload. Hemodialysis may be difficult in the setting of hypotension and coagulopathy. Dialysis may also worsen cerebral edema. Hepatorenal syndrome can be reversed by OLT. Thus, the development of renal failure in ALF should not preclude transplantation.<sup>12</sup>

### Metabolic Abnormalities

Hypoglycemia is commonly seen in ALF. Blood glucose levels should be monitored and hypoglycemia should be treated with a 10 percent dextrose solution. A 50 percent dextrose solution should be used if the blood glucose level is less than 60 mg/dl. Other electrolyte abnormalities include hyponatremia, hypokalemia, hypomagnesemia and hypophosphatemia. ALF patients are extremely catabolic, hence the need for early nutritional supplementations.

### Specific Therapies

Specific therapies are only available for a limited number of causes of ALF. In ALF secondary to **acetaminophen** poisoning, oral N-acetylcysteine is administered in order to restore the glutathione stores. Recent evidence suggests that there may be advantages in starting N-acetylcysteine beyond 15 hours following ingestion of acetaminophen, and even as late as 36 hours following the event.<sup>26,27</sup> ALF due to **herpes simplex or zoster and CMV** should be treated with iv acyclovir and ganciclovir, respectively. Patients with ALF due to the **Budd-Chiari syndrome** may benefit from portal vein decompression with mesocaval or mesoatrial shunts or transjugular intrahepatic portosystemic shunt (TIPSS). Patients with ALF from **autoimmune hepatitis** may benefit from a trial of steroids. *Amanita phalloides* hepatotoxicity may benefit from the administration of silibinin, which is a flavinoid-alcohol, or penicillin G, which interferes with the uptake of alpha-amanitin into hepatocytes. This is useful up to 48 hours after ingestion of the toxin.<sup>28</sup>

Use of steroids in ALF has no effect on mortality or cerebral edema, may further compromise the immune system, and can actually be hazardous in the setting of infection, so their use is no longer recommended in ALF.<sup>29</sup>

### Hepatic Support

Recent research in hepatic failure has focused on the concept of hepatic support. Initial trial with techniques such as human cross-circulation, plasma exchange, plasmapheresis, and charcoal hemoperfusion have shown no significant survival benefit. Eventually,

extracorporeal liver assist devices (ELAD) have been developed which provide acute temporary liver support to optimize the internal milieu, and thus a bridge to recovery or to liver transplantation. Currently, there are two types of ELAD – biological or cell-based and non-biological or non-cell-based.<sup>30</sup> The former contains a bioreactor that houses metabolically active hepatocytes from xenogenic or human source having both synthetic and excretory functions mimicking endogenous hepatocyte functions. The non-biological ELADs have no synthetic functions and based on principles of blood “detoxification” through hemodiafiltration or hemodia-absorption methods. Molecular adsorbent recirculating system (MARS) is a non-cell based device, which is used most frequently. MARS is based on a countercurrent dialysis system using albumin as the transporting medium for toxins to achieve more selective detoxification compared with the earlier generation of devices based on charcoal hemoperfusion. MARS has been safe and easy to use and avoids the potential risk of using xenogenic or tumor-derived cell lines used in some cell-based devices.<sup>30</sup> Although the safety, feasibility and improvements in biochemical parameters with use of MARS has been established, but there is no survival benefit or improvement in clinical outcome.<sup>31</sup>

Both direct hepatocyte transplantation and the use of hepatic growth factors are promising approaches to hepatic support in ALF, but have yet to be developed sufficiently before they are applied clinically.

### Prognosis in ALF

The ability to predict the likelihood of spontaneous recovery or death without liver transplantation remains of paramount importance in patients with ALF. Many criteria have been proposed to anticipate the probability of death without transplant. Various criteria have been proposed by different authors to list the patient for OLT.<sup>11</sup> The most widely accepted criterion is the King’s College criteria for both acetaminophen and non-acetaminophen induced ALF (Table 26.6).

### ORTHOTOPIC LIVER TRANSPLANTATION

Liver transplantation is the only proven therapy of ALF. Selection for liver transplantation depends on the etiology of the disease, prognostic factors, presence or absence of multisystem disease and/or reversible brain damage. Perhaps the most frequently used criteria (Table 26.6) are those proposed by the King’s College Group.

**Table 26.6: Prognostic indicators in ALF and criteria for liver transplantation**

Scheme	Etiology of ALF	Criteria for liver transplantation
King's College	Acetaminophen induced	Arterial pH < 7.3 OR all of the following 1) PT > 100 secs (INR > 6.5) 2) Creatinine > 3.4 mg/dl 3) Grade 3 or 4 encephalopathy
	Non-acetaminophen induced	PT > 100 secs (INR . 6.5) OR any 3 of the following : 1) Non-A Non-B/drug/halothane etiology 2) Jaundice to encephalopathy interval > 7 days 3) Age < 10 or >40 years 4) PT > 50 secs (INR> 3.5) 5) Bilirubin > 17.4 mg/dL
Factor V (Clichy's)	Viral	Age < 30 years: factor V < 20% OR any age: factor V < 30% and grade 3/4 encephalopathy
Factor VIII/V ratio	Acetaminophen induced	Factor VIII/V ratio > 30
Liver biopsy	Mixed	Hepatocyte necrosis > 70%
Arterial phosphate	Acetaminophen induced	> 1.2 mmol/L
Arterial lactate	Acetaminophen induced	> 3.5 mmol/L
Arterial ammonia	Mixed	> 150-200 μmol/L

Liver transplantation could be:

1. *Cadaveric*
  - a. Whole graft—When the whole liver is used.
  - b. Split graft—When the donor liver is used for two recipients.
  - c. Reduced graft—When the donor liver is reduced to suit the size for recipient.
2. *Living related*—When a live donor gives part of his/her liver to recipient.

For liver transplantation, blood group compatibility between the donor and recipient is a must. Cadaveric transplants are very popular in the west while in countries like Japan, Korea, Hong-Kong and India, mostly living related liver transplantation are undertaken. In India, due to lack of awareness and shortage of cadaveric livers, living related liver transplantation is carried out for fulminant hepatic failure presently. In auxiliary liver transplantation, the liver graft is placed in the right upper quadrant beside the native liver. If the native liver recovers function, immunosuppression can be stopped. This is not suitable for transplantation for ALF secondary to metabolic liver disease, as these livers are unlikely to recover and there may be a risk of hepatoma in the cirrhotic liver.

Before considering a patient for liver transplantation, it is important to exclude multisystem disease and to diagnose a mitochondrial disorder (plasma and CSF lactate, muscle biopsy) or erythrophagocytosis (bone marrow aspirate). In neonates and infants, it is less easy to demonstrate irreversible cerebral damage

and edema because the cranial sutures would not have fused and the classical signs of cerebral edema may not be present. The best guide to irreversible cerebral damage is the development of gray/white reversion on CT scan secondary to cerebral ischemia or the development of convulsions.<sup>32</sup>

The 1-year posttransplant survival rate in ALF approximates 60-70% in most series in comparison to 88-92% for end stage cholestatic liver disease. But with the advancement of ICU care, control of cerebral edema, strict vigilance and control of infections, maintenance of asepsis and newer and better immunosuppressants, the 1-year survival rates post-transplant have increased to 90%.<sup>32,33</sup> Authors have unpublished experience of 9 children (7 males, median age at transplant 8 years; range: 4.3-11 years) with ALF who underwent living related liver transplants with 100% survival at a median follow-up of 8 months (range: 3-30 months), but the figures are small and there is selection bias with regard to encephalopathy.

### Conclusion

Improved survival for patients with ALF depends on many factors. Earlier referral to specialized medical centers prevention of hepatitis through vaccines, greater supplies of donor organs, and improved hepatic support systems will all lead to better outcomes. Innovative modalities to treat the complications of ALF may be the most important factors to improve the morbidity and mortality of this serious disease.

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**Upper gastrointestinal bleeding (UGIB)** is the term used to define gastrointestinal bleeding when the site of bleeding is above the ligament of Trietz (at the level of duodenojejunal flexure). UGIB is a commonly encountered problem in children that manifests as hematemesis or melena. Children usually tolerate bleeding better than adults due to absence of co-morbid conditions but their management has to be efficient and timely due to their smaller total blood volumes and risk of rapid depletion.

*The following terms are commonly used to describe UGIB*

**Hematemesis** refers to passage of blood in vomiting and suggests an UGI site of bleeding. It may be bright red or altered coffee-ground depending on the severity of hemorrhage and the duration it stayed in contact with the contents of stomach.

**Melena** refers to passage of black, tarry stools with an offensive smell and suggests an UGI or small bowel site of bleeding. The combination of hematemesis and melena indicates that the bleed is from the upper gastrointestinal tract and significant in amount.

**Hematochezia** is passage of bright red blood in stools and is usually seen with a colonic site of bleed but very brisk upper GI bleeding with fast transit may also present with hematochezia.

**Hemobilia** refers to bleeding from the biliary tree and **hemosuccus pancreaticus** to bleeding from the pancreas.

#### ETIOLOGY

The causes of hemorrhage from UGI tract vary in different age groups and can be subdivided into neonatal-infant and child-adolescent as shown in Table 27.1. It is important to remember that overlap exists across age groups and the commonest causes of massive UGIB are esophageal /gastric varices, vascular anomalies and gastric/duodenal ulcer disease.

There are limited studies on etiology of upper gastrointestinal bleeding in children<sup>1-5</sup> (Table 27.2). Etiology in India differs from that in western countries due to higher prevalence of extrahepatic portal venous obstruction (EHPVO) in India and ulcer disease in the West. Difference in etiology between the Indian studies

**Table 27.1: Causes of upper gastrointestinal bleeding**

Neonate/Infant	Child and Adolescent
Swallowed maternal blood	Esophagitis: reflux, infections.
Esophagitis	Mallory-Weiss tear
Gastritis	Caustic ingestion
Gastroduodenal ulcer/erosion	Foreign body
Vascular malformation	Portal hypertension—esophageal/gastric varices;
Esophageal duplication	congestive gastropathy; gastric antral vascular ectasia (GAVE)
Hemorrhagic disease of newborn (HDN)	Gastritis
Sepsis/coagulopathy	Peptic ulcer (duodenal/gastric)
Milk protein allergy	Arteriovenous malformation, Henoch-Schönlein purpura
Rare: Trauma (nasogastric tube),	Crohn disease, sepsis/coagulopathy
gastric cardia prolapse, heterotopic pancreatic tissue	Tumors—leiomyoma, lymphoma.
	Rare: gastrointestinal duplication, hemobilia, radiation
	gastritis, Munchausen's syndrome by proxy
	Swallowed epistaxis

**Table 27.2: Series on etiology of upper gastrointestinal bleeding in children**

Cause	<i>Yachha et al</i> (n = 75) (Ref 1) Indian	<i>Mittal et al</i> (n = 236) (Ref 2) Indian	<i>Huang et al</i> (n-112) (Ref 3) Taiwan*	<i>Mouzan et al</i> (n – 60) (Ref 4) S Arabia	<i>Cox A et al</i> (n-68) (Ref 5) USA
Varices (esophageal or gastric)	95%	39.4%	10.7%	4.3%	10.2%
Esophagitis/ esophageal ulcer	-	24.2%	30.4 %	36%	14.7%
Gastritis	1.3%	7.3%	44.6%	44%	13.2%
Gastric /duodenal ulcer	-	1.6%	25%	7%	38.2%
Others- HSP, ITP	3.7%	-			
Unknown	none	27.5%	9.8%	~9%	~23.7%

\* 24% subjects had both gastritis and esophagitis; HSP: Henoch-Schönlein purpura; ITP: Idiopathic thrombocytopenic purpura

is due to the difference in referral pattern across studies. Overall, esophagitis, gastritis and varices, are the commonest causes of UGIB in Indian children.

### CLINICAL FEATURES

A detailed history and examination is useful in determining the likely cause of UGIB. Hemodynamic stabilization and initiation of definitive management is done simultaneously as shown in the Flow chart 27.1. The objectives are to answer the following questions:

#### 1. Is it actually blood?

Ingestion of maternal blood may be the cause of hematemesis or melena in an otherwise healthy and stable appearing neonate. An Apt-Downey test should be performed on the emesis to identify the source of bleeding conclusively. Red food coloring agents such as red colored candies, juices, cranberries and beets may impart their color to the stools and are mistaken for blood. Several compounds such as bismuth, iron preparations, spinach, licorice, etc. may mimic melena. These spurious agents have to be excluded by tests for occult blood in stools.

#### 2. Is the child actually bleeding from the gastrointestinal tract?

It is important to assess whether the blood vomited by the child is from the gastrointestinal tract as children with epistaxis or oropharyngeal bleeding often present with blood in vomitus. The oropharynx/ nose should be examined. History of bleeding from multiple sites points towards a systemic cause of bleed like thrombocytopenia/coagulopathy. Hemoptysis can be very easily confused with hematemesis, thus a careful history of chronic cough, and passage of bright red

blood associated with sputum should be enquired into. In the pubertal female child with hematochezia, the onset of menarche should also be considered.

#### 3. What is the hemodynamic status and extent of intravascular volume depletion?

Heart rate, blood pressure, pulse volume, capillary refill time, oxygen saturation (pulse oximetry), skin temperature and urine output are important parameters to be monitored. Minor bleed has no effect on heart rate and blood pressure, moderate bleed is associated with postural hypotension and tachycardia whereas massive bleed is associated with shock.

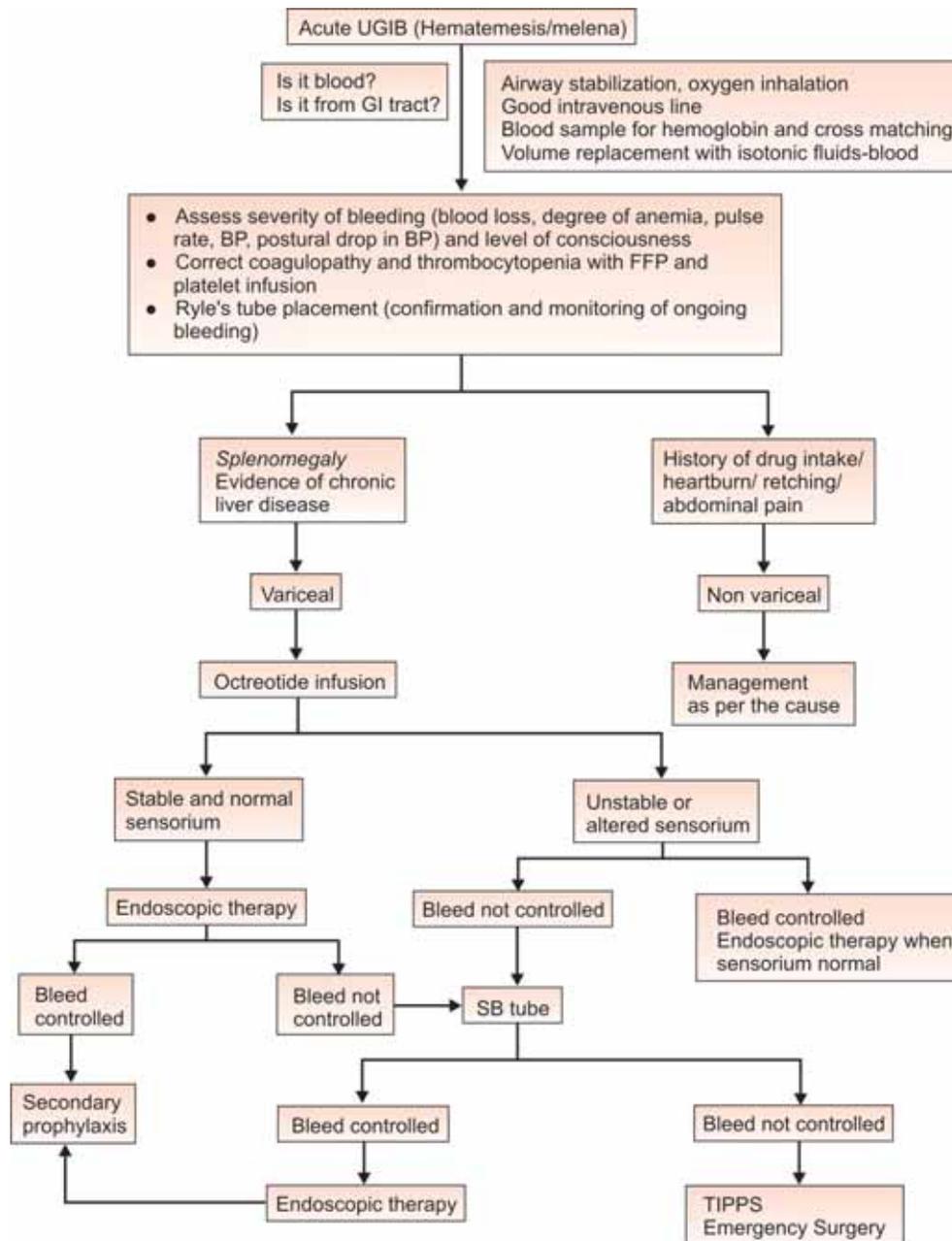
In children shock is defined as tachycardia with signs of decreased organ or peripheral perfusion. Reduced peripheral pulses compared to central pulses, altered alertness, capillary refill time (CRT >2 sec), mottled cool extremities or decreased urine output secondary to reduced renal perfusion are signs of significant blood loss. Measurement of central venous pressure if possible is very helpful in select situations e.g. persistence of hemodynamic compromise despite volume correction and renal failure, etc. Prompt and appropriate fluid management titrated to maintain adequate blood pressure and tissue perfusion is essential.

#### 4. Is it UGIB and what is the likely cause of bleed?

Presence of hematemesis or blood on nasogastric (NG) tube aspiration confirms an UGI source of bleeding. Absence of blood on NG aspiration does not rule out an UGIB (duodenal source or intermittent bleeding from stomach/esophagus can be a cause). Elevated blood urea nitrogen due to absorption of intestinal blood also points to an UGI source.

History of drug ingestion like aspirin/NSAID/steroids/anticoagulants, presence of heart burn/

Flow chart 27.1: Treatment of acute upper gastrointestinal bleeding (UGIB)



regurgitation/abdominal pain, foreign body ingestion /corrosive intake, jaundice, blood transfusion, surgery in the past, previous episodes of hematemesis, family history of peptic ulcer/ inflammatory bowel disease provide clues to diagnosis. Presence of pain points towards esophagitis, gastritis or ulcer disease whereas painless bleeding is typical of variceal bleed.

*A detailed systemic examination is essential:* Presence of splenomegaly points towards portal hypertension (PHT). EHPVO and cirrhosis are the two main causes of PHT in children with EHPVO being more common. A child presenting with recurrent episodes of well tolerated bleed (without liver decompensation) points towards EHPVO whereas presence of jaundice, ascites,

and encephalopathy suggests a diagnosis of chronic liver disease. Peter et al showed that variceal bleeding in absence of jaundice had an accuracy of 97.5% in diagnosing EHPVO on logistic regression analysis<sup>6</sup>. In PHT the spleen may reduce in size and thus be non palpable, just after a bout of hematemesis. Skin should be inspected for petechiae, purpura, spider angioma and hemangioma.

**Investigations are aimed at establishing the site, severity and cause of bleeding. These can be broadly divided into:**

**A. To determine the severity of bleeding**

1. Hematocrit (Hct) is done every 6 hrs at least for the first 2 days to assess severity of blood loss.<sup>7</sup> Fall in hemoglobin (Hb) is documented only after few hours once hemodilution has occurred.
2. Blood grouping and cross matching.

**B. To determine the cause of bleeding**

1. **Coagulation** (PT/APTT) can be deranged in DIC/liver disease.
2. **Complete blood count including platelet count**-Thrombocytopenia is seen in idiopathic thrombocytopenic purpura, DIC and PHT due to hypersplenism. Evidence of pancytopenia may suggest bone marrow suppression.
3. **Liver function tests**/urea/creatinine/electrolytes.
4. In a neonate **Apt test** is useful to differentiate fetal and swallowed maternal blood.
5. **UGI endoscopy** is done after the patient is hemodynamically stable. General anesthesia or conscious sedation with midazolam and ketamine is used. Protection of airway is very important as risk of aspiration is high when the patient is actively bleeding. **It is the most useful investigation both for evaluating the cause and also treating the lesion.**<sup>8</sup> It is important to remember that the maximum yield of endoscopy in terms of determining etiology is when it is done within 48 hours of the acute event.

*The common reasons for missing lesions are as follows:*

- Lesion not actively bleeding
- Lesion obscured by blood
- Pallor of lesion due to anemia and volume contraction.

The lesions located in upper part of fundus, posterior and inferior wall of duodenum, high up on the lesser curvature, anastomotic site (gastrojejunostomy) and hiatus hernia are often missed and hence a complete examination with retroflexion to inspect the fundus and gastroesophageal junction is essential.

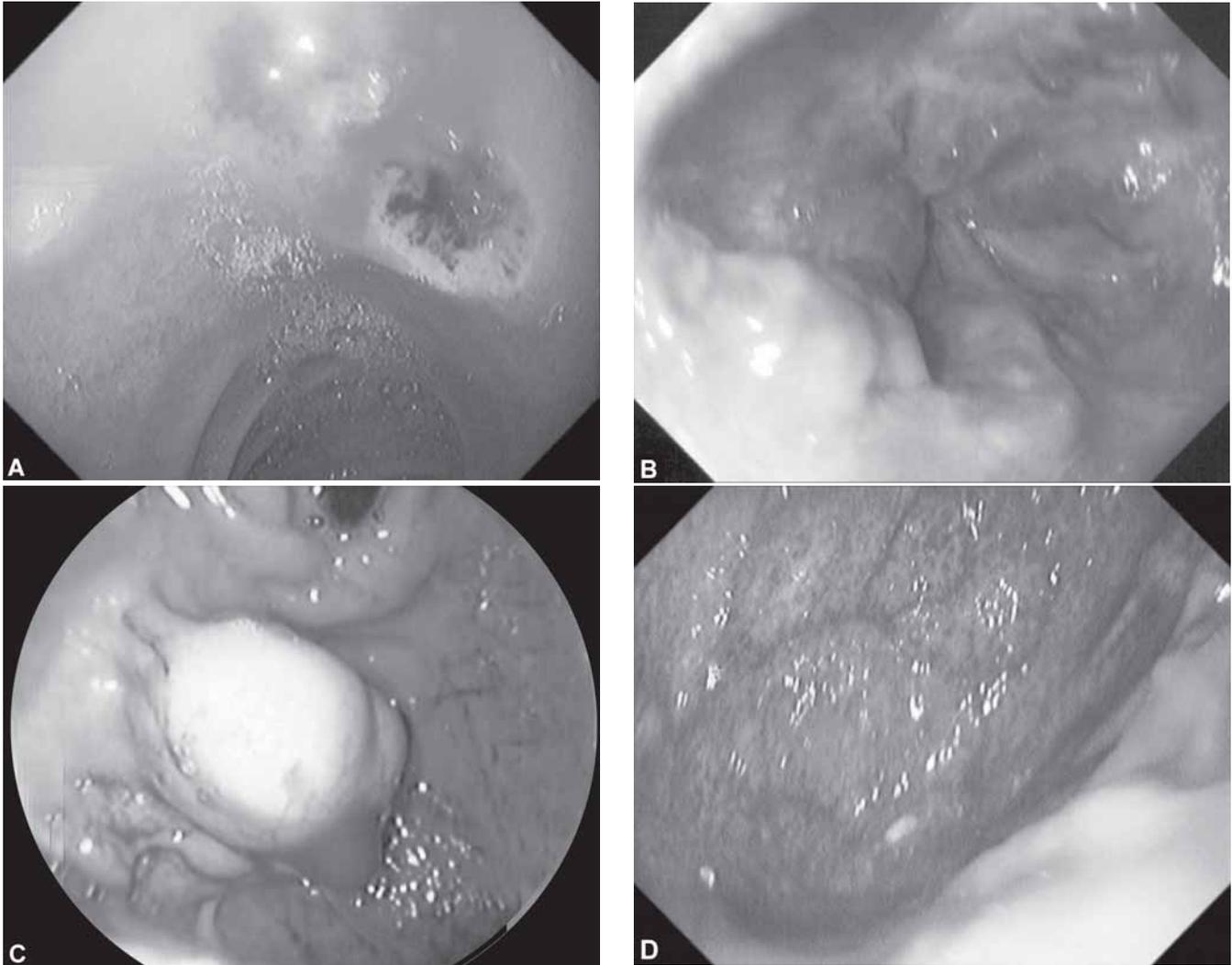
UGI endoscopy is a safe procedure with complications largely due to sedation in diagnostic endoscopy<sup>9</sup> or procedure related (aspiration, bleeding, perforation) in therapeutic endoscopy. The endoscopic appearance of some of the common causes of UGIB is shown in Figures 27.1A to D.

6. **Ultrasound abdomen** helps in confirming presence of portal hypertension and likely etiology of PHT, i.e. chronic liver disease or EHPVO. It is also helpful in subjects with hematemesis and associated mass lesions.
7. **Selective angiography** of celiac trunk may be done occasionally when vascular lesions are suspected and in subjects with hemobilia. On angiography, the pick up of lesions is better if the bleeding is at a rate of >0.5 ml/min. The extravasation of contrast into the GI tract indicates a bleeding lesion and an arteriovenous malformation is identified by an early venous filling. Angiography has the advantage of simultaneous therapy in the form of coil/gel embolization of the abnormal bleeding vessel.
8. **Nuclear scintigraphy (technetium labeled pertechnetate scan)** is rarely required in subjects with history of UGIB. A duplication cyst of proximal gut presenting with UGIB may be picked up on scintigraphy.

Once the cause of bleeding is identified, the management is done accordingly. The condition of the child dictates the rapidity and approach to diagnosis. In a child with minor bleed the priority is towards determining cause of bleed electively whereas in a subject with massive bleed, hemodynamic stabilization is the priority followed by diagnostic and therapeutic procedures.

**General Supportive Measures**

1. **Good venous access:** Intake output monitoring, oxygen inhalation, vital charting.
2. **Hemodynamic resuscitation:** Blood transfusion and crystalloid/colloid infusion for maintenance and replacement of losses.
3. Correction of coagulopathy and thrombocytopenia by FFP (fresh frozen plasma) and/or platelet transfusion if indicated.
4. Correction of electrolyte and acid base abnormality.
5. Placement of nasogastric (NG) tube to look for presence of fresh/altered blood and evidence of active and ongoing bleeding. NG tube should be left in site for gravity drainage to detect any recurrence



**Figs 27.1A to D:** Endoscopic appearance of common causes of upper gastrointestinal bleeding—(A) Duodenal ulcer with bleed, (B) Esophageal varices with red color signs, (C) Gastric varices with ongoing ooze, (D) Diffuse gastritis (For color version see plate 1)

of bleed for 24 hours and vigorous NG suction should be avoided to prevent mucosal trauma.

### Specific Treatment

**UGI bleeding** can be broadly subdivided into two groups: variceal and non-variceal for the purpose of therapy.

### Variceal Bleeding

Esophageal varices are the commonest cause of UGI bleed. Other causes of bleed in a child with PHT include gastric varices, congestive gastropathy and gastric antral vascular ectasia (GAVE). Large esophageal varices (grade III-IV) with red color signs (cherry red spots, red whale marking) are considered

as high-risk varices. The various therapeutic options to stop bleeding<sup>10</sup> are discussed below. The choice of therapy depends on the availability of options, condition of the patient and expertise of the treating physician.

### Pharmacological Therapy Recommended in Children

#### *Somatostatin and Octreotide*

These drugs act by reducing the splanchnic and azygous blood flow and thus reducing the variceal pressure. They also reduce the gastric secretion. The drug dosages are shown in Table 27.3. Infusion should be given for at least 24-48 hours after the bleeding has

**Table 27.3: Drugs used for upper GI bleed<sup>35,36</sup>**

Drug	Dose and comments
Ranitidine	PO 2-4 mg/kg/d BD-TID, max 10 mg/kg/d (300 mg) IV 2-4 mg/kg/d 6-8 hrly
Sucralfate	0.5-1.0 g PO 6 hrly
Proton pump inhibitors	Omeprazole 0.7-3.3 mg/kg/d OD or BD Lansoprazole 15 mg/d if wt <30 kg; 30 mg if wt >30 kg Esomeprazole 10 mg/d if wt <20 kg; 20 mg if wt >20 kg PPI infusion for ulcer bleed: IV pantoprazole 2 mg/kg (max 80 mg) loading followed by 0.2 mg/kg/hr infusion (max 8 mg/hr)
Octreotide	1 µg/kg bolus and then 1 µg/kg/hr infusion, max 5 µg/kg/hr
Somatostatin	250 µg bolus and then 250 µg/hr infusion in adults; pediatric dose not established
Vasopressin infusion	0.002 U/kg/min to a max of 0.01 U/kg/min
Anti <i>H. pylori</i> treatment	
Amoxicillin	↑ 20 mg/kg/dose (max 1000 mg), twice a day
Clarithromycin	↑ 7.5 mg/kg/dose (max 500 mg), twice a day
PPI	as above

stopped to prevent recurrence and care should be taken not to stop the infusion abruptly. Somatostatin and octreotide are equally effective and limited studies in children have shown bleed control in 64-71% cases.<sup>11,12</sup> In India octreotide is preferred due to cost factor. This therapy is well tolerated, with mild side effects like hyperglycemia, abdominal discomfort, nausea and diarrhea.

### Indications

1. As an initial therapy and during transportation to a specialized center to control acute variceal bleeding.
2. In a cirrhotic who has developed encephalopathy following bleeding and thus cannot be subjected to endoscopic treatment.
3. Patients with bleeding from gastric/ ectopic varices.

### Vasopressin

Acts by increasing the splanchnic vascular tone and thus reducing portal blood flow.<sup>12, 13</sup> It has a half life of 30 min and usually is given as an initial bolus followed by continuous intravenous infusion. Doses are as shown in Table 27.3. It is effective in about 50 per cent of children with variceal bleeding. Hypertension, seizures and cardiac arrhythmia are the side effects.

## ENDOSCOPIC THERAPY

### Esophageal Varices

#### Endoscopic Sclerotherapy (EST)

A skilled person and use of appropriate sized fiber optic endoscope is essential for a successful procedure. The

varices are inspected, their location, size and extent are documented and a flexible needle is inserted through the endoscope to inject 2-3 ml of sclerosant (1% ethoxysclerol, 3% phenol, 0.5-1% sodium tetradecyl sulphate) into each variceal column. At each session, all columns are injected. Following emergency EST, the varices are then electively injected at 2-3 weeks interval until all varices are eradicated (no varices). Emergency EST is very effective (>90%) in controlling esophageal variceal bleed.<sup>14,15</sup>

Transient fever and retrosternal discomfort are the commonest complaints post-sclerotherapy and is observed in nearly 30% cases. Major complications include esophageal ulceration (13-32%), perforation (1-1.4%), and later stricture esophagus (4.3-18%).<sup>15-17</sup>

#### Endoscopic Variceal Ligation (EVL)

EVL is done with a device called multiple band ligator that is attached to the tip of the endoscope. The variceal column is sucked into the outer cylinder and the band is deployed by pulling the trip wire around a part of mucosa containing the varix. All variceal columns are ligated in a spiral fashion. One or two bands are applied to each varix in the distal esophagus.

A superficial ulcer develops when the rubber band and necrotic ligated tissue sloughs which heals spontaneously. As the currently available ligators can only be applied to adult size scopes, EVL can only be performed in children > 3 years of age. EVL is not possible in small varices (grade I) and these can be tackled by EST during eradication therapy. Use of sedation/general anesthesia is helpful to minimize the

risk and increasing the ease of procedure. EVL has been shown to have a 90-100% efficacy in controlling bleed.<sup>18</sup>

Retrosternal discomfort and transient dysphagia to solids may develop after EVL. In a randomized controlled trial of EST vs EVL in children by Zargar et al,<sup>14</sup> the efficacy of controlling bleed and rate of variceal eradication was similar in both the groups (100% in both) and (96% EST vs 91.7% EVL) respectively but overall EVL was better as it required lesser number of sessions (3.9 vs. 6.1), had lower re-bleeding (4% vs. 26%) and complication rate (4% vs 25%). EVL does not cause stricture formation.

### Gastric Varices

These are known to bleed more severely but less often than esophageal varices. Moreover the bleed from gastric varices is more difficult to control and associated with higher rebleed rate than esophageal varices. Endoscopic injection of the tissue adhesive (glue) N-butyl 2 cyanoacrylate (marketed in India as Nectacryl) or isobutyl 2 cyanoacrylate is used for gastric varices. These two agents are tissue adhesives that harden within 20 seconds of contact with blood, and lead to more rapid control of active bleeding than is possible with conventional sclerosants. Injections of 0.1 to 1.0 ml of glue are given into a bleeding varix depending upon the size of varix.

Rebleed due to sloughing and ulceration after glue injection may occur. There are very few studies regarding efficacy of glue injection for gastric varices in children.<sup>19,20</sup> In our experience glue injection is safe and highly effective in control of acute gastric variceal bleeding.

In children EHPVO is the commonest etiology and the first line treatment therapy should be endoscopic if expertise is available and the patient is stable and conscious.

### Tamponade of Varices

Sangstaken-Blakemore tube (SBT) is a triple lumen tube with connection to an esophageal balloon, a gastric balloon and one perforated distal end which helps in aspiration of the stomach contents. Experience, choice of right sized tube and observation of simple precautions ensures success of this procedure.<sup>21,22</sup>

*Technique of placement:* An appropriate sized, pediatric SBT is passed through the nose into the stomach. Thereafter, the gastric balloon is inflated with 75-150 ml of air depending on the size of the patient (stomach) and the tube is gently pulled outward till it sits snugly

against the upper dome of stomach and diaphragm and secured safely to the nose. If the bleeding persists, the esophageal balloon is inflated with an air pressure of 20 mm Hg and maintained and monitored with the help of a sphygmomano-meter.

*Precautions:* Plain X-ray film should preferably be taken to check the right placement of gastric balloon in the stomach. The procedure should be done gently and carefully to avoid injury to mucosa. Gastric contents should be allowed to drip under the effect of gravity and without the application of negative suction. Secretions tend to accumulate above the inflated esophageal balloon and these should be removed with a catheter. The esophageal balloon should be deflated after 12-24 hours and the stomach irrigated to watch for the extent of bleeding. If bleed continues, the balloon compression is re-instituted for another 8-12 hours.

Failure to control the bleeding with SBT occurs if bleed is due to gastric varices or duodenal varices. It is a simple, relatively cheap and requires little skill vis-à-vis endoscopic therapy. Efficacy of controlling acute variceal bleed is around 75%. Esophageal necrosis and perforation, pulmonary aspiration and rebleed on deflation of balloon are important complications. Linton Nachlas tube has a larger gastric balloon and is used for tamponade of gastric varices.

### Transjugular Intrahepatic Portosystemic Shunt (TIPSS)

In this procedure a skin puncture is made in the neck and a multipurpose catheter is placed into the jugular vein and superior vena cava. The catheter is then advanced via hepatic vein into a branch of portal vein through the hepatic parenchyma. This track is dilated by a balloon and an expansile metallic mesh prosthesis is placed to maintain the communication directly between the portal vein and hepatic vein. This bypasses the liver resistance and consequently decreases the portal pressure. There is limited experience in children.<sup>23</sup> It is indicated only when the esophageal/gastric variceal bleeding cannot be controlled by medical or endoscopic measures. Overall success rate of the procedure is about 75-85% in children,<sup>24</sup> with abnormal vascular anatomy being a common cause of failure. Control of variceal bleeding varies from 80-90%.

Adverse events include precipitation of encephalopathy in subjects with cirrhosis and shunt occlusion. TIPSS placement is expensive and needs expertise which is available only in a few centers in India. Fortunately this procedure is needed less often in children who mostly have EHPVO and in whom the

bleed is usually controlled easily. In cirrhotics it serves best for a short period of time till liver transplantation is done.

### Surgical Management

Emergency surgery is the only option available in situations where endoscopic and medical therapy fails. It is also required when bleeding is from ectopic varices which are beyond the reach of endoscopic procedures. Two types of surgical options are available for variceal bleeding: portacaval shunts (selective or nonselective) or devascularization with esophageal staple transaction. The results of shunt surgery have improved in the last decade and reports have confirmed efficacy of shunt surgery in children with PHT.<sup>25</sup> Rex- shunt is a physiological shunt and in this a jugular autograft is placed between the left branch of portal vein and superior mesenteric vein in EHPVO subjects. It maintains the hepatopetal blood flow,<sup>26</sup> but it may not be feasible in all due to lack of favorable vascular anatomy or non-availability of expertise. Shunt surgery is not done in subjects with poor hepatic function due to risk of precipitating hepatic encephalopathy.

### Secondary Prophylaxis

After control of acute variceal bleeding secondary prophylaxis is a must to prevent recurrence of bleeding. Beta blockers, EST and EVL are the options available for secondary prophylaxis. There is limited data on efficacy of propranolol in children for secondary prophylaxis<sup>27, 28</sup> and thus generalized use for children cannot be recommended. Until more evidence is available a cautious use of beta blockers in select situations may be offered. Currently endoscopic treatment is preferable, with EVL being better than EST. Regular follow-up is required even after eradication of esophageal varices as there is a risk of esophageal variceal recurrence and appearance of gastric varices and/or portal hypertensive gastropathy in these patients.

### Non-variceal Bleeding

Esophagitis, ulcers or erosions due to stress (from surgery, burns, viral illness, increased intracranial hypertension, and multiple organ failure), medications, ischemia and trauma from foreign bodies are important causes of non-variceal bleed. Medications were the possible risk factor for UGIB in 20% in a study from China.<sup>29</sup> Thus checking for intake of drugs like NSAIDs, steroids, aspirin etc and stopping their intake is a must. Primary duodenal or gastric ulcers are not so common

in Indian children although they are the commonest cause of UGIB in the West.<sup>5,29</sup>

A meticulous UGI endoscopy can diagnose most of the lesions. The endoscopic appearance of the ulcer is of great prognostic value and helps in determining need for endoscopic therapy. Ulcers with active bleed (spurting/oozing), visible vessel or adherent clot should be treated endoscopically to reduce risk of rebleeding and improve outcome. Whereas ulcers with clean base or pigmented spots are considered “low risk” and managed with medical therapy alone. Endoscopic biopsy should be taken in all cases with esophagitis, gastritis or duodenitis. Antral biopsies are taken for *Helicobacter pylori* in subjects with peptic ulcers for rapid urease test, culture, Gram staining and histology.

## TREATMENT

### Medical Therapy

- In subjects with diffuse mucosal bleed, the aim is to increase the pH of the stomach by neutralizing the acid with proton pump inhibitors (Table 27.3).
- Adequate duration therapy with proton pump inhibitors is required for gastroesophageal reflux disease.
- Anti *Helicobacter pylori* medications are essential for *H. pylori* eradication and preventing ulcer recurrence in subjects with *H. pylori* positive ulcer disease.
- Specific antifungal and anti-viral therapy is required for infectious esophagitis depending on the cause.
- Stoppage of milk and milk products is required for infants with UGIB due to cow's milk allergy.
- Proton pump inhibitors are used initially as intravenous infusion for 72 hours followed by oral administration in patients presenting with bleeding peptic ulcers.

### Endoscopic Therapy

Endoscopic treatment is effective in patients with actively bleeding ulcers.<sup>30</sup> About 15% children with ulcers require endoscopic therapy to control bleeding.<sup>29</sup> Injection, electro-coagulation, endoclip and heater probe are all equally effective and are indicated for ulcers with active bleed/visible vessel or adherent clot.<sup>31</sup> Adrenaline and hypertonic saline are preferred for injection therapy.

Hemoclips can be applied on vessels, e.g. Dieulafoy's ulcer (caliber persistent large submucosal artery) to stop the bleeding.

Argon plasma coagulation (APC) is a non-contact form of monopolar coagulation and it has the advantage of limited depth of penetration. In a study

of 12 children (0.05–17 yr) with GI bleed,<sup>32</sup> the bleed was controlled in 8 (66%) and transfusion requirement was decreased in 3 (25%) subjects. It is a very useful method for controlling bleed from vascular lesions, gastric antral vascular ectasia (GAVE) and radiation gastritis.

**Preventive measures:** In the following situations it is useful to give treatment for prevention of the first bleed or its recurrence:

1. Children in intensive care unit (ICU) — Stress associated mucosal damage and bleeding is a well known problem in the critically ill child. In a recent study, nearly half of the children on mechanical ventilation for > 48 hours had evidence of UGI bleed, although significant bleed was seen only in 3.6%<sup>33</sup> ICU patients with coagulopathy, respiratory failure and high PRISM (pediatric risk of mortality score >10) are at an increased risk of bleeding. Prophylactic acid neutralizing therapy with H<sub>2</sub>RA or sucralfate has been shown to be helpful in reducing risk of bleed.<sup>34</sup>
2. Secondary prophylaxis for variceal bleed as discussed above. Prophylaxis for spontaneous bacterial peritonitis should be given to children with cirrhosis and ascites with third generation cephalosporin.<sup>7</sup> Cirrhotics who develop hepatic encephalopathy after variceal bleeding should be treated with lactulose.
3. Peptic ulcer—*H. pylori* eradication therapy to prevent ulcer recurrence. In bleeding ulcers a repeat endoscopy to document healing of ulcer is important.

### Conclusion

Acute UGIB is a potentially serious problem in children and presents with hematemesis or melena. As the causes of UGIB vary with age, it is important to evaluate children for the age specific etiologies. Esophagitis, gastritis and varices are the commonest causes of UGIB in Indian children with peptic ulcer disease being uncommon. The approach to diagnosis is largely dictated by the child's condition. Prompt hemodynamic stabilization is of utmost importance and physical examination and blood investigations are done simultaneously. UGI endoscopy is the most useful diagnostic and therapeutic tool for children presenting with UGIB. Medications like octreotide and PPI are useful in variceal and ulcer bleed respectively with surgery being reserved for cases with continued bleed and failure of endoscopic therapy.

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# 28 Hematologic Emergencies

Tulika Seth

Many critically ill children present with serious hematological manifestations. These emergent situations may arise from a pre-existing hematologic disorder or they may be acquired due to the illness which has affected the hematologic parameters. All hematopoietic cell lines may be affected and the balance of pro and anticoagulant pathways can be adversely perturbed (Table 28.1). Appropriate and timely treatment contributes to a successful outcome, hence every pediatrician needs to be aware of and be able to manage these conditions.

The conditions which will be described in the chapter are important clinical problems encountered in common pediatric practice and in the intensive care unit such as evaluation of a bleeding child, disseminated intravascular coagulation, thrombosis, blood transfusion reactions, crisis in sickle cell anemia patients and severe hemolysis. An outline of other intensive care issues which occur in critically ill children or in children

with preceding hematologic disease are given in Tables 28.2 and 28.3 respectively.

## BLEEDING CHILD

Bleeding is a common problem in many ill or even apparently well looking children. Bleeding can be caused by thrombocytopenia, medications which interfere with platelet function, inherited coagulation factor defects or platelet function disorders, disseminated intravascular disorder, von Willebrand disease, etc. It is important to rule out bone marrow failure or underlying malignancy; as they require urgent identification and treatment.

Children with bleeding may have an inherited or acquired defect. A detailed bleeding history is an essential part of the work up, this includes child's age at presentation, sex, clinical manifestation, past history and family history, response to prior trauma, minor surgery and medications. A detailed description of type of bleeding, sites, seriousness of bleeds and need for prior intervention for bleeding episodes is required. Tables 28.4 and 28.5 for different types of bleeding and factors to differentiate inherited versus acquired causes of bleeding. This helps in speedy evaluation and identification of the possible defect in coagulation mechanism and other relevant diagnostic tests.

Mucocutaneous bleeding (i.e. petechiae, purpura, epistaxis and oral bleeding) is characteristic of platelet and blood vessel disorders. Soft tissue, muscle or joint hematomas are suggestive of coagulation factor deficiency like hemophilias. Early childhood bleeding occurs most frequently in congenital disorders, while a later presentation is more likely to be associated with acquired disorders. A child who is clinically ill may have sepsis and disseminated intravascular coagulation (DIC).

A complete history is followed by laboratory evaluation. Initial laboratory evaluation includes a complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), and a 1:1 mixing study. The 1:1 mixing study helps to identify

**Table 28.1: Hematology parameters that may be deranged and result in serious complications**

1. Hemostatic disorders
  - a. Disseminated intravascular coagulation
  - b. Bleeding—thrombocytopenia, platelet dysfunction, coagulation factor deficiency
  - c. Thrombosis arterial or venous
2. Red blood cell
  - a. Severe anemia
  - b. Hemolysis due to sepsis, autoimmune hemolytic anemia, transfusion reaction, drugs, Glucose 6 phosphate dehydrogenase deficiency,
  - c. Paroxysmal nocturnal hemoglobinuria
  - d. Aplastic crisis- drugs, infections
3. White blood cell
 

Neutropenia—drugs, sepsis, aplastic and infiltrative disorder

Leukemoid reaction

Blast crisis of chronic myeloid leukemia

Acute leukemias
4. Others—Thrombotic thrombocytopenic purpura, hemophagocytic syndrome

**Table 28.2: Hematological complications in critically ill children**

<i>Underlying condition</i>	<i>Complication</i>	<i>Intervention</i>
1. Trauma, hemorrhage, hemolysis, drugs that cause hemolytic anemia (penicillins, rifampicin, sulphonamides, INH etc.), chronic renal failure, acute /chronic disease e.g. systemic lupus erythematosus, rheumatoid arthritis, etc.	Anemia	Identify cause and give specific therapy. Supportive care includes— blood transfusion if severe anemia or hematinics, or erythropoietin if indicated
2. i. Disseminated intravascular coagulation ii. Liver and renal insufficiency, vitamin K deficiency iii. Over heparinization, drug induced thrombocytopenia (heparin, valproic acid, vancomycin, linezolid, etc), heparin induced thrombocytopenia (HIT) iv. Post surgery especially post neuro-surgery, massive transfusion, postpartum hemorrhage v. Acquired inhibitors to factor VIII or IX.	Bleeding	Treat the cause. Blood component therapy, vitamin K, stop offending drug, fresh frozen plasma and cryoprecipitate for dilutional bleeding. For acquired inhibitors- Novoseven and immunosuppressive therapy
3. Prolonged bed rest, postoperative, venous access devices, newborns, post pregnancy deep vein thrombosis	Deep vein thrombosis, pulmonary embolism	Low molecular or unfractionated heparin, evaluate cause and treat appropriately
4. Hemolytic uremic syndrome	Thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction	Supportive care
5. Thrombotic thrombocytopenic purpura	Thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities	Plasmapheresis, fresh frozen plasma avoid platelet transfusions
6. Sepsis, medications	Leukopenia, or bone marrow suppression	Aggressive antimicrobial support
7. Congenital heart disease	Platelet function defect, polycythemia	Anticoagulation therapy

deficiency or inhibitor of a factor. A bleeding time is useful but needs to be done properly to ensure its validity, platelet function studies should be done after excluding all anti-platelet medications. Serious bleeding episodes include intracranial, massive gastrointestinal, bleeding in neck and retroperitoneal bleeds, these sites of hemorrhage may not be diagnosed easily and can lead to shock and even death.<sup>1</sup>

### Mucocutaneous Bleeding

A low platelet count with other complete hemogram parameters being normal, normal PT/aPTT and with large platelets on the peripheral smear, suggests a diagnosis of idiopathic thrombocytopenic purpura (ITP). Idiopathic or immune thrombocytopenic purpura (ITP) is a fairly common condition in children, frequently following a viral infection. The peak age of

occurrence of acute ITP is 2-4 years. In ITP an anti-platelet antibody is produced, typically IgG, against a platelet antigen, e.g. GPIIb/IIIa. The child may have a viral prodrome 10-14 days prior to the presentation. The bleeding symptoms include increased bruising, petechiae and epistaxis. Apart from this the child is typically clinically well.<sup>2-4</sup> Once the diagnosis is established by clinical and laboratory evaluation, then treatment to prevent intracranial hemorrhage and to stop active bleeding may be initiated. Children with mild thrombocytopenia may need only observation (Tables 28.6 and 28.7).

### Risk Factors for Mortality in Immune Thrombocytopenic Purpura

Mortality in patients with acute immune thrombocytopenic purpura (ITP) is rarely encountered,

**Table 28.3: Critical care problems in known hematology and hemat oncology patients**

<i>Underlying condition</i>	<i>Complication</i>	<i>Special note</i>
1. Leukemias, lymphomas, prolonged steroid therapy, post splenectomy, hematopoietic stem cell transplant patients on immunosuppression	Sepsis, fever neutropenia (FN), typhilitis, pneumonias (bacterial, fungal, PCP, CMV)	FN is a life threatening emergency, urgent antibiotics and hospitalization. Post-splenectomy at risk for infection with encapsulated organisms. Patients on steroids may not have fever.
2. Post-chemotherapy, aplastic anemia	Neutropenic mucositis	Antibiotics, may try granulocyte colony stimulating factor
3. Leukemias, other malignancies post chemotherapy, aplastic anemia, thrombocytopenia, Hemophilia A or B, von Willebrand's disease, platelet dysfunction disorders, rare factor deficiency, hypersplenism	Bleeding, intracranial hemorrhage, joint bleed, mucosal bleeding (epistaxis, oral, purpura), menorrhagia	Initial management is hemodynamic stabilization, then promptly find cause of bleeding. Appropriate therapy, e.g. single donor platelet, intravenous immune globulin, factor VIII or IX, fresh frozen plasma
4. Leukemias, Kasabach-Merritt syndrome	Disseminated intravascular coagulation	Supportive care, treat cause
5. Aplastic anemia, myelodysplastic syndrome, megaloblastic anemia	Pancytopenia	A bone marrow examination may be needed to identify cause and treat appropriately
6. Thalassemia major	Cardiac and liver failure due to iron overload, aplastic crisis due to parvo B19, megaloblastic crisis due to folate insufficiency	
7. Thalassemia intermedia	Thrombosis, hypersplenism, pulmonary hypertension, extra-medullary hematopoiesis	
8. Sickle cell anemia	Pain crisis, acute chest syndrome, stroke, aplastic crisis due to parvo B19, splenic sequestration, asplenic sepsis	
9. Thrombophilias, e.g. antiphospholipid antibody syndrome, factor V leiden, deficiency of protein C,S	Deep vein thrombosis,	Specific tests for etiology may be delayed, early therapy reduces sequelae
10. Paroxysmal nocturnal hemoglobinuria	Hemoglobinuria, anemia	May result in severe hemolysis
11. Autoimmune hemolytic anemia, congenital dyserythropoietic anemia, pure red cell anemia, hemolytic anemias e.g. G6PD deficiency	Anemia	May require transfusion support along with specific therapy
12. Chronic myeloid leukemia, polycythemia vera (PV), essential thrombocytosis (ET)	Priapism, hyperleucocytosis. Hyperviscosity, venous thromboembolism (5x more common in PV), hemorrhage, arterial thrombosis (usually in ET)	Emergent management to prevent deformity and cytoreduction

PCP = Pneumocystis carinii, CMV = Cytomegalovirus, APLA = Antiphospholipid syndrome

**Table 28.4: Differences in clinical presentation of mucosal and deep bleeding**

<i>Differentiating features</i>	<i>Mucosal bleeding</i>	<i>Deep bleeding</i>
1. Site of bleeding	Skin, mucous membranes (epistaxis, gum, vaginal, GI tract)	Deep in soft tissues (joints, muscles)
2. Petechiae	Yes	No
3. Ecchymoses (bruises)	Small, superficial	Large, deep
4. Hemarthrosis/muscle bleeding	Extremely rare	Common
5. Bleeding after cuts and scratches	Yes	No
6. Bleeding after surgery or trauma	Immediate, usually mild	Delayed (1-2 days) often severe
7. Cause	Platelet deficiency or functional defect	Coagulation factor disorders

**Table 28.5: Hints to differentiate acquired from inherited bleeding disorders**

	<i>Inherited</i>	<i>Acquired</i>
1. Frequency	Less common	More common
2. Family history	Present/Absent	Absent
3. Manifestations in early Infant/childhood	Bleeding present	Rare
4. Previous hemostatic challenges	Increased bleeding	Well tolerated
5. Recent onset, or concurrent illness	No	Yes

**Table 28.6: Clinical staging of immune thrombocytopenic purpura**

<i>Platelet count per <math>\mu\text{L}</math></i>	<i>Clinical bleeding</i>	<i>Stage</i>
> 20,000 per $\mu\text{L}$	None	I
10,000–20,000 per $\mu\text{L}$	petechiae, purpura only	II
10,000–20,000 per $\mu\text{L}$	mucosal bleeding-epistaxis, gingival bleeding, hematuria or melena	III
< 10,000 per $\mu\text{L}$	other sites of bleeding	IV

Modified from Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood* 2005 Oct 1;106 (7): 2244-51.

**Table 28.7: Management of idiopathic thrombocytopenic purpura**

<i>Stage</i>	<i>Management recommendation</i>
I	Observe; Avoid antiplatelet agents and trauma
II	Observe; Treat prior to surgery or other situations where bleeding is expected
III	Treat with IVIG, anti D
IV	Treat with IVIG, anti D

Modified from Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP) *Blood* 2005 Oct 1;106(7): 2244-51.

however relapsed and refractory ITP may suffer major hemorrhagic episodes such as intracranial bleeds, and chronic ITP children may suffer severe infections due to prolonged steroid use or post-splenectomy sepsis. A number of risk factors have been associated with mortality in these patients, which can help identify those who require closer monitoring or more aggressive therapy. The risk factors of serious complications in children are (1) chronic course refractory to standard therapies (2) history of significant bleeding. (3) structural lesion in CNS or GI tract. (4) concomitant bleeding disorder, e.g. uremia, von Willebrand, etc.<sup>2-4</sup>

### Treatment

Treatment is not indicated for ITP cases with platelet counts greater than 20,000 without active bleeding. If the platelet count is less than 20,000 or if the patient has active bleeding, particularly from the mucous membranes, then give IVIG, 1 g/kg for 1-2 days. Other therapies may include Win-rho (anti-D antibody) 75 mcg/kg IV or steroids (prednisone, dexamethasone or methylprednisolone). Our practice is to perform bone marrow aspirate and biopsy prior to initiating steroids, due to a very small risk of steroids masking acute leukemia. Platelet transfusions are usually ineffectual, since the platelet survival is shortened, but

**Table 28.8: Criteria for significant mucocutaneous bleeding**

- Presence of one or more of the following:
1. Recurrent, prolonged nose bleeds, oral cavity or other mucosal requiring medical treatment and/or causing anemia.
  2. Oral cavity bleeding which lasts for more than one hour or recurrent bleeding.
  3. Prolonged or recurrent skin laceration bleeding with
    - a. Prolonged bleeding associated with or following a dental procedure.
    - b. Spontaneous gastrointestinal hemorrhage unexplained by local cause that requires medical attention and/or leading to anemia
    - c. Menorrhagia requiring medical attention and/or leading to anemia

Modified from Dean JA, Blanchette VS, et al. *Thromb Haemost* 2000;84:401-09.

may be given with steroids to manage serious bleeding episodes.

### Other Causes of Mucosal Bleeding

If there is mucosal bleeding with no thrombocytopenia, or only mild thrombocytopenia with bleeding, then other causes of mucosal bleeding such as acquired or inherited platelet dysfunction, uremia or drugs should be looked for. Severe mucosal bleeding criteria are given in Table 28.8. The diagnosis can be difficult to assess in a critically ill child. The urgent need is to stabilize the child, give platelet transfusion to stop bleeding. If possible send baseline coagulation, platelet function, renal and hepatic studies prior to platelet transfusion. Special care needs

to be taken when evaluating neonatal hematologic parameters (Table 28.9).

### Other Causes of Thrombocytopenia

In pediatric patients with cancer, aplastic anemia or severe sepsis, thrombocytopenia may result from underproduction or excessive consumption of platelets. Although thrombopoietin has strong positive effects on platelet production and has been used in clinical trials, platelet transfusions remain the primary treatment for thrombocytopenia. Platelet transfusions are used as prophylaxis and as a treatment for bleeding. Avoid platelet transfusion in the absence of bleeding if thrombocytopenia is secondary to platelet consumption. Consider empiric platelet transfusion in patients with platelet counts  $< 10 \times 10^9 \text{ L}$  ( $< 10,000/\text{mm}^3$ ) if thrombocytopenia results from underproduction.

Consider empiric platelet transfusion in patients with platelet counts  $< 15\text{-}20 \times 10^9 \text{ L}$  ( $< 15,000\text{-}20,000/\text{mm}^3$ ) if they have acute myeloid leukemia (AML) and are receiving induction chemotherapy. Transfuse platelets in any patient with overt bleeding and a platelet count  $< 50 \times 10^9 \text{ L}$  ( $< 50,000/\text{mm}^3$ ). Platelets are available as single-donor or as pooled random-donor products. Single-donor products are preferred to limit infectious risks. One single-donor platelet pheresis unit contains approximately  $4 \times 10^{11}$  platelets and is equivalent to approximately 6 random-donor platelet units. Studies in adults with normal splenic function, indicate that a dose of 1 platelet  $\text{U}/\text{m}^2$  ( $5.5 \times 10^{10}/\text{m}^2$ ) increases the peripheral platelet count by  $10\text{-}12 \times 10^9 \text{ L}$  ( $10,000\text{-}12,000/\text{mm}^3$ ).

A rise of  $< 5\text{-}6.5 \times 10^9 \text{ L}$  ( $< 5000\text{-}6500/\text{mm}^3$ ) for each transfused unit per square meter (i.e.  $< 50\%$  of expected)

**Table 28.9: Screening tests for neonatal hemostasis**

<i>Lab investigation</i>	<i>Special features</i>
1. Platelet count and morphology	Platelet clumping secondary to activation is common. Hence, search for fibrin strands in sample, falsely low platelet count. The morphology important for evaluating congenital platelet disorders such as Bernard Soulier, grey platelet syndrome, Wiskott Aldrich syndrome
2. Prothrombin time (PT)	Establish 'in-house' normal range. Prolonged by deficiencies of some vitamin K dependent factors.
3. Activated partial thromboplastin time (aPTT)	Establish 'in-house' normal range. Prolonged in healthy neonate because of relatively reduced levels of vitamin K dependent factors and other factors.
4. Thrombin clotting time (TCT)	Prolonged compared to adult because of fetal fibrinogen. Addition of calcium to the buffering system shortens time to adult range and increases its sensitivity.
5. Fibrinogen.	Equivalent to adult normal range, but levels rise in the first week of life.
6. Bleeding time (BT)	Rarely performed. Shorter than adult range. Modified template device for newborns is available.

on two consecutive transfusions suggests active destruction resulting from alloimmunization, which can be confirmed with a low post transfusion platelet count obtained 15-20 minutes after platelet transfusion and by the presence of anti-platelet antibodies. Anti-platelet antibodies cause platelet destruction more rapidly than other forms of consumption, and no substantive rise is noted at 15 minutes after a transfusion. No reliable predictors are available to determine which patients are most at risk for developing antiplatelet antibodies. Once present, alloimmunization requires crossmatching or HLA typing of platelets before transfusion which are extremely difficult in the Indian scenario.

### Diagnosis of Drug-Induced Thrombocytopenia

Often drug induced thrombocytopenia is suspected, the following criteria are helpful for evaluating a patient with such thrombocytopenia. Firstly rule out other causes of thrombocytopenia, e.g. hypersplenism, infection, etc. then evaluate prior history and laboratory tests to evaluate causal relationship (Table 28.10).<sup>6</sup>

### von Willebrand Disease

If the platelet count and the PT are normal and the aPTT is mildly elevated or normal, then von Willebrand disease (vWD) is a likely diagnosis, vWD must be suspected in any patient who has frequent epistaxis, easy bruising or prolonged bleeding from dental surgery. The child may even have iron deficiency anemia from chronic blood loss. vWD is the most common inherited bleeding disorder, with an estimated prevalence of 1 in 100. It is inherited as an autosomal dominant disorder, a family history is frequently elicited, however mild cases may go undiagnosed. von Willebrand factor is a carrier protein for factor VIII in fibrin clot formation. There are three major types. Types 1 and 3 are quantitative deficiencies of vW factor, and

type 2 defects are qualitative. Laboratory evaluation includes a vW factor antigen level, ristocetin cofactor activity (vW factor activity level) and factor VIII activity level. All three values are low in type 1 disease and absent in type 3 disease. Type 2 subtype has normal vW antigen levels but low vW and Factor VIII activity. Type 1 vWD may be treated with DDAVP, which releases stored von Willebrand factor from the reticuloendothelial cells. If the child is not responsive to DDAVP, then Humate-P, a factor VIII concentrate with vW factor may be given. This is required prior to surgical or dental procedures where there is a high risk of bleeding.

### Critically Ill Bleeding Child

A critically sick, bleeding patient in intensive care may have multifactorial causes for bleeding. Vitamin K deficiency, liver disease and disseminated intravascular coagulation (DIC) are common causes of bleeding in sick patients, and distinguishing between them is a common problem. Clinical scenario and laboratory values are useful to differentiate, in some intensive care situations, however, it may be required to measure levels of factors V and VII which can be helpful in separating between these conditions (Table 28.11).<sup>7</sup> It is important to check the fibrinogen level in a child who is profusely bleeding and replace with cryoprecipitate as fibrinogen is required for producing a stable fibrin clot.

### End-Stage Liver Disease

Children with end-stage liver disease have defect of hemostasis due to many factors such as: (1) nutritional deficiencies including vitamin K, ascorbic acid and protein, (2) portal hypertension (3) failure of hepatocellular function (synthetic and excretion), (4) thrombocytopenia (sequestration in spleen, DIC, sepsis, decreased production from bone marrow) (5) underlying cause for hepatic injury (toxin, infection, metabolic), and (6) drugs, platelet dysfunction and dilutional effects of transfusion which results in decreased fibrinogen production, increased fibrinolysis-decreased synthesis of antiplasmin, decreased clearance of tissue plasminogen activator, and further aggravated by DIC and factor deficiencies. Dosing of products in the bleeding child has to be continuously adjusted since the child is unstable.

### Uremic Bleeding

Patients with uremia often have a coagulopathy with oozing from puncture sites and bleeding from mucosal

**Table 28.10: Drug induced thrombocytopenia**

Criterion	Features strongly suggestive of drug induced thrombocytopenia
1.	Both of the following: <ol style="list-style-type: none"> <li>Child treated with the drug before the onset of thrombocytopenia</li> <li>Halting drug resulted in a complete reversal of the thrombocytopenia</li> </ol>
2.	Re-exposure to the drug results in recurrence of the thrombocytopenia

Modified from Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med* 2007;357:580-7.

**Table 28.11: Differentiation of common intensive care bleeding conditions using clinical scenario and factor levels<sup>7</sup>**

<i>Factor V level</i>	<i>Factor VII level</i>	<i>Diagnosis</i>
Decreased	Decreased	Hepatic dysfunction
Normal	Decreased	Vitamin K deficiency, isolated deficiency factor VII (rare)
Decreased	Normal	Disseminated intravascular coagulation (DIC), isolated deficiency factor V (rare)
Normal	Normal	Hemophilia A or B, von Willebrand's disease, platelet or vascular defect.

**Features of Vitamin K deficiency:**

1. Factors II, VII and X are also decreased
2. Response to vitamin K

**Features of DIC**

1. Fibrin degradation products
2. Thrombocytopenia
3. Reduced fibrinogen
4. No response to vitamin K

**Features of liver dysfunction (with generalized deficiency of coagulation factors):**

1. Abnormal liver function tests
2. No response to vitamin K administration

**Limitation:** For optimum benefit of this algorithm, coagulation factor levels need to be readily available. This is unlikely in clinics or small hospitals; whereas platelet counts, fibrin degradation products and liver function tests are more readily available.

Hatem CJ, Kettle WM, et al (editors). MKSAP 12: Hematology. American college of physicians and american society of internal medicine. 2001; 54.

surfaces. The causes of the bleeding are often multifactorial. A variety of therapeutic maneuvers can help control the bleeding, but some may only be effective for a short period of time. Cause of bleeding in uremia are: (1) acquired platelet dysfunction, (2) thrombocytopenia, (3) anemia, (4) increased fibrinolysis, (5) concurrent anticoagulation (e.g. heparin during hemodialysis) and (6) concurrent defects in coagulation factors (vitamin K deficiency). Therapy for platelet quantitative and qualitative defects includes: (1) dialysis (2) platelet transfusion (3) increasing von Willebrand factor availability with cryoprecipitate or desmopressin (DDAVP) and (4) avoidance of medications causing platelet dysfunction.

**Deep Bleeds**

Hemophilia A and B are X-linked inherited bleeding disorders, usually with a positive family history. These children have a prolonged PTT and normal PT. Specific factor assay needs to be done to find the deficient factor VIII or IX deficiency and its level. Undiagnosed hemophilia may present with severe bleeding post circumcision. It can also result in significant ecchymosis with minimal trauma or joint and muscle bleeding, usually in early childhood, mild hemophilia may go unnoticed till later in life. Life threatening intracranial

bleeds can occur in severe hemophilia patients. Treatment involves recombinant factor replacement with bleeding episodes (Table 28.12). Some children may develop inhibitors to factor and need to be referred to specialized centers for therapy. Rare inherited factor deficiency syndromes can present as emergencies and need early treatment (Table 28.13).<sup>1</sup>

**Elevated aPTT without Bleeding**

A prolonged aPTT may be found in otherwise normal children undergoing routine coagulation screening. This frequently is due to transient anti-phospholipid antibody from a previous or current infection. The transient anti-phospholipid antibody is confirmed by lack of the correction of aPTT with a 1:1 mixing study and a dilute Russell viper venom time (dRVVT). It normally disappears within 4 to 6 weeks after resolution of the infection. Occasionally this condition may result in thrombosis or bleeding.

**DISSEMINATED INTRAVASCULAR COAGULATION**

Disseminated intravascular coagulation (DIC) is characterized by excessive activation of blood coagulation with the consumption of clotting factors.

**Table 28.12: Guidelines for factor replacement in management of severe bleeding episodes in patients with hemophilia**

Type of bleeding	Desired level (%)	Factor dose (units/kg)		Duration of therapy**(days)
		F VIII	F IX	
• Life-threatening bleeds				
Intracranial bleed or Retropharyngeal with impending airway obstruction	100	50	100	7-10
• Major trauma	50-75	25-40	50-75	4-6
• Acute severe hemothrosis	20-30	10-15	20-30	until resolved
• Massive GI bleeds	30-50	15-25	30-50	1-3
• Hematuria severe	50	25	50	1-3
	30-50	15-25	30-50	1-7

\* These are guidelines and the dose and schedule should be modified as per severity of bleed. The duration of treatment will depend upon the individual response.

\*\* Need for factor replacement is initially high and is reduced gradually depending upon the response.

**Table 28.13: Results of coagulation tests in inherited disorders of coagulation**

Deficiency/disease	Results	Test
Deficiency of factor XII, XI, IX, VIII	Prolonged	APTT
	Normal	PT
	Normal	TT
Factor XIII deficiency	Normal	APTT
	Normal	PT
	Normal	TT
	Positive	clot solubility test
von Willebrand disease	Prolonged	BT
	Prolonged	APTT
	Normal	PT
	Normal	TT
Fibrinogen deficiency	Prolonged	APTT
	Prolonged	PT
	Prolonged	TT
Deficiency of factor X, V, II	Prolonged	APTT
	Prolonged	PT
	Normal	TT

Because of this, DIC causes both hemorrhage, and thrombosis. In children DIC is most commonly associated with sepsis, acute promyelocytic leukemia, other cancers and bone marrow failure with associated sepsis. More than 80% of the critical care management deals with disseminated intravascular coagulation (DIC).

Following injury, infection or other precipitating factors there is release of cytokines (Tumor necrosis factor alpha, interleukin 1,6 and complement) which changes the endothelium from an anticoagulant to a procoagulant surface and interferes with fibrinolysis. Many of the effects of DIC like hypotension or acute

lung injury are due to the effects of these cytokines. As DIC continues, fibrinogen, prothrombin, platelets and other clotting factors are consumed beyond the capacity of the body to compensate and bleeding ensues. Activated protein C has an anti-inflammatory effect and down regulates tissue factor expression and decreases calcium ion flux. Active protein C is consumed in DIC and its supplementation may have an important role in DIC due to sepsis. Antithrombin (AT) is a serine protease inhibitor that can neutralize thrombin and factor Xa, which is also consumed in DIC.<sup>8</sup>

There are three main pathologic processes involved.

1. **Initiation of fibrin deposition:** Thrombin generation in DIC, is mediated by the extrinsic (tissue factor (TF)) pathway. The TF accumulates on activated platelets by binding to platelet P-selectin which results in thrombin generation.
2. **Amplification role of thrombin:** Thrombin generated amplifies inflammation and clotting by activation of platelets, activation of factor V, VIII and IX leading to more thrombin production. Activated of factor XIII leads to it crosslinking with fibrin clots making them insoluble, while thrombin activatable fibrinolysis inhibitor (TAFI) makes these clots resistant to fibrinolysis.
3. **Propagation of fibrin deposition:** There is suppression of fibrinolysis secondary to sustained increase in plasma levels of plasminogen-activator inhibitor (PAI -1).

### Types of DIC

**Acute DIC:** This is the most common form of DIC seen in clinical practice. Bleeding manifestations predominate and the patient is critically ill.

**Chronic DIC:** This occurs from a weak or intermittent activating stimulus. The process of destruction and production of clotting factors and platelets is balanced, the DIC is 'compensated'. Chronic DIC occurs in patients with giant hemangiomas, certain vasculitic disorders and in some solid tumors.

### Clinical Presentation and Diagnosis

The diagnosis of DIC is mainly clinical. Laboratory tests merely provide confirmatory evidence. The diagnosis of DIC is demonstrated by an elevated PT, an elevated aPTT, and decreased platelet counts. If these are prolonged in the setting of sepsis, the diagnosis of DIC is imminent. In cases of DIC where the procoagulant action is predominant, it is possible to have normal PT/aPTT in such cases it is important to do fibrinogen degradation product (FDP)/D-dimer tests to confirm DIC. D-dimer positivity alone needs to be interpreted with caution. D-dimer is a test with high negative predictive value. If it is negative it excludes DIC but if it is positive, it has to be interpreted along with the battery of tests given above and the clinical profile. Fibrinogen levels may also be decreased with a concomitant elevation of fibrin monomers or fibrin degradation products. Bleeding predominates in this setting secondary to the relative excess of fibrinolytic proteases compared with pro-thrombotic thromboplastic materials released from blast cells. Hemorrhage may also result from the consumption of coagulation factors in the setting of chronic activation of the procoagulation

cascade, or it may result from underproduction of necessary coagulation factors in the setting of severe systemic illness and relative hepatic insufficiency. After treating DIC, the response can be monitored by PT, TT and quantitative d-dimer assays.

### Laboratory Features

Diagnosis of DIC can be made with the following tests: (a) Screening tests-peripheral blood film examination and hemogram, reveal schistocytes and thrombocytopenia. Prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) are prolonged, and the fibrinogen levels is low. (b) Supportive tests-Increase in fibrin degradation products (FDPs) or d-dimers. No single test is diagnostic of DIC. Laboratory information of thrombocytopenia and hypofibrinogenemia (50% drop in either value) are the most sensitive in making a laboratory diagnosis of DIC.

A DIC scoring system has been established by the recommendations of Scientific Standardization Committee of the International Society on Thrombosis and Hemostasis, shown in Table 28.14. An underlying disorder known to be associated with DIC, is a prerequisite for the use of this algorithm. A score of  $\geq 5$  is compatible with DIC.<sup>9</sup>

### Treatment

The aim of treatment is treatment of the inciting cause (sepsis, malignancy, snakebite etc), supportive care and hematological management.

**Table 28.14: The disseminated intravascular coagulation score, diagnostic algorithm for the diagnosis of overt DIC**

1. Risk assessment:  
Does the patient have an underlying disorder known to be associated with DIC.  
(If yes, proceed. If no, do not use this algorithm).
2. Order global coagulation tests  
(platelet count, PT, fibrinogen, soluble fibrin monomers / fibrin degradation products (FDPs))
3. Score global coagulation test results
  - a. Platelet count:  $> 100,000/\text{cu mm} = 0$   
 $50,000-100,000/\text{cu mm} = 1$   
 $< 50,000/\text{cu mm} = 2$
  - b. Elevated fibrin-related marker (e.g.: soluble fibrin monomers/fibrin degradation products)  
(no increase=0, moderate increase=2, strong increase=3)
  - c. Prolonged prothrombin time:  
( $< 3 \text{ sec} = 0$ ,  $> 3 \text{ but } < 6 \text{ sec} = 1$ ,  $> 6 \text{ sec} = 2$ )
  - d. Fibrinogen level: ( $>1\text{g/L}=0$ ,  $<1\text{g/L}=1$ )
4. Calculate score.
5.
  - a. If score  $\geq 5$ : compatible with overt DIC; repeat scoring daily.
  - b. If  $< 5$  suggestive (not affirmative) of non-overt DIC; repeat in 1-2 days.

(Scientific Standardization Committee of the International Society on Thrombosis and Hemostasis.)

1. **Treatment of underlying cause and general care:** The underlying disease must be managed appropriately in order to reverse the process. In cases of sepsis, antibiotics are the mainstay of treatment. In snakebites, appropriate anti-snake venom should be administered. Tissue perfusion and respiratory function must be maintained by replacement with intravenous fluid and provision of oxygen support to correct hypoxia. Coagulopathy may be compounded by vitamin K deficiency, hence vitamin K should be given.
2. **Hemostatic support (replacement therapy):** In patients who have low levels of platelets, fibrinogen and other clotting factors as revealed by prolonged PT, aPTT, TT, replacement of these factors is useful. Replacement therapy is not indicated if there is no clinical bleeding and if no invasive procedures are planned. Monitoring is essential for guiding management and checking adequacy of replacement component support. The blood components commonly used in DIC are: Fresh frozen plasma (FFP), cryoprecipitate, platelet concentrates and packed red cells or whole blood. The required dose of blood and platelets depend on rate and degree of consumption. Replacement therapy can be halted when stabilization in platelet counts, fibrinogen levels and a fall in FDPs is observed.
3. **Heparin therapy:** For a patient who is actively bleeding, heparin aggravates the bleeding. In most typical cases of acute DIC (95% or more of patients) heparin therapy has not proved to be useful and may be harmful. There are some specific indications of heparin therapy. Heparin should be used only in patients with arterial, or large vessel venous thrombosis. Continuation of the hemostatic replacement therapy along with heparin is a must and repeated monitoring of the DIC status and heparin effect by repeated platelet counts, fibrinogen levels and PT, aPTT and TT values is needed.
4. **Other therapies:** Supplementation with recombinant human activated protein C has shown promise in critically ill patients and has anti-inflammatory properties. Despite early promising results, tissue factor pathway inhibitor (TFPI) has not shown any benefit in DIC clinical trials. Patients with DIC have an acquired deficiency of antithrombin (AT III) and administration of this inhibitor in supraphysiologic concentrations showed benefit in some neonatal studies. Novel antithrombin-independent inhibitors of thrombin such as desirudin and related compounds are being tested. Gabexate mesylate is a synthetic inhibitor of serine protease, and is being tested.

Tranexemic acid and Epsilon aminocaproic acid (EACA) can be used for prevention of fibrin degradation by plasmin, they may reduce bleeding episodes in patients with DIC and confirmed hyperfibrinolysis. But these drugs can increase the risk of thrombosis. For the restoration of anticoagulant pathways protein C concentrates have been used to treat purpura fulminans associated with acquired protein C deficiency or meningococemia and is of proven effect. Recombinant factor VIIa should be considered when conventional methods fail to control hemorrhage complicated by disseminated intravascular coagulation. Recombinant factor VIIa directly activates factor X to factor Xa. It has been found to be very effective in arresting bleeding in patients with factor VIII inhibitors and Glanzmann's thrombasthenia.

### DEPRESSION OF BONE MARROW ACTIVITY

The depression of normal bone marrow activity results in anemia, thrombocytopenia, and neutropenia. These signs are best treated with supportive care, irrespective of their etiology. Supportive care includes blood component transfusion, which in the case of newborns, children with malignancies or aplastic anemia on antithymocyte globulin therapy should be irradiated and filtered; to prevent the lethal complication of transfusion associated graft versus host disease.

The use of filtered blood and platelets is recommended to minimize the risk of cytomegalovirus (CMV) contamination and to decrease both the risk of alloimmunization and the incidence of febrile transfusion reactions. Judicious use of blood products is required for newly diagnosed aplastic anemia patients prior to bone marrow transplant as more transfusions leads to higher risk of alloimmunization, platelet refractoriness and increases the risk of graft rejection.

### Anemia

Pediatric patients who are not severely ill usually do not require blood transfusion unless a poor response to hematinics is anticipated and their hematocrit is < 20-25% (Hb level 7-8 g/dL). Transfusion of packed red blood cells (PRBCs) may be necessary to maintain intravascular volume in a patient who has acute hemorrhage, aplastic anemia, or any pre-existing condition which may warrant support. The volume of a PRBCs unit is 250-300 mL, a transfusion 10 mL/kg ideally raises the Hemoglobin (Hb) level by 2-3 g/dL (hematocrit 6-9%). The rate of transfusion should be decreased by at least 50% in patients with heart failure or severe chronic anemia where the Hb level is

$\leq 5$  g/dL (hematocrit  $< 15\%$ ). Blood is a biological product and care is needed prior to and during its administration to reduce risk of infection and complications. With current blood banking practices blood components are safe, however, certain transfusion reactions may still occur and be life threatening.<sup>10,11</sup>

### Neutropenia

Neutropenia is the most common toxic result of myelosuppressive chemotherapy, but it may also result from failure or suppression of the bone marrow. Absolute neutrophil counts (ANCs)  $< 0.5 \times 10^9/L$  ( $< 500/mm^3$ ) are associated with increased risk of infection. Neutropenia persisting longer than 2 weeks is associated with increased risk of systemic fungal infection.

Prolonged neutropenia resulting from myelotoxic chemotherapy is treated primarily with myeloid growth factors, granulocyte colony-stimulating factor (G-CSF). Neutropenia associated with bone marrow failure syndromes may respond to immunosuppressive therapy alone or in combination with androgens and growth factors. Although granulocyte transfusion is a feasible therapeutic modality for patients with neutropenia with active unresponsive bacterial or fungal infection, patients will only benefit if the ANC is expected to recover shortly. In aplastic anemia patients, G-CSF may be tried during episodes of infection to increase the ANC. This should be discontinued if no response by seven days.

Patients with neutropenia who are febrile require thorough evaluation. Physicians should be aware that subtle indications of inflammation should be considered a presumptive sign of infection. Close attention to the sites of central venous catheter, the skin, oropharynx, and the perirectal areas is necessary. Cultures of the blood, skin lesions, and a workup involving chest radiography, chest or sinus CT scan may be performed.

Initial antibiotic therapy should consist of broad-spectrum monotherapy with cefepime, ceftazidime, or imipenem. Dual therapy with an aminoglycoside in combination with antipseudomonal betalactam may be considered, if gram-negative sepsis is suspected. Initial empiric use of vancomycin in combination, is appropriate in the setting of severe mucositis, quinolone prophylaxis, colonization with resistant strains of *S. aureus* or *S. pneumoniae*, catheter-related infections or patients present with hypotension. Antibiotics beyond empiric coverage are needed to treat a confirmed or suspected focus of infection. Typhlitis or perirectal abscess should be managed with additional antibiotic coverage for anaerobic organisms. *C. difficile* enterocolitis requires treatment with metronidazole or

oral vancomycin. Any additional coverage is based on culture organism sensitivities and clinical syndromes. **Thrombocytopenia**, see bleeding section.

### BLOOD TRANSFUSION REACTIONS

**Hemolytic transfusion reactions** are caused by antibodies in the recipient's plasma, directed against donor red blood cell antigens, which rapidly hemolyse the donor cells. This occurs in ABO incompatibility and can be fatal. It results in hemoglobinemia, hemoglobinuria, renal failure, disseminated intravascular coagulation (DIC) and complement-mediated shock. This may occur in a lesser degree due to antibodies against Rh or non-ABO antigens if the patient has had prior exposure through earlier transfusions.<sup>10,11</sup>

**Nonhemolytic febrile reactions** are caused by cytokines (IL-1, IL-6, TNF) produced during the storage of blood components; rarely secondary to bacterial contamination. This type of reaction rarely results in hypotension or respiratory distress.

**Anaphylactic reactions** occur because of proteins in the donor plasma that cause allergic-anaphylactoid reactions. This is most commonly observed with blood components that contain large amounts of plasma whole pooled platelets, fresh frozen plasma or whole blood.

**Transfusion associated Graft-versus-host disease (t-GVHD)** is caused by lymphocytes in the transfused blood which attack the host, this occurs most commonly when the donor is immunocompromised e.g. neonates, suffering from certain malignancies or post bone marrow transplant as then the infused lymphocytes are not destroyed. Transfusion-associated GVHD disease is associated with an 80-90% mortality rate. This can be prevented by the use of irradiated blood products.

**Transfusion-related acute lung injury (TRALI)** is caused by transfusion of plasma-containing blood products which leads to interaction of the patients leukocytes with preexisting donor anti-leukocyte antibodies and the cytokines produced during storage of blood. The result is activation of complement cascade and alteration of pulmonary vascular permeability, the mortality rate of TRALI is 5%.

**Acquired diseases:** Infectious diseases may be transmitted through transfusions, e.g. malaria, hepatitis B, C and HIV, cytomegalovirus (CMV), West Nile virus, syphilis, Filariasis, Jakob-Creutzfeldt disease, etc.

**Massive transfusion** is defined as the replacement of more than one-half of the blood volume within a

24-hour period or the replacement of 10 units of blood over the course of a few hours. Complications of massive transfusion include the following:

1. Coagulopathy is caused by a dilutional effect on clotting factors and platelets.
2. Volume overload.
3. Hypothermia.
4. Hyperkalemia.
5. Metabolic alkalosis and hypokalemia –due to large volume of citrated blood.

### Conditions that may Mask a Hemolytic Transfusion Reaction

A number of conditions may mask the clinical occurrence of a hemolytic transfusion reaction. It is important to be aware and take extra care in these cases so that a transfusion reaction is not missed. Pre-existing febrile illness, acute renal failure, hepatic dysfunction with jaundice, hypotension, shock, DIC, hematuria, autoimmune hemolytic anemia with positive direct antiglobulin test, coma, sedation and premedication with antipyretic agents may make evaluation of hemolytic reactions difficult.

### Evaluation and Management

Whenever a hemolytic transfusion reaction is suspected, stop the transfusion immediately, give normal saline, maintain diuresis with fluids, diuretics, support the airway and circulation as necessary. Administer epinephrine, diphenhydramine, and corticosteroids, if allergic anaphylactic reaction is suspected.

The blood bag should be sent back to the blood bank. The blood bank should perform a repeat type, crossmatch, antibody screen, and direct and indirect Coombs tests.

In the patient examine the serum for free serum hemoglobin, monitor rise in serum bilirubin level, which peaks in 3-6 hours. Haptoglobin binds to hemoglobin and the serum hemoglobin level falls, reaching its nadir in 1-2 days. Check urine for hemoglobinuria. Post-transfusion failure to show expected rise in hematocrit occurs in patients with intravascular or extravascular hemolysis. In GVHD disease, pancytopenia and elevated liver enzymes levels may be present, currently no effective treatment exists, hence awareness is needed for its prevention. In acute transfusion-related acute lung injury, leukopenia and eosinophilia may be documented. In transfusion-related acute lung disease, the chest radiograph is consistent with non cardiogenic pulmonary edema, bilateral alveolar pattern infiltrates are found. Monitor the

patient, report to blood bank and provide supplemental oxygen to maintain oxygen saturation greater than 92%; rarely patients may need intubation. Post massive transfusion, monitoring the platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) to assess for derangement and provide correction after every 5 units of packed red cells or whenever signs or symptoms suggest coagulopathy.

### HEMOLYSIS

Acute hemolysis is most commonly due to acquired hemolytic conditions and can be due to immune disorders, toxins, drugs, antiviral agents (e.g., ribavirin) physical damage and infections. Serious hemolysis can lead to severe circulatory compromise. However, severe episodes of hemolysis may also occur in children with inherited disorders such as erythrocyte membrane or enzymatic defects and hemoglobinopathies abnormalities.<sup>12</sup>

### Work-up

Unexplained pallor with or without icterus, needs to be evaluated. Physical examination in hemolytic anemia reveals signs of anemia, erythrocyte destruction, complications of hemolysis, and may give evidence of an underlying disease. Increased destruction of red blood cells is demonstrated by release of hemoglobin, increase in lactic acid dehydrogenase (LDH), indirect bilirubin, urobilinogen and a decreased haptoglobin level. Reticulocytosis is a hallmark of hemolysis. Jaundice is due to increase in indirect bilirubin, the levels are rarely greater than 4 mg/dL in hemolysis unless complicated by hepatic disease or cholelithiasis. Splenomegaly occurs in hereditary spherocytosis and some other hemolytic anemias, but is usually not present in glucose-6-phosphate dehydrogenase deficiency (G6PD).

Autoimmune hemolytic anemia (AIHA) may result from warm or cold autoantibody types. Most warm autoantibodies are immunoglobulin (Ig) G and can be detected with the direct Coombs test, which is also known as the direct antiglobulin test (DAT). Microangiopathic anemia is found in patients with disseminated intravascular coagulation (DIC) or hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura. Fragmented red blood cells (schistocytes) are also found with defective prosthetic cardiac valves. Autoimmune hemolytic anemia and hereditary spherocytosis are classified as examples of extravascular hemolysis because the red blood cells are destroyed in the spleen and other reticuloendothelial

**Table 28.15: Causes of intravascular hemolysis****Immune hemolytic anemia**

Incompatible blood transfusion  
 Hemolytic disease of the newborn  
 Isoimmune hemolytic anemia

**Drugs and chemicals**

Drugs and chemicals causing hemolysis  
 a. *Drugs*-penicillin, phenacitin, dapsone,  
 b. *Chemicals*-water infusion, lead, nitrobenzene  
 c. *Toxins*-Snake and spider venoms  
 Drugs triggering hemolysis only in presence of G6PD deficiency (see Table 28.2)  
 Drug hypersensitivity- Quinine, phenacitin

**Red cell fragmentation**

Disseminated intravascular coagulopathy  
 Cardiac prosthesis/valvular disease  
 Hemolytic uremic syndrome  
 Unstable hemoglobins

**Infections**

Sepsis, falciparum malaria, clostridial infections

**Others**

Paroxysmal cold hemoglobinuria  
 Paroxysmal nocturnal hemoglobinuria

organs. Intravascular hemolysis occurs in hemolytic anemia due to prosthetic cardiac valves, G6PD deficiency, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and rarely paroxysmal nocturnal hemoglobinuria (Table 28.15).

Complete blood cell (CBC) count documents anemia, leukocyte counts, and differential counts. Platelet counts help to exclude an underlying infection or hematologic malignancy. The platelet count is within the reference range in most hemolytic anemias. Peripheral smear and morphologic examination reveals polychromasia, indicating reticulocytosis may show spherocytes, suggesting congenital spherocytosis or autoimmune hemolytic anemia, schistocytes (fragmented red blood cells, suggesting thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) or mechanical damage.

A decrease in serum haptoglobin is more likely in intravascular hemolysis than in extravascular hemolysis, but it is an acute phase reactant. Changes in the lactic dehydrogenase (LDH) and serum haptoglobin levels are more sensitive to detect hemolysis because the indirect bilirubin is not always increased. An increased red blood cell distribution width (RDW) is a measure of anisocytosis, a high number of reticulocytes also may cause high mean corpuscular hemoglobin

(MCH). A high MCH and mean corpuscular hemoglobin concentration (MCHC) suggest spherocytosis.

A G6PD screen can usually detect deficiency of this enzyme, but results are normal if the reticulocyte count is elevated. Hemoglobin electrophoresis confirms the presence of abnormal hemoglobin. A high cold agglutinin titer of anti-I antibody may be found in mycoplasma infections and a high titer of anti-i antibody may be found in hemolysis associated with infectious mononucleosis. Anti-P cold agglutinin may be seen in paroxysmal cold hemoglobinuria.

Urine hemosiderin may suggest intravascular hemolysis. Red blood cell survival (chromium-51 [<sup>51</sup>Cr] survival) is rarely used, but it can definitively demonstrate a shortened red blood cell survival (hemolysis). This test is ordered when the clinical history and laboratory studies cannot establish a diagnosis of hemolysis.

**Management**

The hemolytic episodes are often self limiting, and may require only supportive treatment. Drug induced hemolysis will usually subside by withdrawal of the offending agent. Transfusions are required to maintain hemoglobin between 6-8 g/dl. Forced alkaline diuresis, prevents the blockage of renal tubules by the hemolysed red cells is indicated to prevent the development of acute renal failure in severe hemolysis. Exchange transfusion in neonates is useful, as not only removes the excess bilirubin but also removes G6PD deficient red cells. Antioxidants such as vitamin E and selenium have no proven benefit for the treatment of G6PD. Future episodes of intravascular hemolysis can be prevented by avoiding the use of oxidant drugs (Table 28.16).

**Table 28.16: Drugs and chemicals causing hemolysis in patients with G6PD deficiency****Antibacterials and antiparasitic**

Nalidixic acid, nitrofurantoin, sulfamethoxazole, sulfacetamide, sulfanilamide, chloramphenicol, dapsone, furazolidone, niridazole, etc.

**Antimalarials**

Pamaquine, pentaquine, primaquine, quinine, chloroquine

**Other drugs**

Aspirin, phenacetin, probenecid, thiazide diuretics, phenothiazine, acetanilid, methylene blue, phenylhydrazine vitamin K, pyridium, quinidine

**Chemicals and toxins**

Napthalene, arsine, toluidine blue, trinitrotoluene, BAL, Favism

**Table 28.17: When to suspect atypical neonatal hyperbilirubinemia**

Features found in neonatal hyperbilirubinemia due to secondary disorder, requiring urgent medical intervention

Clinical finding	Condition
Family history of hemolysis	Hemolytic disease (G6PD deficiency, other)
Onset of jaundice <24 hours	Hemolytic disease
Serum bilirubin rises >0.5 mg/dL per hour	Hemolytic disease
Serum bilirubin shows rapid increase after 24-48 hours	Hemolytic disease
Unexplained anemia, pallor	Hemolytic disease
Positive direct antiglobulin test	Hemolysis (hemolytic disease of the newborn)
Hepatosplenomegaly	Hemolytic disease, sepsis or metabolic disorder
Vomiting, lethargy, poor weight gain, apnea	Sepsis or metabolic disorder
Jaundice persistent > 3 weeks	Cholestasis
Dark urine positive for bilirubin	Cholestasis
Light-colored stools	Cholestasis

G6PD—glucose 6 phosphate dehydrogenase deficiency.

### Special Situations that Warrant Attention

#### Neonatal Hyperbilirubinemia

Newborn hyperbilirubinemia may be secondary to a condition that requires medical intervention, e.g. hemolysis, metabolic disorder or liver dysfunction. This should be suspected if there is an early, steep onset of jaundice, if accompanied by pallor and lethargy (Table 28.17).

#### Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemias are a group of disorders due to autoantibodies, which attack and hemolyze red blood cells. The symptoms may be mild with only pallor, a sense of abdominal fullness and anemia or severe with jaundice, renal failure cardio-pulmonary decompensation and life threatening anemia. Autoimmune hemolytic anemia can occur in any age group or sex, it may be due to infections, drugs and autoimmune disease, the commonest cause is idiopathic autoimmune hemolytic anemia (Table 28.18).<sup>12</sup>

There are two main types of autoimmune hemolytic anemia: warm antibody hemolytic anemia and cold antibody hemolytic anemia. In the warm antibody type, the autoantibodies attach to and destroy red blood cells at temperatures equal to or in excess of normal body temperature. In the cold antibody type, the autoantibodies become most active and attack red blood cells only at temperatures well below normal body temperature. Autoimmune hemolytic anemia is confirmed when either direct (antiglobulin) Coombs' test or indirect Coombs' test is positive with the above clinical picture.

**Table 28.18: Etiology of autoimmune hemolytic anemia**

- Infections:**
  - Bacterial-Tuberculosis, others
  - Viral-Cytomegalovirus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), viral hepatitis and human parvovirus B-19.
  - Others—*Mycoplasma pneumoniae*
- Drugs:** Penicillin, cephalosporin, sulfonamides.
- Immunologic disorders with antibody production:**
  - X-linked agammaglobulinemia
  - Wiskott-Aldrich syndrome
  - IgA deficiency
  - Autoimmune hepatitis
  - Evans syndrome
  - Pure red cell aplasia
  - Systemic lupus erythematosus
  - Sjogren syndrome
- Malignancies:**
  - Lymphomas
  - Acute leukemias

### Treatment

Steroids are the first line of therapy, starting at 1-2 mg/kg with a very gradual, prolonged taper. Alternative immunosuppressive drugs are employed in children who cannot be tapered off steroids or if the side effects are not well tolerated. Options include e.g. cyclophosphamide, cyclosporine and even splenectomy. Folate supplementation is required in all hemolytic anemias. Avoid transfusions unless absolutely necessary, administer packed red blood cells, after proper matching in the blood bank. In autoimmune hemolytic

anemia (AIHA), type matching and cross-matching may be difficult. Use the least incompatible blood if transfusions are indicated and administer the blood slowly.

### SICKLE CELL DISEASE

Sickle cell disease, (SCD) is caused by an autosomal recessive single gene defect in the beta chain of hemoglobin (HbA), which results in production of a mutant hemoglobin S (HbS). Other forms of sickle cell disease may occur if HbS is inherited from one parent and other abnormal hemoglobin is inherited from the other parent (e.g., HbS beta-thalassemia or HbSE). Though sickle cell disease is known in central and coastal areas of the Indian subcontinent, because of marriage and migration it should be suspected in other regions too.

### Pathophysiology

In sickle cell disease valine replaces glutamic acid at the sixth amino acid of the beta globin chain, due to a recessive single gene mutation. Valine fits into the hydrophobic pocket of another hemoglobin molecule, and causes it to polymerise within the red cell, forming long stiff fibers of hemoglobin tetramers, the red cell becomes sickle shaped. This polymerization of sickle hemoglobin can be triggered by hypoxia and acidosis. Splenic sequestration or aplastic crisis can cause circulatory failure and become life threatening in children. Splenic dysfunction increases vulnerability to serious infections. Precipitating factors for vaso-occlusive episodes are not fully understood, but known precipitants include acidosis, dehydration, cold temperatures, extreme exercise, stress and infections. Long-standing intravascular hemolytic anemia and the release of hemoglobin and arginase from lysed red blood cells scavenge and deplete nitrous oxide (NO). The relative NO deficiency causes pulmonary vasoconstriction, endothelial dysfunction and thrombosis.<sup>13,14</sup>

### Workup and Presentation

A positive sickle preparation does not differentiate sickle trait from disease, but is a quick screening test. Diagnosis is made on a pre-transfusion sample of the child by electrophoretic techniques, such as high-performance liquid chromatography (HPLC) fractionation, or by DNA-based assays. If the child has recently been transfused, then parental blood studies are required.

Anemia, jaundice failure to thrive, repeated infections and bone pain are common. The phenotype

**Table 28.19: Predictors of complications in pediatric sickle cell patients**

#### Risk factors for acute chest syndrome

1. Polycythemia
2. Low levels of hemoglobin F
3. Leukocytosis

#### Risk factors for pain crises

1. Polycythemia
2. Low levels of hemoglobin F

#### Risk factors for avascular necrosis of bone

1. Polycythemia
2. Frequent painful crises
3. Presence of alpha-thalassemia
4. Elevated aspartate aminotransferase (AST)

#### Risk factors for stroke

1. Acute anemia
2. Acute chest syndrome
3. Transient ischemic attack
4. Hypertension
5. Absence of alpha-thalassemia

Modified from Quinn CT, Miller ST. Risk factors and prediction of outcomes in children and adolescents who have sickle cell anemia. *Hematol Oncol Clin N Am* 2004; 18:1339-54.

is variable, for predictors of complications in sickle cell children (Tables 28.19 and 28.20).

### Management

Swollen dorsa of hands and feet consistent with hand-foot syndrome, can be presenting symptom in young infants and children. By 2 years of age, 25% of American and 50% of Jamaican children with sickle cell

**Table 28.20: Prediction of risk for severe complications in children with sickle cell disease**

Severe complications from sickle cell disease include

1. Death
2. Stroke
3. One or more episodes of acute chest syndrome
4. Two or more pain crises in 1 year

Factors present before the age of 2 years that are associated with severe complications are:

1. Dactylitis by the age of 1 year.
2. Anemia (with hemoglobin <7 g/dL)
3. Leukocytosis in the absence of infection

Modified from Miller ST, Sleeper LA, et al. Prediction of adverse outcomes in children with sickle cell disease. *N Engl J Med* 2000;342:83-9.

anaemia have experienced at least one episode of dactylitis,<sup>12</sup> this is often a child's first presentation of disease. Earlier onset is associated with worse prognosis.<sup>13</sup>

### Pain/Vaso-occlusive Crisis

Pain crises is a common complication and can be precipitated by cold, dehydration or infection. The crisis may present as skeletal pain due to bone infarction or avascular necrosis, especially of the hip or shoulder. The presentation of a bone vaso-occlusive crisis depends on the age of the patient, in young children, red marrow is present in all bones, including small bones of the hand, and may present as dactylitis. In older children, marrow is found in the epiphyses, infarcts in long bones increasing with age.

NSAIDs are used to treat mild-to-moderate pain, they should be used with caution in patients with hepatic or renal impairment. In sickle cell children, creatinine is a poor measure of renal dysfunction and routine monitoring for proteinuria is needed. Codeine and other opioids are used for the treatment of moderate-to-severe pain. Fluid replacement is required to correct intravascular volume depletion, and compensate for ongoing volume losses caused by fever, hyposthenuria, vomiting and increased urinary sodium lost during the crises. If the dehydration is mild then the oral route is preferred. Give intravenous fluids cautiously if severe anemia or pulmonary hypertension to prevent congestive heart failure. Oxygen is given nasally at a rate of 2 L/minute to patients with moderate hypoxemia (PaO<sub>2</sub> 70-80 mm Hg or O<sub>2</sub> saturation 92 to 95%).

Hydroxyurea can increase hemoglobin F concentration has been studied in prevention of pain crisis and chest syndrome. Its use may be limited by the development of myelotoxicity (fall in absolute neutrophil count  $\leq$  2,000 per  $\mu$ L and platelet count  $\leq$  80,000 per  $\mu$ L) or by a failure to show improvement. Hydroxyurea is usually given is 10-20 mg/kg orally once daily initially, increase by 5 mg/kg/day every 12 weeks monitor hemogram to, maintain neutrophil count  $>$  2500 and platelet count  $>$  95000. The maximum dose is about 35 mg/kg/day, but most children respond to less.

Indications for starting hydroxyurea therapy are one or more of the following: (i) frequent episodes of pain, (ii) history of acute chest or other serious vaso-occlusive complication, (iii) severe symptomatic anemia. The evidence to continue with hydroxyurea therapy must

be evaluated, e.g. reduction in frequency of pain episodes, in a child with history of severe anemia; increase in hemoglobin, increase in percent hemoglobin F and/or MCV, and acceptable myelotoxicity.

### Acute Chest Syndrome

Acute chest syndrome is a frequent cause of death. It is usually clinically indistinguishable from pneumonia. The patient presents with chest pain, fever, dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on the chest X-ray.

### Pneumonia and Other Infections

Investigate all fevers and obtain relevant cultures and imaging studies as required. Give appropriate antibiotics according to the suspected organism with coverage for encapsulated organisms. Bacterial cultures of blood, sputum, urine, stool and/or pus should be obtained in patients with fever and in those who appear toxic. Keep vaccination up to date, ensure pneumococcal and *H. influenzae* vaccination.

### Acute Splenic Sequestration

In infants and children with sickle cell, the spleen may suddenly enlarge due to sequestration, this results in sudden anemia it may cause hypotension and even death. In a severely affected child with hypotension and shock, emergency red blood cell transfusion is lifesaving. Suspect splenic sequestration if sudden massive splenic enlargement, decrease in hemoglobin at least 2 g/dL below baseline values, unexplained thrombocytopenia.<sup>13,14</sup>

### Aplastic Crisis

Rarely infection with parvo virus B19 may lead to an aplastic crisis. This may need urgent blood transfusion and monitoring till recovery. To prevent megaloblastic crisis in this as in other hemolytic anemias, ensure adequate folate replacement.

The high incidence of stroke with surgery and general anesthesia can be decreased by simple transfusion prior to the planned intervention. Exchange transfusions are not better at reducing risk and have more complications. Indications for simple transfusions can include symptomatic anemia, life-threatening vaso-occlusive events, acute organ dysfunction and surgery. A important transfusion risk is over transfusion; this leads to hyperviscosity and volume overload.

## THROMBOSIS

Thrombosis is relatively uncommon emergency in pediatrics. Though the incidence of thrombosis is lower in children than in adults, morbidity and mortality are significant.

### Pathophysiology

The process of hemostasis is divided into cellular and fluid phases. The former involves platelets and the vascular wall, while the latter involves plasma proteins. The physiology of hemostasis is complex and involves a fine balance between flow of blood (i.e. fluid) and local responses to vascular injury (i.e. clotting). The fluid phase is divided into 3 processes:

1. The multiple-step zymogen pathway that leads to thrombin generation,
2. Thrombin-induced formation of fibrin clot and
3. Complex fibrinolytic mechanisms which limit clot propagation.

Children till 6 months of age have lower levels of the vitamin-K-dependent coagulation factors II, IX, and X, compared to adults. Levels of thrombin inhibitors, such as antithrombin and heparin cofactor II, and protein C and S are lower at birth. Protein S levels approach adult values by the age of 3-6 months, but protein C levels remain low even into childhood. Furthermore, plasminogen levels are low in newborns and infants. Thrombin generation is decreased (probably because of low prothrombin levels) and delayed in newborns compared with adults.<sup>15</sup> The incidence of thrombosis peaks in infants younger than 1 year and again during adolescence.

### Work-up

Inquire for a history or symptoms suggestive of congenital heart disease and/or recent cardiac catheterization, which are the most common causes of arterial thrombosis in children. If venous thrombosis is present, look for fever, recent surgery, trauma, central venous catheter use, nephrotic syndrome, varicella and other infections. Elicit a history of any previous thrombosis. Obtain a thorough family history to suggest genetic thrombophilia states (Table 28.21).

### Symptoms and Signs

Symptoms due to deep vein thrombosis (DVT) include pain and swelling of the limb. Pulmonary embolism may present with anxiety, breathlessness, pleuritic chest pain, fever and cough. A high index of suspicion is required to identify early signs.

**Table 28.21: Risk factors for thrombosis in children**

#### Time-limited risk factors

- Indwelling catheters
- Disseminated intravascular coagulation,
- Infections
- Post infectious transient antiphospholipid antibodies
- Surgery
- Surgically correctable congenital heart disease

#### Ongoing risk factors

- Thrombophilia
- Genetic thrombophilia
- Factor V Leiden, prothrombin 20210 mutation
- Deficient/dysfunctional antithrombin, protein C, protein S, AT III
- Elevations in lipoprotein (a), homocysteine
- Other less common genetic disorders of coagulation regulation or fibrinolysis

#### Acquired thrombophilia

- Markers of inflammation (elevations in factor VIII, D-dimer, C-reactive protein)
- Primary antiphospholipid antibody syndromes (lupus anticoagulant, anti-2 GPI antibody, anticardiolipin antibody)
- Acquired decrease in coagulation regulatory proteins (nephrotic syndrome, protein-losing enteropathy)

#### Indwelling catheters

- Leukemia, cancer and chemotherapy (e.g., L-asparaginase)
- Inflammatory diseases (e.g., systemic lupus erythematosus, inflammatory bowel disease)
- Prosthetic cardiac valves
- Sickle cell anemia
- Diabetes mellitus

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AT III Antithrombin III.

Symptoms of CNS thrombosis include vomiting, lethargy, seizures, or weakness in an extremity. Strokes may occur *in utero*, the newborns will present with seizures and lethargy. In older children the presentation is with headaches and acute onset of weakness in an extremity/hemiplegia. Precipitating factors like infection, dehydration and trauma are common. Patients with renal vein thrombosis may present with flank pain and hematuria.

Signs such as limb edema, erythema and tenderness on dorsiflexion of the foot (Positive Homan's sign) are present in DVT. Thrombosis of the inferior vena cava and/or renal vein can cause flank tenderness. Signs of pulmonary embolism are nonspecific and include diaphoresis, tachycardia and tachypnea. Signs of arterial thrombosis include diminished or absent peripheral pulses and a coolness of extremity skin.

### Cerebral Sinovenous Thrombosis

The cerebral sinovenous system in children may develop thrombosis, this system comprises of the superficial cortical veins, superior sagittal sinus, lateral sinuses and deep, straight sinus, vein of Galen, internal cerebral and jugular vein.

The important risk factors for thrombosis in children are infection of the head and neck region, trauma to the head and neck, dehydration. Other factors implicated are perinatal complications in newborn infants (hypoxia, placental abruption etc.) bacterial sepsis, connective tissue disorder, hematologic disorders (e.g. PNH, sickle cell disease, pediatric myelodysplasia and leukemia), other cancers, cardiac disease, indwelling vascular catheter, prothrombotic states (antiphospholipid antibodies or lupus anticoagulant; Factor V Leiden or prothrombin G20210A; acquired deficiency of protein S, protein C or antithrombin III), procoagulant drug (L-asparaginase). Some patients do not have any identifiable risk factor.<sup>16</sup>

### Renal Vein Thrombosis

Neonates may develop thrombosis of a renal vein, risk factors are polycythemia, dehydration, gestational diabetes (as it is associated with polycythemia and respiratory distress), asphyxia, sepsis and hypercoagulable state (protein C deficiency, antithrombin III deficiency). The newborn presents with flank mass, hematuria, hypertension, thrombocytopenia and oliguria. A high clinical suspicion must be kept and appropriate diagnostic testing performed, e.g. ultrasonography. The infant should be evaluated for a hypercoagulable state if no other causative factor is identified.

### Protein C Deficiency

This requires early identification, but may be difficult to differentiate from DIC in a newborn. The patient may have recurrent episodes of purpura fulminans and/or deep vein thrombosis unless anticoagulation therapy is given. The patient will have a marked deficiency of protein C (< 1% of normal), usually associated with a homozygous or double heterozygous deficiency, parents are heterozygous for the protein C defect and consanguinity may be present in the family.

### Laboratory Studies

Many clotting factors are consumed in the clot formation, and the reported low factor (protein C,S) level may be as a result of the existing thrombosis.

**Table 28.22: Initial work-up for thrombosis to evaluate for hypercoagulable state**

Complete hemogram (Hb/TLC/platelet count, DLC) PT/aPTT  
Radiology as indicated by symptoms.

*Further investigations as indicated:*

Activated protein C resistance and/or the factor V Leiden mutation

Antithrombin

Lupus anticoagulant (which may be screened by using the dilute Russell viper venom test)

Anticardiolipin antibodies

Prothrombin gene 20210A mutation

Lipoprotein (a) level

Plasma homocysteine values

Protein C (usually decreased in acute thrombosis)

Free and total protein S (usually decreased in acute thrombosis)

*Note:*

Heparin therapy (both unfractionated and low molecular weight) affects antithrombin, protein C, protein S and activated protein C resistance.

Warfarin affects protein C, protein S and antithrombin.

Neither drug affects results of anticardiolipin antibodies, factor V Leiden, the prothrombin mutation, or lipoprotein(a) or homocysteine levels.

Hence, tests need to take account of the current status and type of anti-thrombotic medications being given. The child should be evaluated to rule out DIC, complete blood count with peripheral blood smear, prothrombin time (PT), activated partial thrombo-plastin time (aPTT) and fibrinogen level. Table 28.22 lists the commonly performed investigations.

### Imaging Studies

Imaging studies are difficult as the child requires sedation, and the small size of blood vessels makes the imaging even more complex.<sup>15</sup> Imaging is not required if there is a very high index of suspicion with corresponding evidence from other tests and no contraindication to anti-coagulation (Table 28.23).

1. Color Doppler imaging is performed in vessels with thrombosis. The Doppler signals are absent and the lumen cannot be compressed with direct pressure in a thrombosed vessel. However, this may not be sufficiently sensitive to detect thrombosis in certain vessels such as subclavian veins, superior vena cava or brachiocephalic veins.
2. Echocardiography is of great utility in detecting vena caval and proximal subclavian vein thrombosis.

**Table 28.23: Contraindications to anti-thrombotic treatment in infants and children***For unfractionated heparin*

Known allergy to heparin  
History of heparin induced thrombocytopenia (HIT)

*For low-molecular-weight heparin*

Known allergy to low molecular weight preparation  
History of heparin induced thrombocytopenia (HIT)  
Invasive procedure within the previous 24 hours

3. A head CT with intravenous contrast material is useful for detecting venous sinus thrombosis. However both MRI and MRA are better at detecting early arterial ischemic strokes. MRI and magnetic resonance angiography (MRA) of the head are the modalities of choice for evaluating a child with suspected CNS thrombosis.
4. Chest radiography can show classic findings of PE include small pleural effusions with a wedge-shaped pleural-based opacity of pulmonary infarction, but frequently the X-ray chest may be normal.
5. MDCT pulmonary angiography, pulmonary CTA studies are successful in visualizing arteries to the level of segmental pulmonary arteries, but the evaluation of subsegmental pulmonary arteries is limited to 80% visualization.<sup>17</sup>
6. Ventilation-perfusion (V/Q) scanning is the procedure of choice in children with suspected PE. As an alternative, if D-dimer levels are elevated and if the V/Q scan indicates intermediate probability, spiral CT may be useful.

### Management

Urgent stabilization is required, if possible screening tests for hypercoagulable state should be sent prior to initiating anticoagulation therapy. If respiratory distress or neurological problems exist then management in an intensive care unit is required. Children with lower-extremity DVT can be fitted for compression stockings. Initial therapy requires heparin (unfractionated or low molecular weight) followed by oral warfarin therapy. Close monitoring is required to prevent overdosage and risk of bleeding, underdosing will hamper resolution of the thrombus. The international normalized ratio (INR); which is PT of patient/to standard is the most useful test for monitoring anticoagulation. The INR therapeutic range is 2-3. The duration of therapy depends on the risk of recurrence; this can be assessed by testing for thrombophilia status usually best done after 3 months of event and after stopping anticoagulants. Unfractionated heparin exhibits antithrombin as well as

anti-Xa activity, whereas the action of low molecular weight heparin (LMWH) is primarily anti-Xa. Because the effects of LMWH on thrombin are minimal, the aPTT prolongation by LMWH is correspondingly small. Some children may need special care in selection of anti-coagulant medication or may need alternative therapy due to a contraindications to anticoagulation, these children may benefit from placement of a temporary inferior vena cava (IVC) filter (Table 28.23).

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The survival of children with malignant disease has improved significantly because of advances in the diagnosis and modern multimodal treatment modalities. The overall 5 year survival rate of children with cancer has reached over 70%.<sup>1</sup> In view of increasing incidence of cancer and improving survival rates, it behoves pediatric oncologists and pediatricians to be aware of and identify the complications of cancer and its treatment.

An oncologic emergency is defined as an acute condition or event that is caused by cancer or its treatment that requires rapid intervention and treatment to prevent death of severe and permanent disability.<sup>2,3</sup> The recognition of oncological emergencies by primary care physicians and pediatricians is of paramount importance to aid prompt referral and management. Oncological emergencies are broadly classified into: (i) structural or local effects of tumor, (ii) hematologic abnormalities of blood and blood vessels, (iii) metabolic emergencies and (iv) complications secondary to treatment.<sup>4</sup> In addition, non-neoplastic conditions must also enter into the differential diagnosis of every oncologic emergency. The approach to definitive therapy is commonly multidisciplinary, involving pediatricians, pediatric oncologists, surgeons, radiation oncologists and other medical specialists. The types of common oncologic emergencies are listed in Table 29.1. In this chapter only the important and relatively common pediatric oncologic emergencies will be discussed.

#### ONCOLOGICAL EMERGENCIES DUE TO STRUCTURAL OR LOCAL EFFECTS OF TUMOR

##### Superior Vena Cava Syndrome

**Definition:** Superior vena cava syndrome (SVCS) comprises the signs and symptoms associated with compression or obstruction to the superior vena cava. The term superior mediastinal syndrome (SMS) is used when features of tracheal compression are also present. In children, tracheal and SVC obstruction mostly occur

**Table 29.1: Pediatric oncologic emergencies**

#### Structural or local effects of tumor

- Superior vena cava syndrome
- Spinal cord compression
- Raised intracranial pressure (Brain herniation)
- Massive hepatomegaly
- Cardiac tamponade

#### Abnormalities of blood and blood vessels

- Hyperleukocytosis
- Leukopenia
- Coagulopathy
- Anemia
- Necrotizing enterocolitis
- Venous thromboembolism

#### Metabolic emergencies

- Tumor lysis syndrome
- Hypercalcemia
- SIADH

#### Complications secondary to treatment effects

- Febrile neutropenia
- Thrombocytopenia

together so that the terms SVCS and SMS are often used synonymously.

**Etiology:** SVCS is a rare but serious oncologic emergency in children. Malignant tumors particularly non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) particularly T-cell ALL and Hodgkin disease are common causes of SMS.<sup>5,6</sup> Rarely neuroblastoma, Ewing sarcoma, rhabdomyosarcoma and germ-cell tumors may present with SVC obstruction. A study from All India Institute of Medical Sciences, New Delhi over a 10 years period (1990-2000), reported 21 children (20 boys and one girl) between the ages of 5 and 12 years with SMS.<sup>7</sup> There were 12 children with ALL, 7 with NHL and one each with Hodgkin disease and Langerhans cell histiocytosis. Vascular thrombosis can sometimes occur following introduction of central venous catheters for chemotherapy and hyperalimentation. Granuloma and histoplasmosis are very rare causes of SVCS.

**Pathophysiology:** The superior vena cava (SVC) is a thin walled vessel and has a low intravascular pressure. It is located in a tight compartment in the right superior mediastinum and is surrounded by chains of lymph nodes that drain the right and lower part of the left thoracic cavity and by the thymus in the anterior superior mediastinum. Thus, it is vulnerable to compression and thrombosis.

**Clinical features:** The common symptoms and signs are cough, hoarseness, dyspnea, orthopnea and stridor. The child has headache, anxiety, confusion, drowsiness and sometimes unconsciousness. There is facial edema, plethora, cyanotic facies, suffusion and edema of the conjunctiva. Venous engorgement of neck, chest and arm with collateral vessels and sometimes signs of pleural effusion and pericardial effusion may be present. There may be fixed elevation of jugular venous pressure. Symptoms may be aggravated in a supine position or when the patient is flexed as for lumbar puncture. The signs and symptoms of SVCS often progress rapidly over hours or days.

**Diagnosis:** Chest X-rays show a anterior superior mediastinal mass and pleural and pericardial effusions may also be present. A definitive diagnosis can be established by a contrast CT scan of the thorax. In addition to providing information on the location and extent of abnormality in SVC obstruction, CT scan can guide the possible biopsy sites. Magnetic resonance imaging (MRI) scan is helpful in patients with contrast dye allergy or in whom venous access cannot be established. MR angiography can yield definitive anatomic diagnosis.<sup>8</sup> Since malignancy is the usual cause of SVC obstruction, it is important to obtain a tissue diagnosis before initiating therapy. However, these children with SVCS tolerate invasive procedure, very poorly. Because of risk of anesthesia in a patient with airway obstruction and embarrassed venous return the diagnosis should be attempted by least invasive means. Irreversible cardiorespiratory arrest that can occur while positioning of patients for procedures further limits an already compromised venous return and airflow. The diagnosis should be made by examination of the peripheral blood smear, bone marrow aspiration/biopsy, thoracentesis and open or needle biopsy of the peripheral lymph nodes under local anesthesia.

**Treatment:** SVCS caused by a malignant neoplasm in a child is often a true medical emergency.<sup>9</sup> There is always a therapeutic dilemma in a child who presents with signs and symptoms of SVCS due to a large mediastinal mass. In situations where tissue diagnosis

is not possible without biopsy under general anesthesia, it is best to give empirical therapy. Survival of the patient is most important immediate concern rather than going for making a correct histologic diagnosis. Management consists of supportive measures such as oxygen, nursing patients in a semi-recumbent position and avoiding upper limb veins for venous access.

The management depends upon the underlying etiology. The traditional treatment has been radiotherapy. It can be given alone or in conjunction with steroids. Steroids also reduce post radiation edematous swelling of the tumor and consequent additional tracheal compression. However, steroids should be administered judiciously in patients with suspected leukemia/lymphoma as they may mask the diagnosis. Similarly, every effort should be made to obtain histological diagnosis prior to radiotherapy. Improvement may be observed within 12 hours of initiating radiotherapy. Chemotherapeutic agents such as prednisolone/dexamethasone, cyclophosphamide, vincristine and anthracyclines are also very effective. Since the most common causes of SVCS are lymphoma and leukemia, the above mentioned chemotherapeutic agents are very effective. If the patient does not improve within 3-4 days, the lesion is likely to be nonmalignant or associated with significant intracaval thrombosis and urgent thoracotomy should be resorted to in such a situation. Endovascular treatment (thrombolysis, angioplasty and stent placement) may be useful in select settings.<sup>10</sup> If tissue diagnosis is not possible by any means, the patient should be treated empirically for the most likely clinical diagnosis.

### Spinal Cord Compression

Acute compression of the spinal cord or of *cauda equina* is an oncological emergency since permanent neurologic impairment can result from prolonged compression. Acute compression of the spinal cord occurs in 2.7 to 5 percent of children with cancer.<sup>11,12</sup>

**Etiology:** The most common causes of spinal cord compression are either due to local extension or metastasis of Ewing sarcoma, neuroblastoma, lymphoma, leukemia, osteogenic sarcoma and soft tissue sarcoma. However, it may occur with almost any type of tumor including Wilms' tumor, germ cell tumor, hepatoblastoma and retinoblastoma. Though it occurs most likely in terminal phases of widely metastatic disease, spinal cord compression may occur at presentation.<sup>3,4,13</sup>

**Clinical presentation and diagnosis:** Back pain either local or radicular is the most common symptom which occurs in almost 80 percent of children with spinal cord

compression.<sup>13</sup> Any child with malignancy and back pain should be considered to have spinal cord compression until proved otherwise. The pain from bony metastasis is often constant and progressive, and exacerbated by movement, recumbency, straining or coughing. Motor weakness, usually presenting as a limp is also quite common. Sensory disturbance including bladder and bowel dysfunction may also occur. Detailed neurologic examination should be performed. Localized tenderness to percussion is found in 80-90 percent of patients. Spine radiographs may show abnormalities in the form of bony erosion, collapse of vertebral bodies or paraspinous soft tissue mass. MRI of the entire spinal axis with contrast enhancement is the procedure of choice for proper evaluation of the presence and extent of the disease.<sup>14</sup> Earlier, CT myelogram was a useful diagnostic modality.

**Treatment:** Once an acute cord compression is apparent, immediate intravenous dexamethasone in a dose of 1 to 2 mg/kg should be administered which serves to reduce local edema and pain.<sup>1,2</sup> Local radiotherapy, surgical decompression and chemotherapy (in children with sensitive tumors) can be used singly or in combination.<sup>15</sup> Laminectomy, surgical decompression is particularly indicated when the cause of primary tumor is not known and only one spinal level is involved. A surgical approach may provide pain relief, halt progression of neurodeficit, provide spine stability and provide histological diagnosis.<sup>16</sup> Chemotherapy is especially effective in chemosensitive tumors like neuroblastoma, NHL, Hodgkin disease, acute leukemia and Ewing sarcoma. The prognosis for neurologic recovery is related to the duration of symptoms and degree of neurologic disability at diagnosis. To avoid permanent neurologic impairment every attempt should be made to diagnose and treat spinal cord compression as early as possible.

### Pericardial Effusion and Cardiac Tamponade

Cardiac tamponade occurs when a rise in intrapericardial pressure limits the diastolic filling of the heart and results in decrease in cardiac output. Malignant pericardial effusion with cardiac tamponade is rare.

**Etiology:** The most common causes are acute leukemia and non-Hodgkin's lymphoma. However, it may occur in primary tumors of the heart muscle and pericardium. Frasher *et al*<sup>17</sup> reported 3 cases of pericardial effusion and cardiac tamponade and reviewed the literature. They found 26 cancer patients presenting with cardiac tamponade. Medary *et al*<sup>18</sup> from Memorial Sloan Kettering Cancer Center, New York, reported 9 cases

of cardiac tamponade over a period of 9 years. The underlying malignancies were ALL in three, AML in one and one each of Hodgkin disease, B-cell lymphoma, medulloblastoma desmoplastic round-cell tumor and rhabdomyosarcoma. Very recently Da Costa *et al*<sup>19</sup> reviewed the literature and found 18 children and adolescents (including their one child) with leukemia presenting with pericardial effusion and cardiac tamponade. At All India Institute of Medical Sciences, New Delhi, we have experienced 8 cases of pericardial effusion and cardiac tamponade in acute leukemia.<sup>20</sup> There were 5 cases of ALL and 3 cases of acute myeloid leukemia (AML-M5).

**Clinical presentation:** Two-thirds of the patients with malignant pericardial effusion are asymptomatic. There should be a high index of clinical suspicion of pericardial tamponade in a patient with malignancy who develops cardiovascular symptomatology in the form of progressive dyspnea, orthopnea, chest discomfort and cough. Sometimes, however, a patient may present with obvious signs and symptoms of pericardial effusion and tamponade. The classical clinical signs include raised jugular venous pressure, muffled heart sounds, pulsus paradoxus, low blood pressure and pericardial rub.

**Diagnosis:** The diagnosis of pericardial effusion is generally made by physical examination, coupled with chest roentgenogram showing cardiomegaly or a globular heart and electrocardiography showing small complexes and occasionally a pattern of electrical alternans. However, the most useful non-invasive test for confirmation is echocardiography which can establish the presence and quantity of pericardial effusion and evaluate its impact, particularly the presence of constrictive or tamponade physiology. Computed tomography scan and MRI are useful adjuncts for demonstration of pericardial effusion, presence of loculation and visualization of the metastatic mass in the myocardium or pericardium. Diagnostic and therapeutic pericardiocentesis should be performed under fluoroscopic control or echocardiographic guidance by needle aspiration.

**Management:** Various treatment modalities, including pericardiocentesis, surgical decompression, radiotherapy to mediastinum and chemotherapy, have been used.<sup>21,22</sup> The immediate treatment of cardiac tamponade is to relieve the cardiorespiratory distress by removal of the fluid by pericardiocentesis. Approaches to prevent reaccumulation include prolonged catheter drainage, obliteration of pericardial space and creation of a pericardial window allowing drainage of fluid into

pleural or peritoneal space. Aggressive supportive measures including maintenance of hydration, administration of oxygen and positioning of the patient to maximize cardiac output are crucial. Radiotherapy to mediastinum has been considered for treatment, but post-irradiation pericarditis is a well known threat. Long-term management of malignant pericardial effusion, particularly following hematologic malignancies, is best treated with systemic chemotherapy.<sup>20</sup> The outcome, however, depends upon the underlying malignancy.<sup>22</sup>

### Raised Intracranial Pressure

Symptoms of raised intracranial pressure can be non-specific, including headache, nausea and vomiting. Patients can develop ataxia, giddiness, confusion, drowsiness, personality change and seizures, while localized mass effect from edema can produce focal neurological deficits and cranial nerve palsies. The tumor mass, together with edema, may produce hydrocephalus and various herniation syndromes, depending on the location of the lesion. Obstruction of cerebrospinal fluid flow pathways by leptomeningeal deposits can also cause increased intracranial pressure and hydrocephalus.

CT and MRI are diagnostic. High dose steroids (dexamethasone) and apt management of raised intracranial pressure are indicated. Neurosurgical intervention in the form of resection, decompression or insertion of ventriculoperitoneal shunt may be necessary. Radiotherapy and more recently radiosurgery are useful modalities in select settings.<sup>15</sup> In addition, intrathecal chemotherapy is useful.

## ABNORMALITIES OF BLOOD AND BLOOD VESSELS

### Hyperleukocytosis

**Definition, etiology and risk factors:** Hyperleukocytosis is defined arbitrarily as peripheral leukocyte count exceeding 100,000/mm<sup>3</sup>. It occurs in 5 to 20 percent of children with leukemia and it is more often seen in acute lymphoblastic leukemia (ALL).<sup>5,23</sup> These patients are particularly vulnerable to metabolic consequences of the acute tumor lysis syndrome. It occurs in ALL because of the exquisite sensitivity of lymphoblasts to chemotherapy. In acute myeloid leukemia the myeloblasts and monoblasts are more likely to cause blood hyperviscosity and hemorrhage in the lungs and brain because of the virtue of their rigidity and stickiness.<sup>24</sup> Risk factors for hyperleukocytosis include younger age (it is most commonly seen in infants),

certain types of leukemia (microgranular variants of acute promyelocytic leukemia [AML-M3v], acute myelomonocytic leukemia [AML-M4], acute monocytic leukemia [AML-M5], and T-cell ALL), and cytogenetic abnormalities (11q23) translocations or presence of the Philadelphia chromosome).<sup>24</sup> The risk of morbidity and mortality increases when the leukocyte count exceeds 300,000/mm<sup>3</sup>. The intracerebral and pulmonary circulations are affected by hyperleukocytosis.

**Clinical presentation:** Patients may remain asymptomatic or may present with frontal headache, confusion, stupor, coma, convulsions, focal neurodeficits, papilledema or retinal venous distension. Pulmonary leukostasis may cause dyspnea, hypoxemia or right ventricular failure.<sup>25</sup> Priapism may occur in severe hyperleukocytosis. Despite a higher incidence and degree of hyperleukocytosis in ALL versus AML, clinically manifest hyperleukocytosis is not commonly seen in ALL.<sup>25</sup>

**Management:** Highest priority should be given to stabilize the patient, who should be monitored closely. Particularly attention should be given to fluid and electrolytes. Hydration and aggressive management of metabolic dysfunction is usually more important in patients with ALL.<sup>24,25</sup> Patients should be hydrated rapidly with 5 percent dextrose and 0.25 percent saline at 3000 ml/m<sup>2</sup>/24 hour with alkalinization of urine by administration of sodium bicarbonate 35-45 mEq/m<sup>2</sup>/24 hour. Allopurinol at 10 mg/kg/day in three divided doses should be given to prevent uric acid nephropathy.

Recombinant urate oxidase (rasburicase) is an alternative drug to prevent tumor lysis and manage hyperuricemia in patients who cannot tolerate allopurinol. Rasburicase converts uric acid to allantoin, which is 5 to 10 times more soluble than uric acid and therefore is rapidly excreted by the kidneys. Disseminated intravascular coagulation or thrombocytopenia, if present should be corrected. Red blood cell transfusion and diuretics should be avoided prior to cytoreduction particularly in patients with acute myeloid leukemia to avoid blood hyperviscosity. Cytoreduction with exchange transfusion, hydroxyurea and leukopheresis are indicated and are effective.<sup>24-26</sup> These means should be rapidly followed by early introduction of specific cytotoxic, induction chemotherapy. In patients with acute promyelocytic leukemia, treatment with all-transretinoic acid should be initiated as soon as possible; all-transretinoic acid stimulates the maturation of the myeloblasts of acute promyelocytic leukemia with a rapid reduction in the white blood cell count.

Future therapies that specifically target cytokines and cell membrane adhesion molecules that mediate blast-blast and blast-endothelium interactions may improve the outcome in patients with acute hyperleukocytosis.

### Neutropenic Enterocolitis

**Definition and etiology:** Neutropenic enterocolitis also known as typhlitis is an acute, life-threatening inflammation of the small and large bowel, often seen in children with malignancies during periods of prolonged or severe neutropenia.<sup>1,27,28</sup> Neutropenia of such severity is common during aggressive chemotherapy particularly for hematological malignancies.

**Pathogenesis:** It occurs where damage to the bowel wall by anticancer agents together with drug induced neutropenia allows invasion, resulting in mucosal ulceration and possible full thickness necrosis and perforation.

**Clinical features, diagnosis and management:** The early signs and symptoms are non-specific and may rapidly lead to intestinal perforation. If managed promptly and aggressively, the prognosis is likely to be good. From India, few cases have been reported.<sup>29,30</sup> A study from All India Institute of Medical Sciences reported 11 cases of necrotizing enterocolitis among 180 consecutive patients with acute lymphoblastic leukemia.<sup>31</sup>

The onset of abdominal pain in the setting of neutropenia can be due to a wide variety of intra-abdominal processes.<sup>32</sup> In addition to the well known and usual causes of abdominal pain, these children may have neutropenic enterocolitis, vincristine induced ileus, L-asparaginase induced pancreatitis, drug induced cholestasis and cholecystitis, fungal infections and intussusception due to bowel tumor or mesenteric lymph nodes.

Roentgenography can aid in clarifying or confirming a suspected diagnosis of necrotizing enterocolitis. CT abdomen may show a diffusely thickened cecum and ascending colon. A high index of suspicion should be kept and maximal supportive therapy with broad spectrum antibiotics to cover gram-negative organisms and clostridia, bowel rest, blood component support and careful surgical vigilance should be instituted. Surgery is indicated for intestinal perforation, persistent nonthrombocytopenic gastrointestinal bleeding and uncontrolled sepsis. If indicated, surgical decision should not be affected by the presence of underlying malignancy in the child. The outcome of these patients is still grim, mortality rates vary from 50 to 100 percent.<sup>33</sup> Five of 11 (45%) patients treated at AIIMS died.<sup>31</sup>

### Venous Thromboembolism

**Etiopathogenesis:** Malignancies are associated with increased risk of thrombosis due to hypercoagulable states, chemotherapy, prolonged immobilization, indwelling central catheters and greater incidence of surgical intervention.<sup>34-36</sup>

**Clinical features:** In patients with swollen extremity, venous thrombosis should be suspected and investigated promptly via an ultrasound Doppler of the limb, even in the absence of other risk factors. Pulmonary embolism should be suspected in patients who present with acute dyspnea, pleuritic chest pain, hemoptysis, dizziness or syncope. Signs include tachycardia, tachypnea, hypotension, raised jugular venous pressure, pleural rub or pleural effusion. ECG most commonly shows tachycardia, right bundle branch block, right ventricular strain pattern or the classical S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub> pattern. Chest X-ray may be normal or show oligemia of the affected segment, a dilated pulmonary artery, linear atelectasis, small pleural effusions or a wedge-shaped opacity. Arterial blood gas analysis shows hypoxemia and hypocarbia. Diagnostic modalities of choice include a spiral CT of the thorax, CT pulmonary angiogram or a ventilation/perfusion scan. Cortical venous sinus thrombosis, seen in ALL patients on L-asparaginase therapy may present with headache, confusion, altered sensorium or sign of raised intracranial pressure. Contrast CT scan or MR venography are diagnostic.

**Management:** Unfractionated and low molecular weight heparins are used for treatment. Thrombectomy and IVC filter placement are surgical modalities of treatment that may be used in patients with recurrent thromboembolism and with contraindications for thrombolysis.

## METABOLIC EMERGENCIES

### Tumor Lysis Syndrome

**Definition:** Acute tumor lysis syndrome is a triad of hyperuricemia, hyperkalemia and hyperphosphatemia (usually with hypocalcemia) occurring as a result of the rapid release of intracellular metabolites at rates exceeding the excretory capacity of the kidneys because of treatment-related or occasionally spontaneous tumor necrosis or apoptosis.<sup>37</sup>

**Etiopathogenesis:** Tumor lysis syndrome may occur before therapy or during the first few days (day 1-5) of starting the specific chemotherapy. Patients with bulky T-cell or B-cell leukemias or lymphomas (Burkitt

lymphoma) are at the greatest risk because both are associated with a large tumor burden and have high sensitivity to chemotherapy.<sup>1,4,9,37,38</sup> However, it may occur in standard risk acute lymphoblastic leukemia and chronic myeloid leukemia patients. Tumor lysis syndrome is very rarely seen in patients with acute myeloid leukemia and other solid tumor.<sup>39,40</sup> One may anticipate development of tumor lysis syndrome in a patient with bulky disease (massive organomegaly and/or hyperleukocytosis) who has elevated serum uric acid, lactate dehydrogenase levels, hypovolemia and deranged renal function.

The tumor lysis syndrome is a direct result of the degradation of malignant cells and of inadequate renal function. All three metabolites – uric acid, phosphate and potassium are excreted by the kidneys. Acute renal failure results from precipitation of calcium phosphate crystals and uric acid crystals in renal tubules.

**Management:** In addition to serum electrolytes, urea, uric acid, calcium and creatinine, urine output, specific gravity and pH should be monitored closely and appropriate intervention (including dialysis) should be instituted to deal with specific abnormalities like hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia.

Prevention is the best treatment for tumor lysis syndrome and appropriate preventive measures should be taken in all patients with ALL and non-Hodgkin lymphoma. These measures are directed towards: (i) decreasing uric acid production, (ii) increasing uric acid solubility and (iii) reducing the concentration of uric acid in the urine. Patients at high risk at TLS should be vigorously hydrated (3000 ml/m<sup>2</sup>/24 hours as a minimum) with a 5 percent dextrose in ¼ or ½ normal saline and diuretics may be given, if necessary, to maintain, a urine output of at least 100/ml/m<sup>2</sup>/h. So long as this urine output is maintained, hyperkalemia with its potentially fatal consequence does not occur. Regular monitoring of biochemical parameters, maintenance of appropriate fluid balance and use of diuretics, when necessary, is indicated.<sup>41,42</sup>

Hypocalcemia should not be treated with intravenous calcium unless the patient is symptomatic (tetany or cardiac arrhythmia). Urine alkalization should be employed by adding 50-75 mEq of sodium bicarbonate per liter, sufficient to keep urine pH above 7.0. The rationale behind urine alkalization is to enable the conversion of uric acid to the more soluble urate salt, thereby diminishing the tendency to uric acid precipitation in the renal tubules. But it has the potential disadvantage of promoting calcium phosphate deposition in the kidney, heart, and other organs in

patients with marked hyperphosphatemia. Sodium bicarbonate administration can create a metabolic alkalosis, worsen calcium phosphate precipitation, and exacerbate renal failure.<sup>37</sup> Allopurinol is given to decrease uric acid production (10 mg/kg/24 hour for 7 days should be given initially and then 5 mg/kg for another 7 days). Dialysis is indicated in patients who develop acute renal failure or severe uremic neurologic symptom.

Urate oxidase is not endogenous to humans, which led to the development of recombinant enzyme rasburicase. A dose of 0.15 to 0.2 mg/kg IV for 5-7 days is recommended. Given the effectiveness in reducing uric acid levels and its less significant side-effect profile, a single dose of rasburicase has been recommended for management of pediatric TLS-related hyperuricemia. The cost, however, is prohibitive.<sup>37</sup>

Prognosis of patients developing TLS, especially in developing countries, remains modest.<sup>23</sup>

### Hypercalcemia

Hypercalcemia is a common metabolic emergency. Its spectrum may range from asymptomatic mild elevation in serum calcium to a life-threatening emergency with acute renal failure. It can occur in hematological malignancies and in solid tumors. Humoral factors released by tumors without bone metastasis and paracrine factors released by bone metastasis mediate bone resorption and intestinal reabsorption of calcium, causing hypercalcemia.

**Clinical presentation:** Signs and symptoms are often non-specific. Early symptoms include polydipsia, polyuria, anorexia, constipation, lethargy, drowsiness. Abdominal discomfort, nausea or change in mental status can also be features.<sup>5</sup>

**Diagnosis** is based on corrected calcium levels, corrected based on albumin levels from the following formula: Corrected Ca (mmol/L) = measured Ca (mmol/L) + [0.02 x (40 – albumin)]. A corrected calcium level of less than 3.0 mmol/L is considered mild, while a calcium level greater than 3.5 mmol/L is severe. Volume status and renal functions need to be carefully assessed.

**Management:** Aggressive fluid resuscitation should be employed. Frequent clinical and fluid status, input-output balance, calcium and electrolyte, renal function monitoring is necessary. Diuretics have little role. Bisphosphonates are the mainstay in the management. However, the cost of bisphosphonate therapy and its side effects (e.g. local reactions, transient fever, impaired renal function, hypophosphatemia, hypomagnesemia) should

be considered while initiating therapy. Calcitonin and corticosteroids are other agents used.<sup>9</sup>

### Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

SIADH is a paraneoplastic condition associated with malignancy.<sup>1-5</sup> It is due to the production of arginine vasopressin by tumor cells. Hyponatremia, symptomatic or asymptomatic, is the commonest sign of SIADH. Patients can present with lethargy, irritability, anorexia, depression, muscle cramps, weakness, behavioral change or coma. The mainstay of management of SIADH is treatment of the underlying malignancy. Acute treatment for patients who are symptomatic and who have severe hyponatremia includes diuresis with loop diuretics and replacement of sodium and potassium lost in the urine. Chronic treatment includes water restriction.

## ONCOLOGICAL EMERGENCIES SECONDARY TO TREATMENT EFFECTS

### Myelosuppression and Consequent Problems

Certain malignancies particularly hematological malignancies (e.g., leukemia, lymphoma) as well as anticancer agents cause bone marrow suppression, which decreases the number of white blood cells, red blood cells and platelets. When the effect is severe the child treated for cancer becomes predisposed to infection, anemia or bleeding depending on which cell line is affected.<sup>43</sup> The degree and duration of neutropenia and thrombocytopenia are directly related to the occurrence of life-threatening infection and bleeding episodes. These events, even if they are not lethal in direct outcome, decrease quality of life, increase cost of therapy and may cause delay in administration of chemotherapy and/or dose reduction.

### Febrile Neutropenia

Neutropenia places patients at risk for bacterial and fungal infection. This common condition is a major problem and may be life-threatening. A patient with an absolute neutrophil count of less than  $500/\text{mm}^3$  is considered neutropenic and should be observed closely for the development of fever which may be the only indication of infection.<sup>44</sup> The risk of bacteremia is very high when the neutrophil count is less than  $100/\text{mm}^3$ . Children with severe and prolonged neutropenia (> 7-10 days) have a high chance of developing fungal infection.

A complete physical examination to try to elucidate the source of infection should be performed, taking care to avoid invasive procedures where possible. Blood cultures from both central and peripheral lines should be obtained as well as cultures of other body fluids (throat, urine, wound and other lesions) should be taken. Chest radiograph should be taken. The most common organisms causing infection are Gram-negative bacteria including *E.coli*, *Klebsiella*, *Pseudomonas* and *Enterobacter* spp., *Staphylococcus aureus*, coagulase negative *Staphylococci* and *Streptococcus pneumoniae* are the common Gram-positive bacteria. Among the fungal infections the most common are *Candida albicans*, *Aspergillus* spp and *Mucor*.

After taking the cultures an appropriate broad-spectrum intravenous antibiotics should be administered. The antibiotics must cover both Gram-negative and Gram-positive organisms.<sup>22</sup> In patients with suspected central line infections, vancomycin should be added although persistent infections may necessitate removal of the line. The antibiotic policy guidelines should be based on local experience and antimicrobial susceptibility. If the febrile neutropenic patient does not improve in spite of appropriate broad spectrum antibiotics for 5-7 days, an antifungal agent should be added. Hematopoietic growth factors G-CSF and GM-CSF have been used in clinical practice which decrease the duration of neutropenia after cytotoxic chemotherapy and may reduce the incidence and duration of infections for high risk patients but its use for patients with a short duration of neutropenia is not routinely indicated.<sup>22,45</sup>

### Thrombocytopenia

Thrombocytopenia is a common therapy related complication. Severe thrombocytopenia is potentially life threatening and related to the degree of myelosuppressive nature of the chemotherapy regimen administered. Frequent monitoring and apt management are imperative.

Thrombocytopenia could be asymptomatic or may manifest with petechiae, purpura, oromucosal bleeding and gastrointestinal bleeding. Occasionally hemoptysis or intracranial bleeding, with or without features of raised intracranial pressure, may be the presenting manifestation.

Severe thrombocytopenia (platelet count  $< 10^{10}/\text{L}$ ) needs urgent correction with platelet concentrates in the doses of 6 units/ $\text{m}^2$  or 0.1 unit/kg. If blood group compatible platelets are not available, platelets of the

next compatible group should be administered. Irradiated platelets reduce the chance of antibody formation. Moreover, whenever possible, platelets collected by single donor apheresis are preferable.

### Conclusion

Emergencies are common in patients with cancer, and these patients frequently seek help in emergency departments and offices of primary care pediatricians and pediatric oncologists. Prompt evaluation that leads to a diagnosis and urgent institution of therapy can be lifesaving or essential to prevent irreversible disability, loss of function or death. With timely intervention and a multidisciplinary approach to therapy, many of these patients can return to their previous level of function and independence. Therefore, it is important that all health care professionals likely to encounter patients with cancer have a sound knowledge of the most common oncologic emergencies.

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# 30 Blood Component Therapy

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Blood transfusion is an essential part of modern health care. Used correctly, it can save life and improve health. However, the transmission of infectious agents by blood and blood products has focused particular attention on the potential risk of transfusion. Advances in blood collection, separation, anticoagulation, and preservation have resulted in component preparation of red blood cells (RBC), platelets, white blood cells (WBC), and plasma, which are superior to whole blood (WB) used in the past.

## APPROPRIATE USE OF BLOOD AND BLOOD PRODUCTS

The salient aspects are:

1. The appropriate use of blood and blood products means the transfusion of safe blood products only to treat a condition leading to significant morbidity or mortality that cannot be prevented or managed effectively by other means.
2. Transfusion carries the risk of adverse reaction and transfusion-transmissible infection. Plasma can transmit most of the infections present in whole blood and there are very few indications for its transfusion.
3. Blood donated by family/replacement donors carries a higher risk of transfusion-transmissible infections, than blood donated by voluntary non-remunerated donors. Paid blood donors generally have the highest incidence and prevalence of transfusion-transmissible infections.
4. Blood should not be transfused unless it has been obtained from appropriately selected donors, has been screened for transfusion-transmissible infections and tested for compatibility between the donor's red cells and the antibodies in the patient's plasma, in accordance with national requirements.
5. The need for transfusion can often be avoided by:
  - The prevention or early diagnosis and treatment of anemia and conditions that cause anemia.
  - The correction of anemia and the replacement of depleted iron stores before planned surgery.

- The use of simple alternatives to transfusion, such as intravenous replacement fluids.
- Good anesthetic and surgical management.

## WHOLE BLOOD

### Description and Storage

A unit of whole blood (WB) collected in CPDA-1, has a volume of approximately 410 ml (350 ml WB plus 63 ml CPDA-1) and a hematocrit of 0.30-0.40, and is stored at 1-6°C and has a shelf life of 35 days. Within 24 hours of collection, the platelets as well as the granulocytes in the unit are dysfunctional and several plasma coagulation factors (in particular factor V and VIII) fall to suboptimal levels.<sup>1,2</sup>

### Indications for Transfusion

There are very few indications for the use of whole blood in modern medicine. These include:

1. Blood priming for extracorporeal circuits (i.e., therapeutic apheresis in small patients, cardiovascular bypass, extracorporeal membrane oxygenation, and continuous hemoperfusion).
2. Neonatal exchange transfusions (WB < 5-7 days old).
3. In patients who have active bleeding with massive volume (> 30% of total volume) loss. However, in most cases, even with massive volume loss, the resuscitation can be achieved by the use of RBC concentrates and crystalloids or colloid solutions. Should plasma coagulation factor replacement become necessary, the levels of coagulation factors V and VIII in stored WB are rarely sufficient to correct the corresponding deficiencies. Given these considerations, most centers preparing blood components provide little or no WB but rather separate WB donation into the more commonly required blood components. In situations where RBC and coagulation factor replacement are needed, "reconstituted" WB (RBC unit and a plasma unit in one bag) can be utilized.<sup>2</sup>

## Dosage and Administration

It should be ABO and Rh compatible. The volume and rate of transfusion depends on the clinical situation. After an initial slow drip (to allow observation for immediate, severe transfusion reactions), the rate of infusion should be as fast as clinically indicated or tolerated and in all cases must be completed within 4 to 6 hours (to avoid bacterial contamination).

The various blood components (RBC, plasma, platelets) can be prepared either from:

1. *Whole blood donation*: The various components in a unit of whole blood have different specific gravities and hence can be separated by centrifugation. An initial soft spin separates RBCs from the platelet rich plasma (PRP). After collection of the RBCs in a separate bag with anticoagulant and preservative, a hard spin is performed. This separates the platelets from the plasma. The term fresh frozen plasma (FFP) is used when the separated plasma is stored at  $-18^{\circ}\text{C}$  within 8 hours of collection.
2. *Apheresis*: This uses an automated instrument wherein blood from a donor is drawn into a circuit, components separated by centrifugation or filtration, the required component collected and the remaining blood returned to the donor. This method of component separation has been traditionally used for platelet, plasma and granulocyte collection. Recently RBC apheresis has also been employed. The advantages of apheresis collection over separation of components from WB are:

1. Larger quantities of the desired component can be separated.
2. The recipient is exposed to fewer donors and hence has a lesser risk of allo-immunization and transfusion related infections.
3. The same donor can donate more frequently.

## RED BLOOD CELLS

### Description and Storage

RBC concentrates are prepared from WB donations. These concentrates can be further modified for use in specific clinical settings. Characteristics of the various RBC preparations, including their contents and storage conditions, are summarized in Table 30.1. The anticoagulant and preservative solution in an RBC unit helps to support the metabolic needs and hence maintain the viability of the red cells. The traditional citrate, phosphate dextrose (CPD) solution acts as an anticoagulant, buffer and the source of metabolic energy for the RBCs. Adenine performs the function of providing higher levels of ATP within cells and hence prolonging the shelf life of a unit. The newer solutions used include Adsol, Optisol and Nutricell, which all increase the shelf life to 42 days.

### Transfusion

#### *Physiologic Responses to Anemia*

Oxygen delivery is dependent on cardiac output and arterial oxygen content. Cardiac output is dependent

**Table 30.1: Characteristics of various RBC preparations**

<i>Component</i>	<i>RBC recovery (%)</i>	<i>Storage</i>	<i>Indication for modified components</i>
RBCs in CPDA-1	> 99	35 days at $1-6^{\circ}\text{C}$	
RBCs in AS	> 99	35-42 days at $1-6^{\circ}\text{C}$	
RBCs, buffy coat poor	> 90	35 days	History of repeated febrile or allergic reactions
RBCs, washed	80	24 h at $1-6^{\circ}\text{C}$	History of repeated reactions unresponsive to buffy coat poor or leukodepleted RBCs; prevention of severe allergic reactions or anaphylaxis due to anti-IgA
RBCs, frozen deglycerolized	80	May be stored frozen 10 years (depending on the glycerol concentration). After thawing: storage at $1-6^{\circ}\text{C}$ for 24 h	Prolonged storage of autologous units or allogenic units with rare RBC phenotypes
RBCs, leukocyte reduced by filtration	> 90	Pre-storage as for CPDA-1 Post-storage: for immediate infusion	History of repeated febrile and/or allergic reaction; prevention of HLA autoimmunization and/or CMV transmission

AS = Adsol

on heart rate and stroke volume and arterial oxygen content is a function of hemoglobin and its saturation with oxygen. Thus, tissue hypoxia occurs if there is decreased Hb and cardiac insufficiency.

### *Physiology of Anemia*

With a fall in hemoglobin there is an increase in cardiac output with increase of stroke volume in children but an increase of heart rate (primarily) in neonates. The tissue oxygen extraction ratio (ER) also increases from 25 percent basal but in heart and brain the ER is 55-70 percent under basal conditions, thus there is very little scope for increasing the ER in these two organs.<sup>3,4</sup>

Rightward shift of the oxygen dissociation curve occurs due to increased levels of 2, 3 diphosphoglycerate DPG. Infact children have normally increased levels of 2,3 DPG and thus a lower hemoglobin normally. Freshly collected units have a higher level of 2,3 DPG and thus allow better delivery of oxygen to tissues.

### *Indications for Transfusion*

Despite the large numbers of RBC transfusions administered to children, there is a remarkable paucity of scientific data on which to base RBC transfusion decisions. Recommendations for RBC transfusions in children are, therefore, for the most part based on expert opinion and experience and not on scientific studies. The decision to transfuse should not be based on the hemoglobin level alone, but also on a careful assessment of the child's clinical condition. Both laboratory and clinical assessment are essential. A child with moderate anemia and pneumonia may have more need for increased oxygen carrying capacity than one with a lower hemoglobin level who is clinically stable.

If the child is stable, monitored closely and is treated effectively for other conditions, such as acute infection, oxygenation may improve without the need for transfusion. The specific indications for transfusion are:<sup>1,2</sup>

1. Hemoglobin concentration of 4 g/dL or less (or Hct 12%).
2. Hemoglobin concentration of 4-6 g/dL if any of the following clinical features is present:
  - Clinical features of hypoxia
  - Acidosis (usually causes dyspnea)
  - Impaired consciousness
  - Hyperparasitemia in malaria (>20%)
3. Symptomatic perioperative anemia
4. Emergency surgery with anticipated blood loss
5. Mechanical ventilation in patients with ARDS
6. Patients on chemotherapy and radiotherapy protocols as per the requirements of the protocol.

The volume of red cells used is as follows. Volume of RBCs to be transfused =  $TBV \times ([\text{desired Hb}] - [\text{actual Hb}]) / [\text{Hb}]$  of RBC unit. The hematocrit of packed red cells is around 50-60%. Hence a transfusion of 12-15 ml/kg will raise the Hb by 3 g/dL. In patients with severe anemia in overt or impending congestive cardiac failure due to anemia, small aliquots of 5 ml/kg of packed red cells with frusemide is advised with regular monitoring of hemodynamic status. The other way to calculate the volume of packed cells to be given as an aliquot is to multiply the hemoglobin in g/dL by 2 and get the figure in mL of packed cells to be given/kg body weight.

### **RBC Transfusions for Acute Blood Loss**

In the presence of acute hemorrhage it is important to remember that the first priority is to correct the hypovolemia (with crystalloids and/or colloids) and to attempt to stop the bleeding. In patients with hematologic problems, the latter will often include the need to correct thrombocytopenia and/or deficiencies of coagulation factors, treatment to decrease bleeding from damaged mucosal barriers (e.g., with histamine blockers or antifibrinolytics) and or reversal of the effects of anticoagulant therapy. In patients with normal or near-normal Hb levels prior to the onset of hemorrhage, RBC transfusions are usually only necessary if the patient remains unstable following volume resuscitation. However, careful ongoing evaluation of a child with acute blood loss is essential as the signs of shock can initially be subtle. If acute hemorrhage totals > 15 percent of blood volume, signs of circulatory failure (tachycardia, decrease of intensity of peripheral pulses, delayed capillary refill and cool extremities) will be observed. However, hypotension will not be present until 25-30 percent or more of the child's blood volume is lost.<sup>5-7</sup> It is also important to realize that in the setting of rapid ongoing hemorrhage with hypovolemia, the hemoglobin concentration may not be an accurate indication of the actual RBC mass.

The classification of hemorrhagic shock in children based on systemic signs is shown in Table 30.2 and guidelines for resuscitation are summarized in Flow chart 30.1.<sup>8,9</sup>

### **RBC Transfusion for Acute Hemolysis**

Unlike acute hemorrhage where the patient suffers from both hypovolemia and a decreased RBC mass, patients with acute hemolysis are usually normovo-lemic. The Hb concentration therefore more accurately reflects RBC mass. The decision to administer RBC transfusion

**Table 30.2: Classification of hemorrhagic shock in pediatric patients based on systemic signs**

System	Class I Very mild hemorrhage (<15% TBV loss)	Class II Mild hemorrhage (15-25% TBV loss)	Class III Moderate hemorrhage (26-39% TBV loss)	Class IV Severe hemorrhage (>40% TBV loss)
Cardiovascular	Heart rate normal or mildly increased Normal pulses Normal blood pressure Normal pH	Tachycardia Peripheral pulses may be diminished Normal blood pressure Normal pH	Significant tachycardia Thready peripheral pulses Hypotension Metabolic acidosis	Severe tachycardia Thready peripheral pulses Significant hypotension Significant acidosis
Respiratory	Rate normal	Tachypnea	Moderate tachypnea	Severe tachypnea
Central nervous system	Slightly anxious	Irritable, confused, combative	Irritable or lethargic, diminished pain response	Coma
Skin	Warm, pink Capillary refill brisk	Cool extremities, mottling Delayed capillary refill	Cool extremities, mottling, pallor Prolonged refill	Cold extremities, pallor or cyanosis
Kidneys	Normal urine output	Oliguria, increased specific gravity	Oliguria, increased BUN	Anuria

BUN—blood urea nitrogen; TBV—Total blood volume.

depends upon a combination of factors, including ongoing clinical evaluation, etiology of hemolysis, actual Hb concentration and rate of decrease in Hb and presence or absence of other treatment options, e.g. steroids or IVIG for immune hemolysis. In cases of severe life threatening autoimmune hemolytic anemia, the “least incompatible unit” should be used for transfusion if cross matching is difficult due to a positive Coombs test.

### RBC Transfusion for Chronic Anemia

Factors to be considered should include:

- Presence or absence of symptom and/or abnormal physical signs and the likelihood that these are due to anemia.
- Presence or absence of underlying diseases, particularly cardiac diseases which may decrease the patient’s capacity for cardiovascular compensation.
- Likely evolution of the underlying disease causing the anemia.
- Likely evolution of the anemia and its consequences, with or without transfusion in both the short- and long-term.
- Possibility of using alternate, safer therapies for the treatment of the anemia.

### RBC Transfusion for Thalassemia

Hypertransfusion regimen, in which endogenous erythroid production is suppressed by maintaining a

minimum pre-transfusion hemoglobin level of 9.5–10.5 g/dL and a post-transfusion Hb of 13–13.5 g/dL is the approach.<sup>10,11</sup>

Children with thalassemia (and other transfusion dependent anemias) should ideally be transfused PRBC units, which are leukodepleted. In our country, bedside WBC filters are the commonly used method of leukodepletion. Leukodepletion not only decreases the incidence of transfusion related febrile reactions but also decreases the chance of alloimmunization in those children for whom bone marrow transplantation may be an option in the future. Regular monitoring of iron load by ferritin measurement and adequate iron chelation is vital in the care of these children.

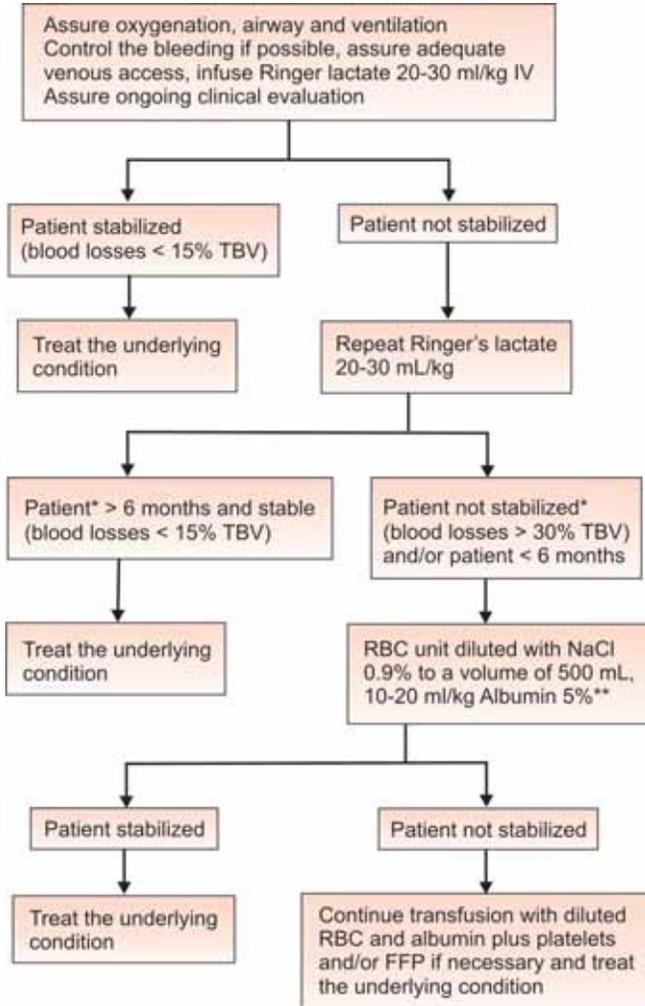
### Special Considerations for Newborns

#### Indications for RBC Transfusions

There are three major factors contributing to small volume RBC transfusion requirements in VLBW infants.

1. A rapid decline in Hb level occurs in the first few weeks of life to a nadir at 2 months of life.<sup>12,13</sup> It must be remembered that concomitant with the decrease in absolute Hb levels, the switch from HbF to HbA production is also occurring, so that the change in oxygen-carrying capacity is not so marked as the change in the total Hb might suggest.
2. The associated respiratory illnesses often present in these neonates first as respiratory distress syndrome and then as bronchopulmonary dysplasia. There is

**Flow chart 30.1:** Approach to the treatment of hemorrhagic shock in infants and children. Red blood cells (RBC); total blood volume (TBV); fresh frozen plasma (FFP)



\* Patient with significant degree of anemia prior to acute blood loss will require RBC transfusion support following smaller hemorrhagic losses.

\*\* The use of albumin for fluid resuscitation is controversial<sup>12</sup>

necessity of maintaining hemoglobin values at a predetermined level in these neonates.<sup>14,15</sup>

3. **Phlebotomy losses:** Because of the need for laboratory monitoring of sick neonates and the relatively large volumes of blood required in relation to these tiny infant's total blood volumes, phlebotomy losses contribute significantly to the need for RBC transfusions in VLBW infants.<sup>16</sup>

There are 3 clinical settings in which newborns may require large volume RBC transfusion—exchange transfusion, surgery with cardiopulmonary bypass or during treatment with extracorporeal membrane oxygenation.<sup>17</sup>

*Practical Considerations*

RBC units for transfusion to neonates are often chosen from a fresh (< 5 days old) RBC unit at the time of his/her first small-volume RBC transfusion. In settings of large-volume RBC transfusion, replacement of plasma coagulation factors is often also required so that WB or reconstituted WB, i.e., a RBC unit mixed with a unit of fresh frozen plasma (FFP), can be used. For WB, or the RBC unit for reconstituted WB, the choice of ABO group is the same as that for small volume RBC transfusions (Table 30.3). The ABO group of the FFP must also be compatible with baby's RBCs. This may mean that the ABO groups of the RBC unit and the FFP unit are different, e.g., for a group A baby with maternal anti-A in his plasma, a unit of reconstituted WB would be prepared using a group O RBC unit and a group A FFP unit. To limit donor exposure, some experts use group O whole blood in this setting, although group O donors with high anti-A titers should be excluded. WB units or RBC units for large volume transfusions should be relatively fresh, i.e. not > 5-7 days old. The main reason for this precaution is the high potassium concentration in stored WB or RBC units and not the low 2-3 DPG levels. The indications for small volume RBC transfusions based on current guidelines are summarized in Table 30.4.

**Modification of Blood Products in Special Situations**

- A. Leukocyte reduction: Lymphocytes present in RBC or platelet units cause the following problems related to transfusion.
  1. Febrile non-hemolytic transfusion reactions are due to the donor WBCs or the cytokines produced during storage of the unit.

**Table 30.3: Possible choices of ABO blood groups for red blood cell (RBC), plasma and platelet transfusions**

Recipient blood group	RBCs	Plasma	Platelets
O	O	O	O
A	A	A, B, AB	A, B, AB
B	B	A	A
AB	O	AB	AB
	B	B	B
	O	AB	AB
	AB	AB	AB
	A, B, O	A	

Acceptable ABO group of blood component to be transfused.

**Table 30.4: Indications for small volume red blood cell (RBC) transfusions in neonates**

<i>United States Guidelines</i> <sup>18</sup>	<i>Hemoglobin concentration</i>
Severe pulmonary or cyanotic heart disease / congestive heart failure	<15 g/dL
CPAP/MV with mean airway pressure > 6–8 cm H <sub>2</sub> O	<12 g/dL
FIO <sub>2</sub> >35% via oxygen hood	
CPAP/MV with mean airway pressure <6 cm H <sub>2</sub> O	<10 g/dL
FIO <sub>2</sub> < 35% via oxygen hood	
On nasal canula	
Significant apnea/bradycardia, tachypnea, tachycardia	
Low weight gain (<10 g/d over 4 days)	
Low reticulocyte count and symptoms of anemia	<7 g/dL
<i>British Guidelines</i> <sup>19</sup>	<i>Hemoglobin concentration</i>
Anemia in first 24 hours of life	<12 g/dL
Neonate receiving intensive care	<12 g/dL
Chronic oxygen dependency	<11 g/dL
Late anemia, stable patient	<7 g/dL
Acute blood loss	10% TBV
Cumulative blood loss in 1 week, neonate requiring intensive care	10% TBV

2. Alloimmunization can occur due to presence of WBCs. Patients in need of recurrent transfusions (e.g., platelets) may become refractory to the product used.
3. Transmission of cytomegalovirus (CMV)

Patients at high-risk of CMV include:

- a. Premature, seronegative neonates less than 1250 g who require blood component support.
  - b. Recipients of hematopoietic stem cell and solid-organ transplants
  - c. Other individuals who are severely immunocompromised.
- While CMV negative blood products are the ideal in these situations, the non-availability of the same makes leukoreduction a useful approach in this group of recipients.
4. Lymphocyte mediated lung toxicity like ARDS.
  5. Increased chances of graft rejection in recipients where future bone marrow transplant is planned.

Ideally, all transfusions should be leukodepleted especially in patients needing recurrent transfusions and in immunocompromised hosts. WBC filters, gamma irradiation, and using washed cell units can achieve leukodepletion.

WBC filtration can be either pre-storage (ideal) or at the bedside just prior to transfusion. Pre-storage filtration is done at the blood bank while

bedside filters are used for selected patients where a new filter is used for every transfusion. Pre-storage filtration is superior to bed-side filters as during storage cytokines are released which can contribute to transfusion reactions.

- B. *Gamma irradiation*: In immunocompromised patients the WBCs in the transfused units may cause transfusion associated—graft versus host disease (TA-GVHD). TA-GVHD carries a near 100% mortality risk. Gamma irradiation at 2500 cGy inactivates the donor WBCs and prevents TA-GVHD. Irradiated blood products are indicated in the following patients:
  - a. Patients who have hematologic malignancies and cancer patients undergoing intensive chemotherapy or immunomodulatory therapy (i.e., fludarabine and other purine analogs).
  - b. Bone marrow transplant recipients
  - c. Congenital immunodeficiencies (T cell)
  - d. Preterm neonates < 1200 g  
Irradiation should be done as close to the time of transfusion as possible.
- C. *Washed red cells*: Washing RBC units with sterile saline allows for removal of plasma proteins, microaggregates and cytokines that can cause allergic transfusion reactions. It removes only 90% of lymphocytes and is less efficient than WBC filters in that aspect. This is specially indicated in patients with IgA deficiency who can develop severe reactions during transfusions.

## PLASMA

### Description and Storage

A typical unit of plasma has a volume of 160-250 ml if obtained from a WB donation or 400-600 ml when obtained by plasmapheresis. Immediately following collection from a normal donor, plasma contains approximately 1 unit/ml of each of coagulation factors. Factors V and VIII, known as the labile coagulation factors, are not stable in plasma stored at 1-6 degree C. Plasma frozen within 8 hours of donation contains at least 0.70 unit/ml of Factor VIII and is referred to as fresh frozen plasma (FFP). In plasma frozen 8-72 hours after collection, referred to as frozen plasma the concentration of coagulation factors V and VIII may be reduced by as much as 15 percent.<sup>2</sup> FFP may be stored for 12 months at -18° C or colder. Storage at -30° C or colder is recommended for optimal maintenance of Factor VIII levels.

### Indications and Contraindications for Transfusion

As for RBC transfusion, the indications for FFP transfusions in children are most often generalized from observations in adult patients and/or based on expert opinion.

There is broad consensus that the appropriate use is limited almost exclusively to the treatment or prevention of clinically significant bleeding due to a deficiency of one or more plasma coagulation factors.<sup>1,3,20,21</sup> The common indications for FFP transfusions are:

1. Unknown factor deficiency presenting for the first time.
2. Isolated congenital coagulation factor deficiencies for which a safer and/or more appropriate product does not exist. (e.g., protein C or factor II, V, X, XI, or XIII deficiency).
3. A diminution of coagulation factors due to treatment with vitamin K antagonists.
4. Severe liver disease with abnormal coagulation profile, as prophylaxis or to control bleeding.
5. Disseminated intravascular coagulation (DIC) with bleeding.
6. Massive transfusion.

### Reversal of Warfarin Effect

Patients on warfarin are deficient in the functional vitamin K-dependent coagulation factors. Depending on the urgency and severity of the clinical situation, warfarin reversal may be attained by stopping or modifying warfarin therapy, by oral or parenteral

vitamin K administration, by plasma transfusion or in rare situations by the administration of a virus-inactivated plasma derived prothrombin complex concentrate.

### Severe Liver Disease

Severe liver disease is associated with multiple abnormalities of hemostasis and coagulation including:

1. Deficient biosynthesis of antithrombin III, proteins C and S, plasminogen, antiplasmin and coagulation factors.
2. Aberrant biosynthesis of several coagulation factors.
3. Accelerated destruction of coagulation factors.
4. Deficient clearance of activated coagulation factors and plasminogen activators.
5. Thrombocytopenia and platelet dysfunction.
6. Loss or consumption of coagulation factors in ascitic fluid.<sup>22</sup>

The consensus is that patients who are not bleeding or about to undergo an invasive procedure should not receive plasma merely to correct abnormal coagulation tests.<sup>2,20</sup> One exception to this may be patients with life-threatening acute fulminant hepatitis and extremely elevated INRs.

Three retrospective studies found that patients with liver disease and mild coagulopathy, i.e., a PT 1.5-fold or less than the mean of the normal range (corresponding to an INR of approximately 2.2), did not have excess bleeding with liver biopsy or minor invasive procedures such as paracentesis or thoracentesis.<sup>3,23,24</sup> Most guidelines recommended plasma transfusion prior to invasive procedures or surgery in patients with liver disease and PT levels > 1.5-fold normal or an INR > 2.2, although there are no studies to support or refute these recommendations.

### Disseminated Intravascular Coagulation

Acute DIC is characterized by the abnormal consumption of coagulation factors and platelets and may lead to thrombocytopenia, hypofibrinogenemia and increased PT, INR and/or activated partial thromboplastin time (APTT) with uncontrolled bleeding from wound and puncture sites. Retro-spective and uncontrolled evidence suggests that the transfusion of plasma, along with other blood components, may be useful in limiting hemorrhage, provided aggressive measures are simultaneously undertaken to overcome the triggering disease. Plasma transfusion is generally not recommended in the absence of bleeding or in chronic DIC.

### Massive Transfusion

Massive transfusion is usually defined as the replacement of a patient's total blood volume with stored blood in < 24 hours. However, even within this definition, the degree and rapidity of blood loss can be quite variable as can the underlying etiologies and associated complications. Thus, assessment of the need for replacement of coagulation factors by FFP transfusion must be individualized. Pathologic hemorrhage in the massively transfused patient is more often caused by dilutional thrombocytopenia than by the depletion of coagulation factors.

Past recommendations advocated routine transfusion of plasma (e.g., the administration of two units of plasma for every 5 units of red blood cells transfused) to reduce the risk of abnormal bleeding due to coagulation factor depletion during massive transfusion. But, to the extent that it is possible, blood transfusion therapy in the setting of massive transfusion should be guided by both the ongoing clinical evaluation of the patient and laboratory measurements of hemostasis.

### Congenital Coagulation Factor Deficiencies

Plasma has long been used to treat congenital deficiencies of hemostatic or anticoagulant proteins. It is the treatment of choice in an emergency, where a child presents with a severe bleed and a coagulopathy is suspected, but not yet diagnosed. Once more detailed evaluation as to the cause of the coagulopathy is available, more appropriate alternatives now exist for most of the congenital factor deficiency disorders.

Several investigators have studied the use of FFP in the treatment of pediatric HUS.<sup>25-27</sup> Experts have reached the consensus that plasma is not indicated for classic childhood HUS, i.e. the syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure following diarrhea associated with enterohemorrhagic *Escherichia coli* infection.<sup>28</sup> HUS and thrombotic thrombocytopenia purpura (TTP) may be indistinguishable pathologically, and the clinical manifestations of HUS occasionally approach those of TTP. In the absence of definitive studies, and in light of the adult TTP studies, plasma exchange seems to be a reasonable consideration in treating children with unusually complicated HUS, particularly those with atypical HUS and neurologic complications.<sup>29</sup>

### Special Considerations for Newborns

FFP is indicated for the treatment of clinically significant bleeding, or its prevention in the case of an

impending invasive procedure, due to a decrease in one or more coagulation factors, where a safer, appropriate, alternative therapy does not exist. In particular, for the neonate as for other patients, FFP is not indicated for the treatment of volume expansion or resuscitation alone. The problems in the neonate are compounded due to:

1. Difficulty in obtaining blood specimens.
2. Low levels of vitamin K-dependent factors.
3. Rapid depletion of the above factors in situations like DIC.

It may thus be reasonable to administer FFP transfusion relatively sooner in these situations to newborns and infants under 6 months of age than in older infants and children.

In vitamin K deficiency, life-threatening bleeding may require FFP treatment or in rare situations treatment with coagulation factor concentrates.

The use of FFP has been advocated for prevention of periventricular intraventricular hemorrhage (PVH-IVH) in the preterm infant, but the current evidence does not support the routine use of prophylactic FFP in preterm infants at risk for PVH-IVH.

In addition to the contraindications for FFP transfusion discussed above, in the newborn FFP should not be used as a fluid for hematocrit adjustment in erythrocyte transfusions nor as a replacement fluid in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome. As discussed above, FFP is used in newborns to prepare reconstituted whole blood where this product is indicated.

### Dosage and Administration

Compatibility tests before plasma transfusion are not necessary. Plasma should be ABO compatible with the recipient's RBCs (*see* Table 30.3). Usually, Rh group need not be considered. However, when large volumes of FFP are given to RhD-negative pediatric patients or women of childbearing age, prevention of RhD immunization by the use of Rh immunoglobulin should be considered. Because FFP undergoes a process of freezing, WBCs are killed or nonfunctional. Hence no leukodepletion or irradiation is required for FFP units. FFP may be thawed in a water bath at 30-37°C for 20-30 min in the blood bank. Thawed FFP should be used immediately especially if it is being used for correction of factor VIII deficiency.

The dose of FFP depends on the clinical situation and the underlying disease process. When FFP is given for coagulation factor replacement, the dose is 10-20 ml/kg. This dose will usually raise the level of coagulation factors by 20-40 percent immediately after

infusion. Post-transfusion monitoring of the patient's coagulation status (PT, APTT and/or specific coagulation factor assays) is important for optimal treatment.

It must be remembered that FFP can lead to allergic reactions, anaphylaxis and can cause all the plasma borne infections. Hence, its use should be reserved for the above conditions only. Some of the conditions where FFP use is inappropriate are listed below:

#### FFP not Indicated<sup>1,2</sup>

1. Intravascular volume expansion or repletion (where crystalloids, synthetic colloids or purified human albumin solutions are preferred).
2. Correction or prevention of protein malnutrition (where synthetic amino acid solutions are preferred).
3. Correction of hypogammaglobulinemia (where purified human immunoglobulin concentrates are preferred).
4. Treatment of any other isolated congenital procoagulant or anticoagulant factor deficiency for which a virus-inactivated plasma-derived or recombinant factor concentrate exist.
5. As replacement fluid in therapeutic apheresis procedures for disorders other than thrombotic thrombocytopenic purpura/adult HUS unless proven to be beneficial.
6. Prevention of periventricular bleeds in preterm neonates.

## PLATELETS

### Description and Storage

A platelet concentrate (PC) may be prepared from a random WB donation or by a apheresis procedure in which a single donor donates the equivalent of 4-8 PC.

Platelets collected by apheresis procedure are referred to as apheresis PC. PC contain a minimum of  $5.5 \times 10^{10}$  platelets/unit, approximately 50 ml of plasma, trace to 0.5 ml of RBCs and, depending upon the preparation techniques, varying number of leukocytes (predominantly monocytes and lymphocytes) up to levels of  $10^8$ /unit. Apheresis PC contain a minimum of  $3 \times 10^{11}$  platelets, approximately 250-300 ml plasma, trace to 5 ml of RBCs and, depending on the apheresis technique or instrument,  $10^6$ - $10^9$  leukocytes. PC and apheresis PC are stored for up to 5 days at 20-24°C with continuous gentle agitation. Storage at cold temperature is detrimental to platelet function. Due to the higher temperatures of storage, bacterial contamination is a problem and hence platelet lifespan is only 5 days.

### Indications for Transfusion

The suggested guidelines for platelet transfusion support in neonates are summarized in Table 30.5. The indications for platelet transfusion in pediatric subjects include.

### Decreased Platelet Production

1. Congenital or acquired aplastic anemia
2. Bone marrow infiltration with malignant or nonmalignant etiology
3. Myeloablative chemotherapy
4. Platelet functional disorders with active bleeding
5. In a bleeding patient platelet count should be maintained at  $> 50 \times 10^9/l$

In the 1970s and 1980s several studies addressed the issue of prophylactic versus therapeutic platelet transfusions for thrombocytopenic patients with acute

**Table 30.5: Suggested guidelines for platelet transfusion support in neonates**

Prophylactic platelet transfusion:

- Stable preterm neonates with platelet counts  $<30 \times 10^9/l$
- Stable term neonates with platelet counts  $<20 \times 10^9/l$
- Sick preterm neonates with platelet counts  $<50 \times 10^9/l$
- Sick term infants with platelet counts  $<30 \times 10^9/l$
- Preparation for an invasive procedure, e.g. lumbar puncture or minor surgery in neonates with platelet counts  $<50 \times 10^9/l$

Platelet transfusions in neonates with clinically significant bleeding:

- Neonates with platelet counts  $50 \times 10^9/l$
- Neonates with conditions that increase bleeding (e.g. DIC) and platelet counts  $<100 \times 10^9/l$
- Neonates with documented significant platelet functional disorders (e.g. Glanzmann thrombasthenia) irrespective of the circulating platelet count

DIC = Disseminated intravascular coagulation

leukemia. At a consensus development conference addressing platelet transfusion therapy sponsored by the National Institutes of Health in 1986, the panel concluded that patient with severe thrombocytopenia may benefit from prophylactic transfusions but that the commonly used threshold value of  $20 \times 10^9/l$  may sometimes be safely lowered<sup>30</sup> Slichter, in a review published in 1991, recommended that only patients with platelet counts  $< 5 \times 10^9/l$  should automatically get platelet transfusions. In others clinical judgment should be used to assess the need for platelet therapy.<sup>31</sup> Prophylactic transfusions at higher platelet counts should be reserved for patients in whom additional risk factors exist.<sup>32</sup>

While these stringent prophylactic platelet transfusion policies may be appropriate for many patients, 2 groups of leukemic patients appear to be at particularly high risk of fatal hemorrhage during induction chemotherapy, namely those with hyperleukocytosis and/or acute promyelocytic leukemia.

The risk factors for hemorrhage in patients with solid tumors are similar to those in leukemic patients, although an additional consideration is the predisposition to hemorrhage associated with local tumor invasion.<sup>33,34</sup>

In summary, just as the indication for a RBC transfusion should not be determined solely on the basis of an Hb level, the decision to administer a platelet transfusion should also be individualized, taking into account the clinical situation as well as the platelet level.

Prophylactic platelet transfusions are indicated for thrombocytopenic patients undergoing invasive procedures. At least one study suggests that major surgical procedures can be safely performed at platelet counts of  $50 \times 10^9/l$ .<sup>35</sup> Bone marrow aspiration and biopsy can be safely performed (with respect to local bleeding) at any platelet level. A Cochrane review addressing the optimal use of platelet transfusions in oncology and bone marrow transplant patients had inconclusive results. Their observations were that most studies done to provide guidelines for prophylactic platelet transfusions were done on small numbers of patients and hence underpowered.<sup>36</sup> Suggested guidelines for prophylactic platelet transfusions for pediatric patients with thrombocytopenia due to decreased platelet production are summarized in Table 30.6.<sup>1,2,37</sup>

### Massive Transfusion

Thrombocytopenia is frequently associated with massive transfusion. Depending on the underlying

**Table 30.6: Suggested guidelines for prophylactic platelet transfusions in pediatric patients with thrombocytopenia due to decreased platelet production**

- Platelet count  $<10 \times 10^9/l$
- Platelet count  $<20 \times 10^9/l$  and bone marrow infiltration, severe mucositis, DIC, anticoagulation therapy, a platelet count likely to fall below  $10 \times 10^9/l$  prior to next possible evaluation, or risk of bleeding due to local tumor invasion
- Platelet count  $<30-40 \times 10^9/l$  and DIC (e.g. during induction therapy for promyelocytic leukemia), extreme hyperleukocytosis, or prior to lumbar puncture or central venous line insertion
- Platelet count  $<50-60 \times 10^9/l$  and major surgical intervention

etiology of the bleeding, the thrombocytopenia may be dilutional from platelet loss through hemorrhage and/or due to platelet consumption. Platelet transfusion therapy should be based on consideration of several factors including platelet count, an assessment of the role of the thrombocytopenia in the observed bleeding and the estimated hemostatic platelet count necessary for the patient's given clinical situation.

### Platelet Dysfunction

Platelet dysfunction may be congenital thrombasthenia or secondary to patients taking platelet inhibitory drugs, sepsis, liver or renal failure and congenital platelet dysfunction. Patients with thrombasthenia should be transfused platelets only during significant bleeding episodes as frequent platelet transfusions makes them refractory to platelets due to alloimmunization. Platelet dysfunction due to platelet inhibitory drugs is unlikely to contribute to bleeding if the platelet count is  $>50 \times 10^9/l$ .

### Special Considerations for Newborns

Newborns should receive platelet transfusions in the same clinical settings as described above for older children. However, since newborns frequently manifest thrombocytopenia and since preterm infants are at risk for PVH-IVH, it is possible that the platelet level at which prophylactic platelet transfusions should be administered to newborns is higher than that recommended for other patients. The platelet levels at which prophylactic platelet transfusions were given to neonates varied tremendously: from  $< 20 \times 10^9/l$  to  $> 50 \times 10^9/l$  in stable preterm infants and  $< 20 \times 10^9/l$  to  $> 80 \times 10^9/l$  in sick preterm infants.<sup>38</sup> The non-bleeding premature infants

with platelet counts higher than  $60 \times 10^9/l$  should not receive prophylactic platelet transfusions.<sup>39</sup>

Neonates with thrombocytopenia due to maternal platelet alloantibodies require special consideration with respect to the indications for platelet transfusion.

### Dosage and Administration

ABO-incompatible platelets (i.e., platelets with A and/or B antigens given to a donor with corresponding antibody) are usually clinically effective. However, in some patients, particularly those receiving multiple platelet transfusions, there may be a poorer post-transfusion response than that obtained with ABO-compatible platelets, and some studies have suggested that the transfusion of ABO incompatible platelets is associated with the development of platelet refractoriness.<sup>40,41</sup> Also, there are reports of acute intravascular hemolysis following the transfusion of platelet concentrates containing ABO antibodies incompatible with the recipient's RBC's.<sup>42,43</sup> Therefore, it would seem prudent, particularly in small children where the volume of plasma may be relatively large with respect to the patient's total blood volume, to try to use ABO-matched platelets. If these are not available, units with plasma compatible with the recipient's RBC's should be chosen. If this is also not possible, units with low titers of anti-A or B should be selected or platelets may be volume reduced. Testing of PCs for RBC compatibility is not necessary unless red cells are detected by visual inspection.

Platelets do not carry Rh antigens.<sup>44</sup> However, the quantity of RBCs in platelet concentrates is sufficient to induce Rh sensitization even in immunosuppressed cancer patient.<sup>45,46</sup> Rh sensitization caused by platelet transfusion in Rh-negative patients can be prevented by the administration of Rh immunoprophylaxis.<sup>47,48</sup> A dose of 25  $\mu$ g of anti-D immunoglobulin will protect against 1 ml of RBCs.<sup>49</sup> If available, it is preferable to use a preparation of anti-D which can be administered intravenously.

A suitable starting platelet dosage that can be expected to raise the platelet level by  $50 \times 10^9/l$  is 1 PC/10 kg body weight. PC may be pooled before administration or infused individually. An equivalent dose for apheresis platelets is approximately 5 ml/kg. Patients with increased platelet consumption (e.g. with septicemia or DIC) or splenomegaly may require larger amounts of platelets and do not have the expected rise of platelet count. In patients who do not have a good platelet increment following a platelet transfusion, the following test can be performed. After obtaining a baseline platelet count a platelet transfusion is given

and a platelet count is performed at one hour and 24 hours after the transfusion. If both post-transfusion counts are low an immune mediated mechanism should be considered. If the 1-hour count is adequate but the 24-hour count is low then mechanisms like sepsis or hypersplenism should be considered.

PC or apheresis platelets may be volume reduced prior to infusion. However, this extra manipulation leads to platelet loss and if not carefully performed, may adversely affect platelet function and/or be a cause of bacterial contamination. Volume reduction should therefore be limited to patients who require severe volume restriction or situations where ABO-incompatible platelets are the only available PC for a neonate or child.

## GRANULOCYTES

### Description and Storage

Like other blood components, granulocytes are collected by apheresis. To assure clinical efficacy, granulocyte concentrates should contain a minimum of  $10^{10}$  polymorphonuclear cells (PMN)/unit. Leukapheresis collections of  $6-8 \times 10^{10}$  PMN/unit following donor stimulation with granulocyte colony stimulating factor G-CSF or steroids or both has been reported.<sup>2,50,51</sup>

There is a report of the preparation of granulocytes by pooling buffy coat layers separated from 4-8 units of fresh whole blood. In pediatric patients (ages 2 to 13 years), the mean leukocyte dose transfused was  $0.6 \times 10^9/kg$ .<sup>52</sup>

Granulocyte function deteriorates rapidly during storage. Thus, granulocytes should be transfused as soon as possible following collection and should not be given if stored for >24 hours. For the time between collection and infusion, granulocyte concentrates should be kept at 20-24°C, with little or no agitation.<sup>53</sup>

### Indication for Transfusion

Currently, granulocytes transfusions are reserved for patients with profound neutropenia not expected to recover within a week, more severe forms of congenital neutrophil dysfunction, in whom a severe bacterial or fungal infection has been documented and who are clinically deteriorating despite optimal antimicrobial therapy.<sup>54,55</sup> A Cochrane review of granulocyte transfusion use reported inconclusive evidence from RCTs to support or refute the generalized use of granulocyte transfusions in neutropenic patients. In their analysis studies using a higher granulocyte dose showed a lower mortality.<sup>56</sup>

### Special Considerations for Newborns

Newborns normally have a transient neutrophilia in the first week of life with mean normal absolute neutrophil counts ranging from  $11.0 \times 10^9/l$  at birth to  $5.5 \times 10^9/l$  at 1 week of life.<sup>57</sup> Septic newborns frequently develop neutropenia, defined in the newborn as an absolute neutrophil count below  $3.0 \times 10^9/l$ . Between 1981 and 1992, 5 controlled trials of granulocyte transfusions for neonatal sepsis have shown encouraging results. But, its use has not become widespread, possibly because of the difficulty of obtaining granulocytes as rapidly as would be required in this setting.

### Dosage and Administration

Once the decision to administer granulocyte transfusions has been made, they are administered daily until there is evidence of recovery of peripheral neutrophil counts or clinical evidence of recovery from the infection. For neonates and small children, a daily infusion of  $1 \times 10^9$  PMNs/kg should be given and for larger patients,  $2-3 \times 10^{10}$  PMNs. As there is significant RBC contamination, units must be ABO compatible and if possible RhD negative for RhD-negative recipients and must undergo the usual compatibility testing. Granulocyte transfusions are frequently associated with fever, chills and allergic reactions. These can be severe and lead to hypotension, respiratory distress and acute lung injury. Premedication to avoid reactions and close monitoring during transfusion is required. The granulocyte transfusion should be separated from amphotericin B infusion by 10-12 hours due to the chances of acute lung injury.<sup>2</sup> Alloimmunization frequently occurs in patients receiving granulocyte transfusions and may render the transfusions ineffective and/or be associated with adverse reactions including respiratory distress.<sup>55</sup> For patients, with HLA-and/or granulocytes-specific alloantibodies, only granulocytes from HLA-and/or neutrophils antigen-compatible donors should be used. Ideally all units should be irradiated before use. The transfusion is usually administered over 2-3 hours.

## CRYOPRECIPITATE

### Description and Storage

Cryoprecipitate is the precipitate formed when FFP is thawed at  $1-6^\circ\text{C}$ . The precipitate is then refrozen with 15 ml of the donor plasma and stored at  $-18^\circ\text{C}$  or less for a period of up to 1 year. Cryoprecipitate contains 80-100 units of factor VIII, 100-250 mg of fibrinogen and 40-70 percent of the von Willebrand factor and

30 percent of the factor XIII present in the original unit of plasma.

### Indication for Transfusion<sup>1,2,20</sup>

These include:

1. Hemophilia A
2. von Willebrand disease
3. Congenital deficiencies of fibrinogen (afibrinogenemia, dysfibrinogenemia, hypofibrinogenemia)
4. Factor XIII deficiency
5. DIC with bleeding.

### Dosage and Administration

Compatibility testing of cryoprecipitate units is unnecessary. However, cryoprecipitate does contain anti-A and B so the use of ABO-compatible units is preferable. Rh group need not be considered. The number of units of cryoprecipitate required is usually based on the amount necessary to obtain a hemostatic level of fibrinogen, i.e. a fibrinogen level  $> 0.8-1.0$  g/L. If the units are carefully pooled this can usually be accomplished by the transfusion of 1 unit/5-10 kg recipient weight.

Cryoprecipitate is prepared for transfusion by thawing at  $30-37^\circ\text{C}$  and mixing the thawed precipitate with 10-15 ml of sodium chloride 0.9 percent if necessary, according to the amount of plasma in the cryoprecipitate unit. The required number of units is then pooled.

Thawed cryoprecipitate should be stored at room temperature and transfused immediately after thawing or within 6 hours after thawing if used as a source of factor VIII. All pooled cryoprecipitate units must be used within 4 hours of pooling.

### Adverse Effects of Transfusions

Acute transfusion reactions are adverse effects seen at the time or within 24 hours of a blood product transfusion.<sup>1,2</sup>

They are of 2 types: (i) Immune related, (ii) Non-immune related.

Any form of a transfusion reaction is an emergency. The transfusion should be stopped immediately, the component bag checked for any possible error in transfusion, the immediate symptoms should be treated (as detailed below) and the blood bank informed. Fever during a transfusion could be due to both, benign or more serious complications of the transfusion. Fever can be caused by blood group incompatibility, bacterial contamination, febrile non-hemolytic transfusion reactions and allergic reactions.

### Acute Hemolytic Transfusion Reactions

These are often due to clerical errors with the inappropriate unit being transfused. The usual presentation include fever, chills, nausea, vomiting, shortness of breath, chest pain, renal angle tenderness, hypotension vasoconstriction, and hemoglobinuria. If severe it can progress to DIC and acute renal failure. The severity of the reaction is proportionate to the volume of mismatched transfusion already received.

### Febrile Non-hemolytic Transfusion Reactions

These are due to release of pyrogenic cytokines, interleukin (IL)-1 $\beta$ , IL-6, and IL-8 and tumor necrosis factor, by leukocytes within the plasma during storage. Prestorage leukoreduction and washing the blood product helps to decrease the incidence. Pre medication with antipyretics – is controversial.

### Allergic Reactions

These are the most common transfusion related reaction. It is due to soluble plasma proteins in the blood unit. The common symptoms range from mild localized urticaria, pruritus, and flushing to bronchospasm and anaphylaxis. Fever is usually absent. Antihistaminic help to control these reactions and pretreatment helps prevent recurrence.

### Transfusion Related Acute Lung Injury (TRALI)

This is an uncommon but potentially fatal immune related reaction. It presents acutely during or within 4 hours of a transfusion. The pathophysiology involves non-cardiogenic pulmonary edema characterized by hypoxia, acute respiratory distress and hypotension. There are two theories regarding the pathogenesis of TRALI. The first involves anti-neutrophil antibodies which cause sequestration of neutrophils within the lung leading to endothelial damage and vascular leakage. The second theory is called the neutrophil priming hypothesis. In this theory, the neutrophils are said to be primed by underlying conditions like sepsis or a hematological malignancy. Transfusions are thought to trigger activation of neutrophils by providing factors like cytokines and antibodies. The activated neutrophils subsequently cause a pulmonary edema like condition. Therapy may require mechanical ventilation, fluids and vasopressor support. Improvement usually occurs in 48-96 hours but up to 10-15% are fatal.

### Transfusion Related Infections

Transfusion related having stringent criteria for recipient safety prevents risk of infections. Blood banks follow protocols with regard to donor selection and screening with the aim of preventing transfusion related infections.

1. Donors who have received blood or blood products within the last 6 months are deferred from donating blood.
2. Persons giving history of viral hepatitis are deferred for donating for 1 year.  
Persons testing positive for hepatitis B or C are deferred permanently. All units are tested for hepatitis B and C.
3. Questionnaires are given to all donors, which include questions regarding their risk behavior related to HIV, and clinical symptoms related to AIDS. Such persons are deferred permanently from donating blood. ELISA based testing is used to detect units positive for HIV I/II. Some blood banks have facilities for nucleic acid testing of units for HIV. This testing is superior to ELISA based testing in that it reduces the window period for detection of the blood borne virus.
4. Donors giving history of STDs or past treatment for the same are deferred permanently. All units are tested for VDRL.
5. Persons with a history of malaria are deferred from donating blood for a 3-month period. All units are tested for the malarial parasite.

### Summary

There are very few randomized controlled studies on blood component therapy in the pediatric patient. Majority of the recommendations are based on extrapolation of the data from adults and on experience. Nevertheless there is a consensus on majority of the recommendations. It is most important to realize that in today's world there is hardly any place for using whole blood and majority of the situations require components to be used. Blood transfusion should be considered a serious procedure and used only when required.

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Type 1 diabetes (T1DM), earlier called insulin dependent diabetes mellitus (IDDM), juvenile diabetes or childhood onset diabetes, was believed to be rare in India.<sup>1</sup> It is now being realized that the incidence in North India is not very different from that in Western Caucasian populations; no population-based data is available, but ICMR has now initiated a registry. In terms of long-term need for medical care and attention, diabetes is one of the most demanding chronic disorders of childhood.

Diabetic ketoacidosis (DKA) is a major cause of hospital admission in T1DM, and the commonest cause of diabetes-related deaths in children. In Indian children, whether in India or abroad,<sup>2</sup> it continues to be the most common initial presentation; and to have a high mortality.<sup>3,4</sup> Our early experience showed that DKA accounted for 91 percent of deaths in childhood onset diabetes, all of them within a few hours, weeks or months of diagnosis.<sup>4</sup> A recent study of population-based cohorts shows that the most common cause of death in developing countries like Estonia and Lithuania continues to be DKA, with the country of origin and the age at diagnosis being significant predictors of mortality.<sup>5</sup> This underlines the importance of prevention, and of a high index of suspicion followed by early and appropriate management if these children are to survive.

Glucometers and test-strips for urine ketones are available across India, so diagnosis and monitoring of T1DM are possible even in the *smallest* set-up. Thus, every child presenting with polyuria, nocturia (recent bed wetting), weight loss, dehydration, tachypnea, drowsiness or unconsciousness, should be screened for diabetes. Also, it is no longer necessary to assume that *every* diabetic who goes into coma has hypoglycemia, and blindly give a trial of intravenous glucose. It is worthwhile to spend a couple of minutes testing blood glucose (BG), and avoid pushing a high glucose still further in case of hyperglycemia.

### Definition

DKA can be said to exist if the triad of hyperglycemia (BG >300 mg/dl), ketosis (ketonuria, i.e. urine ketones “moderate” or “large”, ketonemia i.e., plasma ketones > 3 mmol/l), and acidosis (plasma bicarbonate <15 mEq/L) are present.<sup>6</sup>

### Etiology

DKA may be the initial presentation of T1DM. If carefully asked for, a recent history of polyuria, polydipsia, polyphagia and weight loss in spite of normal or increased appetite is usually available. In a known diabetic, DKA is usually due to inadvertent or deliberate omission/reduction in insulin dosage,<sup>7</sup> and can develop very rapidly, occasionally within hours of missing a dose.<sup>6</sup> Therefore, sick day guidelines (see below) must be taught and frequently reinforced. Physical (illness, infection, trauma or surgery) or mental stress worsens matters. However, most children do not have clinical features of infection at presentation; the leukocytosis commonly encountered is most likely reflective of the severity of DKA rather than the presence of infection.<sup>8</sup> Adolescence is a period of physical and emotional turbulence with higher insulin requirements, in which DKA may occur more often. Users of insulin pumps have a higher frequency of DKA as any discontinuation of insulin supply (e.g., kinked or disconnected catheter) leads to a rapid fall in insulin levels.

All patients of DKA may not be comatose at presentation. Conversely, other causes of coma should be thought of when a diabetic child presents with drowsiness/unconsciousness. These include causes related to diabetes, such as hypoglycemia or hyperosmolar nonketotic coma (HNKC), and those unrelated to diabetes, such as head injury, hepatic coma, neurological infections, and salicylate poisoning, (Table 31.1).

Table 31.1: Differential diagnosis of diabetic ketoacidosis

Parameter	DKA	HNKC	Meningoencephalitis	Salicylate poisoning	GE with acidosis
Drowsiness	+	+	++	±	±
Respiration	Acidotic	Shallow	Central deep	Acidotic	Acidotic
Urine output	High	High	Normal	Normal	Low
Dehydration	++	+++	-	++	+++
Blood glucose	High	Very high	Normal	Normal	Normal
Ketones	+++	±	-	-	-
Bicarbonate	Low	Normal/low	Normal	Low	Low

DKA—Diabetic ketoacidosis, HNKC—Hyperosmolar nonketotic coma, GE—Gastroenteritis

### Pathophysiology

Absence or reduction in insulin levels, with increase in the counter-regulatory hormones, leads to hyperglycemia and ketosis.

*Insulin* stimulates anabolic processes in the liver, muscle and adipose tissue to permit glucose utilization and storage of the energy obtained from digested food. Insulin deficiency leads to lipolysis and glycogenolysis to supply energy needs. The resultant increase in free fatty acids leads to the increased formation of ketone bodies.

The *counter-regulatory hormones* (glucagon, epinephrine, cortisol and growth hormone) affect catabolic processes directly and indirectly by inhibiting the action of insulin. The essential paradox in DKA is that despite high BG levels there is a glucose deficit at the cellular level.<sup>9</sup>

*Hyperglycemia* leads to osmotic diuresis and loss of water. This in turn leads to dehydration, volume contraction, hyperosmolality, electrolyte imbalance and a reduction in glomerular filtration rate (GFR).

*Sodium* levels tend to be normal despite the free water loss. The high osmolality leads to a shift of intracellular water to the extracellular fluid. Factitious hyponatremia may be caused by the high triglyceride levels seen in severe DKA.

*Potassium* is the most severely affected electrolyte. Dehydration stimulates aldosterone activity, which worsens the effect of the osmotic diuresis. Vomiting further increases the potassium loss. Rehydration also leads to hypokalemia due to the dilution of serum potassium, improved GFR accelerating renal losses, correction of acidosis, and therapy with insulin leading to the return of potassium into the cells. *Phosphate* concentrations are also similarly affected.

Renal dysfunction and increased catabolism of protein lead to elevation of blood urea nitrogen and creatinine. The ketoacids, beta-hydroxy-butyric acid and acetoacetic acid are strong acids resulting in severe metabolic

acidosis, which adversely affects the functioning of several organs. Serum *bicarbonate* is usually low but the deficit is decreased by peripheral metabolism of lactic acid and ketoacids into bicarbonate. Supplementation of bicarbonate is hardly ever required.

*Hypocapnia* (caused by hyperventilation) leads to cerebral vasoconstriction and reduced cerebral blood flow. Depression of the vasomotor center leads to decreased arterial smooth muscle tone and depression of myocardial contractility. Potassium depletion as well as metabolic acidosis lead to paralytic ileus.<sup>10,11</sup>

### Clinical Features

The child with frank DKA usually presents with a history of progressive polyuria and polydipsia associated with malaise, lethargy, increasing drowsiness, nausea, vomiting, abdominal pain, deep, rapid, sighing respiration with a fruity odor of the breath. Dehydration may be of variable severity: assessment in young children may be difficult. Severity of dehydration is often overestimated. In a known diabetic, a precipitating cause like missed doses of insulin or a febrile illness can usually be obtained. Fever may not be present due to peripheral vasodilatation causing cooling. The precipitating event must be carefully looked for as it may merge imperceptibly with the signs and symptoms of DKA. An acute gastrointestinal illness may be diagnosed due to the vomiting and dehydration. However, the severity of dehydration in children with DKA is out of proportion to the severity of vomiting because of the continued fluid losses due to osmotic diuresis. The nausea, vomiting and abdominal pain may suggest a diagnosis of 'acute abdomen'. This usually improves with the correction of the DKA.

### Diagnosis

The diagnosis is usually straightforward, based on the history, physical examination and the presence of significant glucosuria and ketonemia, which can be estimated quickly at the bedside. It should be kept in

mind that capillary level of glucose may be inaccurate in the presence of poor peripheral circulation and severe acidosis. Plasma or serum acetone measurement is critical and can be done at the bedside using ketostix or nitroprusside powder.<sup>12</sup> One ml of serum or plasma (using oxalated blood) is diluted serially with the addition of normal saline to produce a set of tubes containing undiluted to 1:8 or 1:16 serum-saline mixture. From each dilution, 2 drops of serum (or plasma) are placed on separated small amounts of ketostix (or nitroprusside) and the color read at 2 minutes. Deep violet corresponds to 4+ (large), light purple to 3+ or 2+ (moderate) and light lavender to 1+ (trace). Multiplying the dilution with a correction factor of 0.4 (e.g. positive test in 1:16 dilution =  $16 \times 0.4$  mmol/L = 6.4 mmol/l) gives the approximate plasma ketone concentration.

Samples should simultaneously be sent to the laboratory: blood for estimation of glucose, urea, sodium, potassium, blood gas studies, and culture; urine for glucose, ketones and culture. Plasma osmolality should either be measured directly or calculated from sodium, glucose and urea values as it is the main determinant of severity and outcome. In assaying plasma creatinine, it should be remembered that acetoacetate (not  $\beta$ -hydroxybutyrate) causes severe interference of the alkaline picrate (Jaffe) assay; enzymatic assays lack this interference.<sup>13</sup>

### Management

Where available, the child should be in an intensive care unit experienced in the care of diabetes. The main steps of therapy are:

- i. The ABC of resuscitation.
- ii. Correction of fluid and electrolyte abnormalities.
- iii. Correction of metabolic acidosis.
- iv. Provision of adequate insulin to prevent ketosis and reduce hyperglycemia.
- v. Prevention and monitoring of complications.
- vi. Identification of precipitating factors and an attempt to avoid them in future.
- vii. Stabilization on a suitable insulin regime to achieve adequate control of hyperglycemia.
- viii. Reinforcement and teaching of sick day guidelines.

### The ABC

In the first few minutes, rapid physical examination should be done including assessment of airway, breathing and circulation, of level of dehydration and sensorium, while a brief history is taken. Intubation may be done if the patient is comatose; venous access (preferably two) is established, sampling of blood and urine done, and ECG monitoring started. The comatose child should also have stomach emptied by nasogastric suction to prevent aspiration, and catheterization of the urinary bladder. Strict monitoring and charting is the key to successful management. An ideal monitoring log is given in Table 31.2.<sup>14</sup>

### Fluid Resuscitation

The aim of therapy is to replace the calculated fluid deficit over 48 hours and to reduce the blood sugar levels as smoothly as possible. Potassium levels and ketonemia may take longer to normalize. The average losses of water and electrolytes during DKA are given in Table 31.3.

Table 31.2: Diabetic monitoring sheet

Hours after admission	0	0.5	1	2	3-3.5	4-4.5	5-5.5	6-6.5	7-7.5	8-9	10-12
Blood glucose using strips	+	+	+	+		+		+		+	+
Ketostix	+			+				+			+
Na <sup>+</sup> /K <sup>+</sup>	+							+			+
Ca <sup>2+</sup> /PO <sub>4</sub> <sup>3-</sup>	+								+		
Blood gases	+			+				+			+
Urea	+										
Creatinine	+										
Urine glucose	+										
Insulin U/kg		+		+	+		+	+			+
Fluid in		+									
Fluid out	+	+	+					+		+	+
Blood pressure	+	+	+					+		+	+
Heart rate	+	+	+			+		+		+	+
Respiratory rate	+	+	+					+		+	+
ECG	+		+								+

**Table 31.3: Average losses of fluids and electrolytes**

Components	Losses mean (range)	Maintenance requirements (per day)
Water	100 ml/kg (60-100)	1500 ml/m <sup>2</sup>
Sodium	6 mEq/kg (5-13)	45 mEq/m <sup>2</sup> (3 mEq/kg)
Potassium	5 mEq/kg (4-16)	35 mEq/m <sup>2</sup> (2 mEq/kg)
Chloride	4 mEq/kg (3-9)	30 mEq/m <sup>2</sup> (2 mEq/kg)
Phosphate	3 mEq/kg (2-5)	10 mEq/m <sup>2</sup> (0.7 mEq/kg)

If the child is in shock, 10-20 ml/kg of normal saline should be given rapidly over 20-60 minutes, and repeated if peripheral pulses remain poor. Ringer lactate may be used as an alternative to normal saline as the initial fluid. Advantages are the low levels of chloride and the presence of lactate, which is slowly metabolized to bicarbonate. The small amount of potassium present is not contraindicated unless the patient is anuric.

The volume deficit, usually of the order of 7-8%, is replaced over 36-48 hours, given along with maintenance fluids and replacement of ongoing losses. Recalculation of fluids every 2-4 hours based on the child's condition is mandatory, to safeguard against the development of fluid overload and cerebral edema. The BG will begin to fall with initial rehydration, even without insulin, which should be started once shock has been corrected.

#### Potassium

Total body potassium is always significantly depleted, though serum levels may be low, normal, or high, at admission. Serum potassium should be urgently obtained, or an ECG done to look for evidence of hypo- or hyperkalemia. Unless the child is hyperkalemic and/or anuric, potassium chloride should be added following initial resuscitation, at a rate of 40 mEq/l, before insulin is given. If there is documented hypokalemia, potassium should be added to the fluids even in the first hour, at a rate of 20 mEq/l. Potassium should be given throughout the period of IV therapy. Salts other than chloride (phosphate, acetate) may be used, but have not been proven to be preferable.

#### Insulin

Insulin should be started only after shock is reversed, and a normal saline/potassium rehydration solution begun. The most popular and physiological method of insulin infusion is the low dose continuous administration, which causes slow, steady and predictable improvement.

An infusion of soluble (regular) insulin at the rate of 0.1 unit/kg/hr (0.05 unit/kg/hr for very young children) should be started. Ideally a solution containing 1 unit/ml of saline should be given using an infusion pump; if a pump is not available, a solution containing 1 unit/10 ml can be used with a burette set. An initial intravenous bolus is not recommended. Insulin may be given through a separate line or piggybacked onto the running line using a Y-connection. After the initial fall of BG by 15-20% due to hemodilution, there is a predictable fall by about 10% every hour. Advantages of using low dose infusion are:

- i. It reduces BG slowly and predictably.
- ii. It saturates all insulin receptors.
- iii. It is as effective in inhibiting glycogenolysis, lipolysis and secretion of counter-regulatory hormones as higher dose infusions.
- iv. It corrects acidosis more slowly.
- v. It causes less hypokalemia and hypoglycemia.
- vi. It allows rapid adjustments of rate as and when needed.

Relative disadvantages are the need for microinfusion devices (intravenous sets can be used if such devices are not available) and for constant surveillance as inadvertent discontinuation results in rapid deterioration.

Once the level falls < 300 mg/dL, 5% dextrose is added to the fluids. This may be increased to 10% when needed, while maintaining the rate of insulin infusion at the rate of 0.1 U/kg/hr till acidosis resolves. BG falls very rapidly, dextrose can be added even before the level reaches 300 mg/dL. If intravenous infusion of insulin is not possible, intramuscular injections of 0.1 U/kg may be given hourly into the deltoid muscle. This regimen has all the advantages of the IV regimen, but may not be as effective if the patient is in shock.

A common mistake is to stop insulin infusion abruptly when blood glucose drops. IV glucose should be added to the infusion, but the insulin administration should continue at a rate of at least 0.05 U/kg/hr, as it promotes anabolism and reduces ketosis. Another common mistake is the failure to administer subcutaneous insulin 20-30 minutes before stopping IV infusion. This results in a rapid drop in insulin levels, and a worsening of hyperglycemia.

#### Bicarbonate

Bicarbonate should not be used, as there is no evidence either for its necessity or safety, and bolus doses have been shown to be associated with cerebral edema. Its use may be considered only if there is impaired cardiac

contractility in the presence of persistent shock. If used, it should be infused slowly (1-2 mmol/kg over 1 hour) and cautiously.<sup>15,16</sup>

### Supportive Therapy

Urine output must be carefully recorded throughout, but catheterization should be avoided except in the comatose patient. In the initial 6-10 hr, nothing should be given orally and gastric lavage may be necessary in the drowsy child who is vomiting. However, once the acidosis is resolved, the child has recovered full consciousness and can sit up and eat, he/she should be encouraged to do so. A long period of "nil orally" may result in hypoglycemia, particularly in the presence of fever and hepatic or renal disease.<sup>17</sup>

Routine use of prophylactic antibiotics should not be encouraged. If suspected, every attempt should be made to identify the precipitating infection, which should then be aggressively treated using appropriate antibiotics.

The suggested protocol for management is outlined in Table 31.4.

### Complications

1. **Severe shock:** This is an important complication, which may result in death. If there is no improvement in blood pressure after 1-2 hours of hydration, Gram-negative sepsis should be considered.<sup>18</sup>
2. **Cerebral edema:** Persistence or development of coma during therapy is often due to cerebral edema,
3. **Hypo/hyperkalemia:** Hypokalemia at presentation and hyperkalemia later in the course of the

which remains an important complication of DKA during childhood and is associated with very high morbidity and mortality.<sup>19,20</sup> The prognosis worsens if coma has lasted for over 8 hours. Factors implicated in the pathogenesis are large bolus doses of bicarbonate, rapid infusion of fluid, or too rapid a fall in BG levels. It is most likely to occur in the first 24 hours of therapy, often presenting with a worsening of the sensorium in spite of biochemical improvement. Warning signs and symptoms include headache, lethargy or irritability/restlessness, falling heart rate, rising blood pressure, decreased oxygen saturation, increased intraocular pressure, unequal or dilated pupils, and eventually convulsions, papilledema and respiratory arrest. Treatment should be early and aggressive: reduction in rate of IV fluids and elevation of the head end of the bed, administration of IV mannitol (0.5-1 g/kg over 20 min) and/or hypertonic saline (3%: 5-10 ml/kg over 30 min), dexamethasone and, if necessary intubation. Hyperventilation is no longer recommended, but the prognosis is very poor. Therefore, prevention with cautious fluid replacement, avoidance of BG fluctuations and very restricted use, if at all, of bicarbonate is recommended.<sup>21</sup> After treatment for cerebral edema is initiated, a head CT should be done to look for intracranial hemorrhage/thrombosis/other causes of coma, which would require specific treatment.

Table 31.4: Summary of management

Time	Aim	Method
1. Hour 0	ABC of resuscitation	Airway (intubate if comatose) Breathing Circulation
2. First 2-5 minutes	Establish the diagnosis	Brief history Assess sensorium, pupils, vitals Establish venous access Take blood and urine samples
3. Next 5-10 minutes	Volume repletion	20 ml/kg saline or plasma if in shock, otherwise as per 10% deficit
4. Next 20-30 minutes	Lowering of blood glucose Correction of ketosis	IV fluid infusion IV insulin infusion at 0.1 U/kg/h
5. Hour 1	Fine tuning of biochemistry	Change to N/2 saline Add potassium: adjust according to biochemistry reports
6. Hours 2-6	When blood glucose falls < 300 mg/dL	Add 5% dextrose to infusate Careful monitoring Careful maintenance of records

management due to overzealous therapy, may cause arrhythmias and even cardiac arrest. Hence therapy must be cautious and guided by frequent monitoring of serum potassium and ECG.

4. **Severe metabolic acidosis:** Prognosis worsens if pH is 6.9 or less, but bicarbonate therapy has its own problems, as discussed earlier.
5. **Acute renal tubular necrosis:** This may occur due to prolonged hypotension, due to delay in reporting to hospital or inadequate fluid therapy.

### Stabilization to Daily Insulin Requirements

Although vomiting is usually present during the first 12-24 hours of treatment, most patients will be well controlled within the first few hours and should be encouraged to take orally if they so desire. This can be even as early as 12 hours of therapy, initially with sips of water, and later with semi-solid and then solid food. Insulin should be changed to the subcutaneous route once BG levels are stabilized below 300 mg/dL, making sure that this is given at least half an hour before disconnecting the intravenous insulin. Regular insulin is given to cover each meal, switching to a split-mix or multiple daily injection regimen over the next 2-3 days.

### Sick Day Guidelines

Clear guidelines for sick days should be reinforced repeatedly. The main points are:

1. Never miss insulin completely, even if no food has been eaten or vomiting is present.
2. On sick days, test urine ketones and BG 4-6 times/day, and if hyperglycemia occurs, give a supplemental dose of insulin equal to 10% of total dose.
3. If food is not being tolerated, give whatever can be tolerated, including fruit juices, soups, lemonade, etc. Plenty of oral fluids are a must.
4. Rest and avoid exertion. If hyperglycemia or ketosis persists, consult the doctor immediately.

### Prognosis

In developed countries the overall mortality in uncomplicated DKA in children has been reduced from 40-60% to about 7%.<sup>17,21</sup> In developing countries like ours, the situation continues to be dismal,<sup>4,5</sup> especially as diabetics in remote areas may not have access to timely medical care. Hence, prevention of DKA and identifying factors associated with childhood diabetes assumes great importance.<sup>22,23</sup>

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The most common emergencies encountered in infancy and childhood which may have an endocrine basis include hypoglycemia, diabetic ketoacidosis, hypocalcemia, adrenal crisis and very rarely thyroid storm.<sup>1</sup> Two conditions in infancy which are not conventionally thought of as crises but do need rapid action by medical care givers, are congenital hypothyroidism (CH) and ambiguous genitalia. This chapter will deal with adrenal crisis and thyroid storm, and touch upon CH and ambiguous genitalia. Hypocalcemia, hypoglycemia and diabetic ketoacidosis are covered elsewhere.

### ADRENAL CRISIS

Adrenal insufficiency may be:

- *Primary*. This is due to insufficient secretion of glucocorticoid, mineralocorticoid hormones and/or adrenal androgens at the level of the adrenal cortex, or
- *Secondary/central*: This is due to insufficient secretion of ACTH/corticotrophin by the pituitary/ hypothalamus.

In primary causes, the gland is usually atrophic, with involvement of all the adrenal hormones, while in secondary causes, mineralocorticoid secretion is spared since it is not regulated by ACTH. Causes may be congenital or acquired (Table 32.1).

Like iabetic ketoacidosis, acute adrenal insufficiency or Addisonian crisis may occur as the first sign of the disorder, or in treated patients, precipitated by sepsis or surgical stress. Parents of children on steroid replacement, or in whom steroid therapy is being tapered off, should be frequently reminded to increase the dose of steroids during illnesses, and inform the Emergency Room doctor if the child needs to be taken to the hospital, because failure to do so may precipitate a crisis.

It is usually a life-threatening crisis with high mortality unless treated immediately. The common clinical presentation in an infant or child is weakness, fever, abdominal pain, tachycardia and tachypnea, hypotension, dehydration, cyanosis, and acute shock,

**Table 32.1: Causes of adrenal insufficiency**

#### Primary

##### *Congenital*

- Congenital adrenal hyperplasia (CAH)
- Congenital adrenal hypoplasia
- ACTH unresponsiveness: isolated/Triple syndrome (achalasia, alacrima)
- Aldosterone deficiency
- Adrenoleukodystrophy

##### *Acquired*

- Autoimmune: isolated/part of polyglandular syndrome
- Chronic infections: Tuberculosis, HIV
- Acute infections: Waterhouse-Friderichsen syndrome
- Others: Hemochromatosis, tumors, metastasis, trauma (delivery, surgery), drugs

#### Secondary

##### *Congenital*

ACTH deficiency: isolated/multiple hormone deficits  
Idiopathic/Associated with anatomic defects

##### *Acquired*

- Idiopathic: isolated/multiple hormone deficits
- Autoimmune
- Others: Tumors (e.g. craniopharyngioma), trauma (hemorrhage, surgery), drugs

associated with hypoglycemia, hyponatremia, hyperkalemia and acidosis. The nonspecific constellation of symptoms means that the diagnosis may be missed unless thought of and looked for. Diagnosis may often be delayed because it is not thought of.

Preceding these symptoms may be a history of anorexia, fever, or abdominal pain, weight loss, generalized fatigue, hypotension, skin pigmentation (usually involving axillae, groin, hand creases, nails, nipples, and buccal/vaginal mucosa) or salt craving. There may be history of a severe infection which can cause adrenal hemorrhage, e.g. meningococemia; of an underlying disorder which required steroids for therapy (e.g. nephrotic syndrome, malignancy), or of an autoimmune disorder (e.g. a child with type 1 diabetes, who suddenly starts having frequent hypoglycemic episodes).

Since the major deficiency is of mineralocorticoid hormones, the causes are usually primary adrenal failure. Age of onset depends on the cause.

### *During Infancy*

The causes are likely to be:

- Genetic (congenital adrenal hyperplasia [CAH]; more rarely, congenital hypoplasia, metabolic disorders)
- Traumatic (delivery) or
- Due to fulminant infection resulting in adrenal hemorrhage and thus insufficiency (Waterhouse - Friderichsen syndrome).

If the delivery was normal, and the presentation is at 1-2 weeks of life, the most likely cause is CAH. Girls with CAH have varying degrees of genital ambiguity due to *in utero* virilization, and so may get detected early. Affected boys or very severely virilized girls may be missed initially unless genital pigmentation is noticed, and be present in hypotension at age 1-2 weeks, or develop premature puberty in later childhood. Important clinical indicators are failure to thrive; shock disproportionate to the fluid loss; generalized and especially genital pigmentation; an empty scrotum (suggesting a highly virilized girl); or a family history of early neonatal deaths, genital ambiguity, or consanguinity. A high 17-hydroxyprogesterone (17-OHP) level is diagnostic. Congenital adrenal hypoplasia is a much rarer condition, which would present with severe salt losing syndrome, low serum cortisol and high ACTH levels, but not the characteristic hormonal profile of CAH. It may be inherited as the autosomal recessive form or the X-linked form.

In any sick infant, it is critical that before steroids are given during resuscitation, a serum sample is drawn and the lab given strict instructions that the serum is to be saved for any analysis which may be thought of later, e.g. 17-OHP or ACTH levels.

### *In Later Childhood*

A crisis may be the first presentation of Addison disease or CAH, or occur in a child known to have the disorder. Addison disease may be due to autoimmune destruction (features of other autoimmune disorders may be present); tuberculosis or HIV infection, or any fulminant infection like meningococemia; or as part of polyglandular syndromes or adrenoleukodystrophy. A child on high doses of steroids may go into crisis if the steroids are suddenly withdrawn for any reason, or if a stress situation develops when the steroids are being withdrawn. Central deficiency due to pituitary problems like tumors (e.g. craniopharyngioma), surgery,

hemorrhage, or hypophysitis would have features of other pituitary deficiencies. Additional features of these illnesses (thyroid disorders, hypoparathyroidism, hypogonadism, short stature, vitiligo, pigmentation, CNS deficits, etc.) may provide a clue.

### *Investigations*

Serum ACTH levels distinguish primary (high) from secondary causes (inappropriately low). An ACTH stimulation test is a sensitive assessment of adrenal reserve, which can be performed at any time of the day. A bolus dose of ACTH (0.25 mg) is given IV or IM, and serum cortisol, tested at 0 and 60 minutes; normally cortisol increases to 30 µg/dl. A stimulated cortisol level of < 15 µg/dL confirms insufficiency. 17-OHP levels can be tested before and after ACTH injection similarly, or simultaneously, if needed. The low dose ACTH test (1 µg instead of the standard 250 µg) has been proposed as being more sensitive, and may be particularly useful in mild deficiency states and in secondary hypoadrenalism/ panhypopituitarism. If panhypopituitarism is suspected, levels of other hormones should be tested. MRI of the pituitary or adrenal area may give the anatomic diagnosis. However, all these investigations must be deferred till after management of the acute crisis is over.

### **Management**

Acute management consists of rapid correction of fluid and corticosteroid deficiency.<sup>2</sup> Large doses of corticosteroids take care of the mineralocorticoid needs in the acute stage.

- In the first hour, 5% dextrose in normal saline should be given at double the maintenance rate (20 ml/kg) to correct dehydration and hypoglycemia. If the child is in shock, a 10-20 ml/kg bolus of normal saline should be given over the first hour. Over the next 24 hours, 60 ml/kg fluids should be given IV.
- Hydrocortisone is given intravenous as a stat bolus dose (25 mg/m<sup>2</sup>: 50 mg for infants, 100-150 mg for older children) followed by 100 mg/m<sup>2</sup>/day as a continuous infusion in the fluids. Once the child is stable, this can be slowly tapered off (reduce by one-third every day, reach maintenance by day 5).
- Once the daily hydrocortisone dose is less than 100 mg, fludrocortisone (0.05 mg/day in infants, 0.1 mg/day in older children and adults) should be added. Glucocorticoid replacement should be done with hydrocortisone, which is the most physiological. It is given at the dose of 15-25 mg/m<sup>2</sup>/day, preferably

in 2-3 divided doses, early in the morning, evening and late night. The need for frequent doses often leads to poor compliance, to improve which substitution by prednisone (2.5 mg/m<sup>2</sup>/day in 2 divided doses) can be tried. However, the very small doses of prednisone required are difficult to give, so smooth control is usually not achieved in young children with prednisone.

### Prevention

Family members of children on replacement steroids should be clearly instructed and frequently reminded about the need for stepping up the dose 2-3 times during stress conditions like illnesses, and for parenteral dosing when oral intake is reduced, or during severe stress. It is equally important to emphasize that stress doses should be returned to normal as quickly as possible, to avoid Cushingoid changes.

### THYROID STORM (ACCELERATED HYPERTHYROIDISM)

Thyrotoxicosis is unusual in children, thyroid storm even more so. Hyperthyroidism in children is almost always due to Graves' disease, and tends to develop insidiously, so the diagnosis may be missed initially. *Storm* may be precipitated in the untreated child during stress induced by surgery, trauma, sepsis, or radioiodine therapy, and needs a high index of suspicion to be detected. If missed or inadequately treated, it is associated with a high mortality of up to 90%.

### Clinical Features

Thyroid storm starts abruptly and is characterized by hyperthermia (fever > 38.5° C) and sweating; high output cardiac failure with marked tachycardia which is out of proportion to fever; mental disturbances: restlessness, confusion, delirium, convulsions, or coma; nausea, vomiting, abdominal pain and occasionally jaundice. Because children tolerate the hypermetabolic state much better than adults, symptoms may not be as marked as in adults, but usually a history of restlessness, with a drop in school performance, weight loss in spite of an increased appetite, tiredness, poor and restless sleep, heat intolerance, diarrhea and enuresis, may be available. Goiter is almost invariable,<sup>3</sup> while eye and skin signs are rare.

### Diagnosis

Diagnosis is simple, once it is suspected, with high serum T4, and low or undetectable TSH. Levels are not

necessarily very deranged. If thyroid antibodies are looked for, they are frequently positive, and if a thyroid scan is done, it shows a diffusely increased uptake.

### Management

Management in children is similar to that in adults:

- Provide resuscitation if necessary and ensure adequate airway, circulation and respiration.
- Reduce body temperature quickly with hydrotherapy.
- Administer beta blockers (e.g. propranolol 2 mg/kg/day in 3-4 divided doses).
- Control thyroid hormone levels rapidly: initially using Lugol's iodine (5-6 drops orally three times a day) or iopodate 0.01 µg/kg/day given for 2-3 days; later adding neomercazole (0.5 mg/kg/day). Earlier, propylthiouracil (PTU) was preferred in thyroid storm as it was thought to give an additional benefit of blocking peripheral conversion of T4 to T3. With documentation of liver failure with PTU, its use has currently fallen out of favor.
- Give hydrocortisone (2 mg/kg as IV bolus, followed by 30-40 mg/m<sup>2</sup>/day IV in 4 divided doses).
- Treat precipitating causes, if any.

### Neonatal Graves Disease

This is very rare because thyrotoxicosis in pregnancy is unusual, and neonatal disease occurs in less than 2% of those affected. It is due to transplacental passage of stimulatory antibodies from the mother, whose Graves disease may be active or inactive. The infant presents with irritability, flushing, tachycardia, hypertension, goiter, exophthalmos, and failure to thrive, with eventual cardiac failure and death. There may be hepatosplenomegaly, jaundice, and thrombocytopenia. Diagnosis is simple, with suppressed TSH and high T4, free T4, and T3, but may be missed if the mother's Graves disease is not active. Therefore a high index of suspicion is required if the mother has had any thyroid disorder in the past.

Spontaneous resolution in 3-12 weeks, as the effect of maternal antibodies wanes, is the norm. Treatment consists of sedatives, digitalization, iodine or iopanoic acid (250-500 mg orally every 3-4 days), and antithyroid drugs in the doses mentioned above, along with propranolol and high dose corticosteroids if needed, and fairly rapid discontinuation of medication as the condition resolves. Iodine/ iopanoic acid should not be given for very long as they can themselves induce thyrotoxicosis later, and their administration should be accompanied by neomercazole.

### CONGENITAL HYPOTHYROIDISM

Ideally, all newborns should have screening for congenital hypothyroidism (CH), since clinical features are absent in 90-95% affected newborns. Developed nations have adopted neonatal screening as a mandatory policy, as its cost effectiveness has been proven beyond all doubt. In India, the large population and uneven distribution of health resources may make universal screening a dream at present, but several large hospitals in urban areas are doing universal screening for the last few years. The experience of screening several thousand newborns at Vellore suggests that the incidence of CH may be as much as 1 in 1100 rather than 1 in 3000-4000 deliveries seen in Western countries [personal communication]. Given the easy access to thyroid hormone testing, screening should be aggressively offered wherever possible. For example, pediatricians/gynecologists can ensure that a cord blood sample for TSH be taken in all hospital deliveries, in hospitals they work in. A cord blood TSH of > 25-30  $\mu\text{U}/\text{ml}$  is suspect, and a venous sample should be taken as early as possible for testing T4 and TSH to confirm the diagnosis. Almost 90% of infants with proven CH have TSH levels > 50  $\mu\text{U}/\text{ml}$ . Once the diagnosis is made, replacement with thyroxine (12-15  $\mu\text{g}/\text{kg}/\text{day}$  as a single daily dose) should be started as soon as possible, but definitely before the age of 2 weeks. If a Tc thyroid scan can be conveniently done before or within a day or two of starting replacement, it would help in giving the etiological diagnosis. Thyroid dysgenesis (ectopia, agenesis) may be easily diagnosed, while dyshormonogenesis may be suspected in the enlarged gland. However, treatment should not be delayed for obtaining a scan.

If the cord blood has not been collected, the thyroid surge which occurs in all newborns can interfere with interpretation of results. TSH levels rise sharply within a few minutes of birth, and fall to < 10-15  $\mu\text{U}/\text{ml}$  by 48-72 hours. Thereafter, TSH levels of up to 10  $\mu\text{U}/\text{ml}$  are normal till the age of 10-12 weeks of life. Therefore sampling can be done at any time, as long as the age (in days) is kept in mind and the appropriate cut off used. Sampling should be done soon, so that if the TSH is high the confirmatory repeat sample can be taken, and treatment can be started by 2 weeks of age.

If the newborn's TSH was not tested at all, it should be done whenever the baby is first seen by a pediatrician, so that if CH is present, any further delay in replacement does not occur. *It should be remembered*

*that delaying the diagnosis and start of therapy, or inadequate initial therapy has been shown to reduce IQ permanently by about 5 points every month.* Confirmation of the diagnosis of CH and initiation of early, adequate thyroxine replacement therapy is therefore a medical emergency.

Monitoring of therapy should be done by testing serum T4 every 2-4 weeks initially and every 2-3 months after the first 3 months till 3 years of life. TSH levels should not be checked before 4-5 weeks after a dose change. Serum T4 should be maintained in the high normal range, and TSH within the normal "adult" range. The dose requirements gradually come down to the adult dose of 1-2  $\mu\text{g}/\text{kg}/\text{day}$ .

### AMBIGUOUS GENITALIA

The birth of a child with ambiguous genitalia continues to remain a social emergency in India. It is critical to make an **accurate** assignment of sex early, but without undue haste, and taking into consideration existing sex of rearing, parental preferences, and ease of surgery. For this a team approach is best, involving family, pediatrician, pediatric endocrinologist, geneticist, and if available, a psychologist familiar with the issues involved. Correction of genitalia should not be rushed. A newborn with salt losing CAH may also develop a medical emergency in the form of an adrenal crisis (discussed above) if the ambiguity is missed or ignored. Diagnosis requires estimation of 17-hydroxyprogesterone. If values are equivocal, an ACTH stimulation test is helpful: 250  $\mu\text{g}$  IV or IM bolus of ACTH is given, and 17-OHP tested before (0 minutes) and 60 minutes after the injection. Early treatment with moderate doses of hydrocortisone (15-25  $\text{mg}/\text{m}^2/\text{day}$ ) and fludrocortisone, and education of the family on how to increase the dose of hydrocortisone during periods of stress, help ensure normal growth and avoidance of crisis.

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Calcium plays an integral role in membrane electrical conduction, muscle contraction, enzyme activity and skeletal mineralization. Calcium exists in three fractions: ionized or free calcium, accounting for about 50 percent of total calcium; protein bound calcium, accounting for 40 percent; and calcium complexed with phosphate, citrate or bicarbonate, accounting for the remaining 10 percent. Ionized calcium is the physiologically active portion which is tightly regulated. Therefore serum calcium level estimation should also include the ionized calcium level.

Calcium homeostasis is maintained by vitamin D and parathyroid hormone (PTH). Hypocalcemia causes an increase in PTH secretion, which through several different actions, restores serum calcium to normal. PTH increases calcium retention by promoting renal reabsorption of calcium, blocking renal reabsorption of phosphate, and increasing the activation of 25(OH)D to the bioactive 1,25(OH)<sub>2</sub>D, i.e. calcitriol. Calcitriol increases the gastrointestinal absorption of calcium and phosphate, mainly in the duodenum and upper jejunum, and facilitates the action of PTH on distal tubule absorption of calcium. Calcitriol increases serum calcium and phosphate, and promotes mineralization of bone; whereas PTH, by activating osteoclasts to release calcium and phosphate from the bone, increases bone resorption. Calcitonin, by opposing PTH action, inhibits bone resorption and enhances renal tubular excretion. These regulatory mechanisms maintain ionized calcium level between 4 to 5 mg/dL and the total calcium 8.5 to 10.5 mg/dL.

Nearly, 80-90% of protein bound calcium is bound to albumin. When the serum albumin level is reduced, total serum calcium is decreased without necessarily altering the ionized calcium. With each decrease of 1 g/dL of albumin, there is a decrease of 0.8 mg/dL of total calcium. Besides serum protein concentration, acid-base changes also influence protein binding of calcium and thereby, the ionized calcium level.

Acidosis increases while alkalosis decreases ionized calcium levels by affecting competitive binding of hydrogen ions to albumin binding sites.

Calcitonin is secreted by thyroid parafollicular C cells, and antagonizes the bone and renal actions of PTH, with no measurable effects on the intestine. No changes in calcium homeostasis are seen after thyroidectomy, so the role of calcitonin in normal calcium homeostasis is uncertain, but because it causes calcium deposition in bone, it can be used in the acute treatment of hypercalcemia and osteoporosis.

### HYPOCALCEMIA

Hypocalcemia is defined as total serum calcium less than 8.5 mg/dL in children, less than 8 mg/dL in neonates and less than 7 mg/dL in preterm neonates. Ionized calcium level less than 2.5 mg/dL is also an important criterion for diagnosis of hypocalcemia. It is a common cause of seizures, especially in neonates; but may present as tetany, laryngospasm, or altered sensorium. In neonates, apart from seizures, presentation may be with high pitched cry, tachypnea, or apnea. In a seizing or otherwise sick child, hypocalcemia is most often due to abnormalities in parathyroid function or vitamin D metabolism. It appears to be encountered more often with rising prevalence of vitamin D deficiency (VDD). Serum calcium should be routinely tested in acutely sick children who have an underlying condition, which can predispose to calcium abnormalities, e.g. thalassemia, malabsorption, malnutrition, chronic kidney or liver disease or who have findings such as papilledema (or bulging anterior fontanelle) or subcapsular cataracts. In critically ill children, hypocalcemia is frequently observed simply as an asymptomatic laboratory abnormality due to impaired PTH secretion; in this setting, particularly in neonates, its treatment is controversial. However, infants and children with hypocalcemia are reported to have a higher mortality rate in pediatric intensive care units (PICU) than children with normal calcium levels.

### Etiology

The common causes of hypocalcemia in critically sick children are mentioned in Table 33.1.

**Table 33.1: Etiology of hypocalcemia in critically sick children**

- Septicemia, burns
- Use of citrated preserved blood exchange blood transfusion
- Hypomagnesemia
- Neonatal hypocalcemia
- Drugs: Steroids, furosemide, albumin, plasma expanders, phenytoin, phenobarbitone, aminoglycosides, ketocanazole, pentamidine, bisphosphonates, antineoplastic agents (plicamycin, asparaginase, cisplatin, cytosine arabinose, doxorubicin)
- Nephrotic syndrome
- Hyperphosphatemia due to renal failure or hemolysis
- After neck surgery, thyroidectomy, parathyroidectomy, tracheal reconstruction
- Cardiac surgery with cardiopulmonary bypass
- Acute pancreatitis, tumor lysis, rhabdomyolysis
- Vitamin D deficiency; metabolic disorders (e.g. in malnutrition, GI or liver disease)
- Hypoparathyroidism (autoimmune, DiGeorge and other syndromes), parathyroid dysfunction (thalassemia, hemochromatosis)
- Hungry bone syndrome

### Clinical Features

Hypocalcemia developing in critically sick children mainly affects the central nervous system, neuromuscular and cardiovascular systems.

- Neuromuscular irritability:** Numbness and tingling of lips, hands and toes, carpopedal spasms, muscle cramps, muscle twitching and laryngeal stridor.
- CNS manifestations:** Tremors, generalized seizures, and apnea. Latent tetany may be detected by positive Trousseau sign (tonic and clonic contractions of the hand muscles induced by decreasing blood flow to the extremity) and Chvostek sign (spasms of facial muscles evoked by tapping the facial nerve anterior to external auditory meatus).
- CVS manifestations:** Hypotension due to decrease in systemic vascular resistance and cardiac contractility, poor myocardial contractility, catecholamine unresponsiveness, prolongation of corrected QT interval, T wave inversion, and bradycardia.

Hypokalemia has a protective effect over cardiac manifestations of hypocalcemia.

### Investigations

The following investigations are useful in hypocalcemia:

#### Laboratory Studies

- *Serum calcium, total and ionized:* Measurement of ionized calcium level is essential to differentiate true

hypocalcemia from a mere decrease in total calcium concentration. A decrease in total calcium can be associated with low serum albumin and high pH.

- *Serum magnesium:* During critical illness, hypomagnesemia is an important cause of hypocalcemia, since low magnesium levels impairs the regulatory response to low calcium concentrations.
- *Serum phosphorus:* This should be checked simultaneously with calcium. A high P suggests low PTH activity (unless there is renal failure), and is ominous because  $Ca \times P$  more than 70 predisposes strongly to deposition of insoluble calcium phosphate in tissues such as the kidney and joints. Levels fall in early rickets.
- *Serum alkaline phosphatase:* This rises in states of high bone turnover, and thus is also useful to establish the cause of hypocalcemia. It is usually elevated in patients with rickets.
- *PTH:* PTH is indicated if hypocalcemia persists in the presence of normal magnesium and normal or elevated phosphate levels.
- *Vitamin D:* For diagnosis of vitamin D deficiency (VDD), serum 25(OH)D level should be checked, as it has a long serum half life. Under the influence of raised PTH, the level of serum 1,25(OH)<sub>2</sub>D may initially actually be higher in VDD and therefore misleading.
- Urinary calcium, phosphorus, magnesium and creatinine should be assessed in patients with suspected renal tubular defects and renal failure.
- *Serum electrolytes and glucose:* Seizures and irritability may be due to hypoglycemia or sodium abnormalities.

#### Imaging Studies

- *Chest radiography:* To evaluate for thymic shadow, which may be absent in patients with DiGeorge syndrome.
- Ankle and wrist radiography to evaluate evidence of rickets.

*Electrocardiograph:* To evaluate various ECG changes of hypocalcemia.

### Management

Severe, symptomatic hypocalcemia should be treated immediately, with 10-20 mg of elemental calcium/kg infused intravenously over 10-20 minutes under ECG monitoring. Commonly 10% calcium gluconate (1 ml = 9.3 mg of elemental calcium) is used. An alternative is 10% calcium chloride (1 ml = 36 mg of elemental calcium). Continuous IV calcium infusion: 20-80 mg/kg/day may be needed to maintain normocalcemia. The following precautions should be taken while giving

calcium intravenously: (i) It should be given diluted slowly to avoid thrombophlebitis; (ii) There should be no extravasation, as it causes tissue necrosis (a central line is preferable); (iii) It should be given slowly under cardiac monitoring; (iv) Bicarbonate or phosphate containing solutions cannot be administered concomitantly; and (v) With severe hyperphosphatemia, calcium administration may lead to soft tissue calcification. Hypomagnesemia, if present, is corrected with 25-50 mg magnesium/kg of a 50% solution of  $MgSO_4$  given IV or IM every 4-6 hourly. Neonates require a dose of 10-20 mg/kg.

For treating asymptomatic hypocalcemia or maintaining normocalcemia, oral calcium supplementation is preferred, in a dose of 25-100 mg/kg/day, divided in 4-6 doses. Simultaneously, calcitriol (10-50 ng/kg/day) should be started, except in VDD, when oral vitamin D 1200-1600 IU/day or 1 sachet of 60,000 IU/month for 2-6 months is adequate (and much less expensive). Serum and urine calcium levels must be followed carefully, aiming for a low normal serum calcium (just enough to prevent symptoms), and making sure hypercalciuria does not occur.

If hypocalcemia is severe or persistent, hypomagnesemia should be considered. If present, it should be treated with 0.5 ml of 50% magnesium sulfate IM twice daily followed by 25-50 mg/kg/day orally. Treatment of underlying cause for hypocalcemia is important.

## HYPERCALCEMIA

Hypercalcemia, defined as total serum calcium more than 11 mg/dL, is not commonly seen in children.

### Etiology

Hypercalcemia occurs when more calcium comes in from the intestine or bone than the kidney can throw out, or renal reabsorption of calcium is too high. Causes can thus be divided into abnormal vitamin D or parathyroid metabolism, abnormal calcium sensing or handling. Table 33.2 enumerates the causes of hypercalcemia in children.

### Clinical Features

Symptoms occur consistently in severe hypercalcemia (serum total calcium > 13.5 mg/dL), but may be seen even in mild hypercalcemia (12-13.5 mg/dL). Symptoms mainly involve the gastrointestinal and nervous systems: nausea, vomiting, dehydration, altered sensorium, convulsions, and coma; neonates may present with

**Table 33.2: Causes of hypercalcemia**

- Immobilization
- Excessive vitamin D administration, or granulomatous disorders like TB, sarcoidosis
- Malignancies
- Hyperparathyroidism: primary or secondary (renal failure)
- Hyperthyroidism
- Idiopathic hypercalcemia of infancy (William syndrome)
- Subcutaneous fat necrosis
- Use of thiazide diuretics

**Table 33.3: Clinical features of hypercalcemia**

#### *Nervous System*

- Personality changes
- Malaise
- Headache
- Hallucinations
- Unsteady gait
- Proximal muscle weakness
- Irritability
- Confusion

#### *Gastrointestinal System*

- Anorexia
- Nausea, vomiting
- Constipation
- Abdominal cramps
- Paralytic ileus
- Symptoms of pancreatitis
- Gastritis

#### *Renal Symptoms*

- Renal stones
- Nephrogenic diabetes insipidus
- Bone pains
- Bradycardia
- Hypertension
- Pruritus
- Conjunctivitis, keratopathy
- ECG changes: Shortened QT interval, widened T wave
- Renal failure

respiratory distress or apnea. A level over 14 mg/dL is potentially life-threatening, as it may cause ventricular ectopics, drowsiness and coma.

The clinical features are summarized in Table 33.3.

Laboratory studies include serum calcium, phosphate, magnesium, alkaline phosphatase, parathormone, vitamin D metabolites, creatinine and urinary calcium levels. Imaging studies include plain radiography for pathological fractures, bone cysts (osteitis fibrosa cystica), bony metastases and demineralization of bones. In addition, ultrasonography, intravenous pyelography, CT scan study and/ or nuclear scan studies may be needed.

### Management

Hypercalcemia is managed by correction of dehydration, restriction of calcium intake and increasing calcium excretion. General measures include mobilization of the patient, discontinuation of calcium containing fluids, avoidance of rich sources of calcium,

hydration with diuretic therapy and correction of other electrolyte disturbances, with careful monitoring of fluids and electrolytes during therapy. Medication can be summarized as follows:

- i. Hydration: 4-10 ml/kg/hour normal saline with potassium supplementation
- ii. Furosemide: 1 mg/kg/IV every 4-6 hourly
- iii. Calcitonin: 4-8 units/kg/SC every 6-12 hourly
- iv. Steroids: prednisolone 1-2 mg/kg/day
- v. Bisphosphonates: zoledronate IV single dose, or pamidronate 0.5-1 mg/kg/dose
- vi Peritoneal or hemodialysis
- vii. If available, mitramycin 25 mg/kg/day

If parathyroidectomy is necessary, calcium and vitamin D supplements should be given immediately postoperative to prevent hypocalcemia due to "hungry bones".

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# 34 Management of Severely Malnourished Children

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Malnutrition in children is widely prevalent in India. It is estimated that 57 million children are under-weight (moderate and severe). More than 50% of deaths in 0-4 years are associated with malnutrition.<sup>1</sup> The median case fatality rate is approximately 23.5% in severe malnutrition, reaching 50% in edematous malnutrition.<sup>2</sup> There is a need for standardized protocol-based management to improve the outcome of severely malnourished children. In 2006, Indian Academy of Pediatrics undertook the task of developing guidelines for the management of severely malnourished children based on adaptation from the WHO guidelines.<sup>3</sup> We summarize below the revised consensus recommendations (and wherever relevant the rationale) of the group.

## Definition of Severe Malnutrition

Severe malnutrition is defined in these guidelines as the presence of severe wasting (< 70% weight-for-height or  $\leq 3SD$ ) and/or edema. Mid-upper arm circumference (MUAC) criteria may also be used for identifying severe wasting. The following parameters are associated with an increased risk of mortality:

- Weight for height/length < 70% NCHS median or  $\leq 3SD$ .
- Visible severe wasting.
- Bipedal edema.
- MUAC < 11 cm.<sup>4</sup>

## Initial Assessment of a Severely Malnourished Child

The initial assessment of a severely malnourished child involves a good history and physical examination. The key points to be covered include history of: (i) Recent intake of food and fluids; (ii) Usual diet (before the current illness); (iii) Breastfeeding; (iv) Duration and frequency of diarrhea and vomiting; (v) Type of diarrhea (watery/bloody); (vi) Loss of appetite; (vii) Fever; (viii) Symptoms suggesting infection at different sites; (ix) Family circumstances (to understand

the child's social background); (x) Chronic cough and contact with tuberculosis; (xi) Recent contact with measles and (xii) Known or suspected HIV infection.

On examination, it is essential to look for: (i) Anthropometry-weight, height/length, mid arm circumference; (ii) Signs of dehydration; (iii) Shock (cold hands, slow capillary refill, weak and rapid pulse); (iv) Lethargy or unconsciousness; (v) Severe palmar pallor; (vi) Localizing signs of infection, including ear and throat infections, skin infection or pneumonia; (vii) Fever (temperature  $\geq 37.5^{\circ}C$  or  $\geq 99.5^{\circ}F$ ) or hypothermia (rectal temperature  $<35.5^{\circ}C$  or  $<95.9^{\circ}F$ ); (viii) Mouth ulcers; (ix) Skin changes of kwashiorkor; (x) Eye signs of vitamin A deficiency and (xi) Signs of HIV infection.

## Management

The current guidelines recommend in-patient management of all severely malnourished children. The treatment guidelines are divided into ten essential steps as shown below:

1. Treat/prevent hypoglycemia.
2. Treat/prevent hypothermia.
3. Treat/prevent dehydration.
4. Correct electrolyte imbalance.
5. Treat/prevent infection.
6. Correct micronutrient deficiencies.
7. Initiate re-feeding.
8. Achieve catch-up growth.
9. Provide sensory stimulation and emotional support.
10. Prepare for follow-up after recovery.

Table 34.1 depicts the time-frame for initiating/achieving these 10 steps.

### Step 1: Treat/Prevent Hypoglycemia

All severely malnourished children are at risk of hypoglycemia, hence blood glucose should be measured immediately at admission by using glucose estimating reagent paper strips such as dextrostix-reagent strips. There is evidence to suggest association between the

**Table 34.1: Time table for the management of child with severe malnutrition<sup>3</sup>**

Steps	Stabilization		Rehabilitation Weeks 2-6
	Days 1-2	Days 3-7	
1. Hypoglycemia	→		
2. Hypothermia	→		
3. Dehydration	→		
4. Electrolytes	→		→
5. Infection	→	→	
6. Micronutrients	→		→
7. Initiate feeding	→	→	
8. Catch-up growth			→
9. Sensory stimulation			→
10. Prepare for follow-up			→

hypoglycemia and risk of mortality in severely malnourished children (Table 34.2).<sup>5</sup>

### Diagnosis

Blood glucose level < 54 mg/dL or 3 mmol/L is defined as hypoglycemia in a severely malnourished child. If blood glucose cannot be measured, assume hypoglycemia and treat.

Hypoglycemia may be asymptomatic or symptomatic. Symptomatic hypoglycemia manifests as lethargy, unconsciousness or seizures. Sympathetic manifestations of hypoglycemia like pallor and sweating are rare in severe malnutrition but may occur. Peripheral circulatory failure and hypothermia may be a manifestation of hypoglycemia.

Hypothermia, infection and hypoglycemia generally occur as a triad. Hence, in the presence of one of these, always look for the others.

### Treatment

If the child has hypoglycemia, but is conscious:

- Give 50 mL of 10% glucose or sucrose solution (1 rounded teaspoon of sugar in 3½ tablespoons of water) orally or by nasogastric tube followed by the first feed (see Step 7 for type and amount of feed).

- Start feeding 2 hourly day and night (Initially one can give 1/4th of the 2 hourly feed every 30 minutes till the blood glucose stabilizes).

- Start appropriate antibiotics.

If the hypoglycemic child is symptomatic (unconscious, lethargic or seizing):

- Give 10% dextrose i.v. 5 mL/kg (if unavailable give 50 mL 10% dextrose or sucrose solution by nasogastric tube).
- Follow with 50 mL of 10% dextrose or sucrose solution by nasogastric tube.
- Start feeding with the starter F75 diet as quickly as possible and then continue the feeds 2-3 hourly day and night (Initially one can give 1/4th of the 2 hourly feed every 30 minutes till the blood glucose stabilizes).
- Start appropriate antibiotics.

### Monitoring

If the initial blood glucose was low, repeat an estimation using finger or heel-prick blood after 30 min. If the blood glucose is again low, repeat 50 mL of 10% dextrose or sucrose solution (as described above). Blood glucose monitoring may have to continue every 30 min till the blood glucose becomes normal and stabilizes; thereafter, start 2 hourly feeding.

**Table 34.2: Association between hypoglycemia and mortality<sup>5</sup>**

	No. of cases	% weight deficit for length	Blood sugar (mg/100 mL) rate (%)			Mortality
			Max	Mean	Min	
Kwashiorkor	10	26	100	77	45	0
Marasmic infant, blood glucose > 50 mg%	18	29	81	68	51	16.6
Marasmic infant, blood glucose < 50 mg%	15	29	50	34	14	26.6
Marasmic infants with symptomatic hypoglycemia	21	29	25	11	0	52.1

In case the body temperature falls (axillary temperature is less than 35°C or rectal temperature is less than 35.5°C) or consciousness deteriorates measure the blood sugar.

### Prevention

The cornerstone of prevention is feeding at regular intervals.

- Feed 2 hourly starting immediately (if necessary, rehydrate first).
- Ensure the child is fed regularly throughout the night.

### Step 2: Treat/Prevent Hypothermia

All severely malnourished children are at risk of hypothermia due to a lowered metabolic rate and decreased body fat. Children with marasmus, concurrent infections, denuded skin and infants are at a greater risk. Always look for and manage hypoglycemia in a hypothermic child.

### Diagnosis

- Hypothermia is diagnosed if the rectal temperature is less than <math>35.5^{\circ}\text{C}</math> or 95.5°F. If axillary temperature is less than 35°C or 95°F or does not register on a normal thermometer, assume hypothermia. Use a low reading thermometer (range 29–42°C), if available.
- Hypothermia can occur in summers as well.
- Always measure blood glucose and screen for infections in the presence of hypothermia.

### Treatment

- Feed the child immediately (if necessary rehydrate first).
- Clothe the child with warm clothes and use a warm blanket. Ensure that the head is also covered well with a scarf or a cap.
- Provide heat with an overhead warmer, an incandescent lamp or radiant heater. Do not point the heater directly at the child and avoid contact with hot water bottles, so as to prevent burns. Indirect warming with warm pads could be attempted.
- Or the child could be put in contact with the mother's bare chest or abdomen (skin to skin) as in kangaroo mother care to provide warmth.
- Give appropriate antibiotics.

### Treatment of Severe Hypothermia (Rectal Temperature <math>< 32^{\circ}\text{C}</math>)

- Give warm humidified oxygen.
- Give 5 mL/kg of 10% dextrose IV immediately or 50 mL of 10% dextrose by NG route (if IV access is difficult).
- Start IV antibiotics (see section below).
- **Rewarm:** Provide heat using radiation (overhead warmer), or conduction (skin contact) or convection (heat convector). Avoid rapid rewarming as this may lead to dysequilibrium.
- Give warm feeds immediately, if clinical condition allows the child to take orally, else administer the feeds through a nasogastric tube. Start maintenance IV fluids (pre warmed), if there is feed intolerance/contraindication for nasogastric feeding.
- Rehydrate using warm fluids immediately, when there is a history of diarrhea or there is evidence of dehydration.

### Monitoring

- Measure the child's temperature 2 hourly till it rises to more than 36.5°C.
- Monitor temperature especially at night when the ambient temperature falls and ensure the child is always well covered (particularly the head) and fed on time.
- Check for hypoglycemia whenever hypothermia is found.

### Prevention

- Feed the child 2 hourly starting immediately after admission.
- Ensure feeds are administered through the night.
- Always keep the child well covered. Ensure that head is also covered well with a scarf or a cap.
- Place the child's bed in a draught-free area away from doors and windows to prevent exposure to cold air.
- Minimize exposure after bathing or clinical examination.
- Minimize contact with wet clothes and nappies and keep the child dry always.
- Let the child sleep in close contact with the mother.
- The child could also be put in contact with the mother's bare chest or abdomen (skin to skin) as in kangaroo mother care to provide warmth.

### Step 3: Treat/Prevent Dehydration

#### Diagnosis

Dehydration tends to be overdiagnosed and its severity overestimated in severely malnourished children. This is because it is difficult to estimate dehydration status accurately in the severely malnourished child using clinical signs alone. However, it is safe to assume that all severely malnourished children with watery diarrhea may have some dehydration. It is important to recognize the fact that low blood volume (hypovolemia) can co-exist with edema.

#### Treatment

Do not use the IV route for rehydration except in cases of shock. The IAP recommends the use of reduced osmolarity ORS with potassium supplements given additionally (Table 34.3).

**Table 34.3: Composition of reduced osmolarity ORS**

Component	Concentration (mmol/L)
Sodium	75
Chloride	65
Potassium	20
Citrate	10
Glucose	75
Osmolarity	245

Add 20 mmol/L of additional potassium as syrup potassium chloride (15 mL of the syrup provides 20 mmol/L of potassium).

- Give the reduced osmolarity ORS, orally or by nasogastric tube, much more slowly than you would when rehydrating a well-nourished child:
- Give 5 mL/kg every 30 minutes for the first 2 hours, then give 5-10 mL/kg/hour for the next 4-10 hours.

#### Special Note

WHO suggests that when using the new ORS solution, containing 75 mEq/L of sodium the ORS packet should be dissolved in two liters of clean water. 45 mL of potassium chloride solution (from stock solution containing 100 g KCl/L) and 50 g sucrose should be dissolved in this solution. These modified solutions provide less sodium (37.5 mmol/L), more potassium (40 mmol/L) and added sugar (25 g/L). IAP Task Force feels that reduced osmolarity ORS without further dilution can be used safely as recommended above, given slowly over a period of 8-10 hours. Extrasugar and potassium can be provided as described in Step 1 and Step 6.

The exact amount depends on how much the child wants, volume of stool loss, and whether the child is vomiting.

Feeding must be initiated within two to three hours of starting rehydration. Give F75 starter formula on alternate hours (*e.g.*, hours 2, 4, 6) with reduced osmolarity ORS (hours 3, 5, 7) (see Step 7 for volume of feed).

Then continue feeding with starter F-75 feeds (see composition Tables 34.6 and 34.7).

#### Monitoring

Monitor the progress of rehydration half-hourly for 2 hours, then hourly for the next 4-10 hours:

- Pulse rate
- Respiratory rate
- Oral mucosa
- Urine frequency/volume
- Frequency of stools and vomiting.

Be alert for signs of overhydration (increasing respiratory rate by 5 per min and pulse rate by 15 per min, increasing edema and periorbital puffiness), which can be dangerous and may lead to heart failure. If you find any sign of overhydration, stop ORS immediately and reassess after one hour. Do not use diuretics in this setting. Decrease in the heart rate and respiratory rate (if increased initially) and increase in the urine output indicate that rehydration is proceeding. The return of tears, a moist oral mucosa, less sunken eyes and fontanelle, and improved skin turgor are also indicators of rehydration; however, these changes may not be seen in some severely malnourished children even when fully rehydrated.

Stop ORS for rehydration if any four hydration signs are present (child less thirsty, passing urine, tears, moist oral mucosa, eyes less sunken, faster skin pinch).

#### Prevention

Measures to prevent dehydration from continuing watery diarrhea are similar to those for well-nourished children (see Treatment Plan A of Management of Acute Diarrhea),

- If the child is breastfed, continue breastfeeding.
- Initiate refeeding with starter F-75 formula.
- Give reduced osmolarity ORS between feeds to replace stool losses. As a guide, give 50-100 mL (approx. 5-10 mL/kg) after each watery stool. Do not confuse frequent passage of small unformed stools with profuse watery diarrhea; the former does not require fluid replacement.

### Severe Dehydration with Shock

It is important to recognize severe dehydration in severely malnourished children. The management is targeted at replenishment of the intravascular volume by use of intravenous fluids to improve the perfusion to the vital organs. In children with severe malnutrition who present with shock, it may be difficult to distinguish severe dehydration from septic shock. Severely malnourished children must be lethargic/unconscious to be diagnosed with 'shock'.<sup>3</sup> History of profuse watery diarrhea and rapid improvement on intravenous fluids favor the diagnosis of shock due to severe dehydration.

*Note:* A severely malnourished child with signs suggesting severe dehydration but without a history of watery diarrhea should be treated for septic shock.

### Fluid Management for Severe Dehydration (Flow chart 34.1)

Intravenous fluids should be given to severely malnourished children if they have signs of shock and are lethargic or have lost consciousness. In case of inability to secure intravenous access, intraosseous route should be used. Ideally, Ringer's lactate with 5% dextrose should be used as rehydrating fluid. If not available, use half normal (N/2) saline with 5% dextrose. The other alternative is to use Ringer's lactate solution.

- Give oxygen
- Give rehydrating fluid at slower infusion rates of 15 mL/kg over the first hour with continuous monitoring (pulse rate, pulse volume, respiratory rate, capillary refill time, urine output).
- Administer IV antibiotics.
- Monitor pulse and respiratory rates every 10-15 min. If there is improvement (pulse slows; faster capillary refill) at the end of the first hour of IV fluid infusion, consider diagnosis of severe dehydration with shock. Repeat rehydrating fluid at the same rate over the next hour and then switch to reduced osmolarity ORS at 5-10 mL/kg/hour, either orally or by nasogastric tube.
- If there is no improvement or worsening after the first hour of the fluid bolus, consider septic shock and treat accordingly.

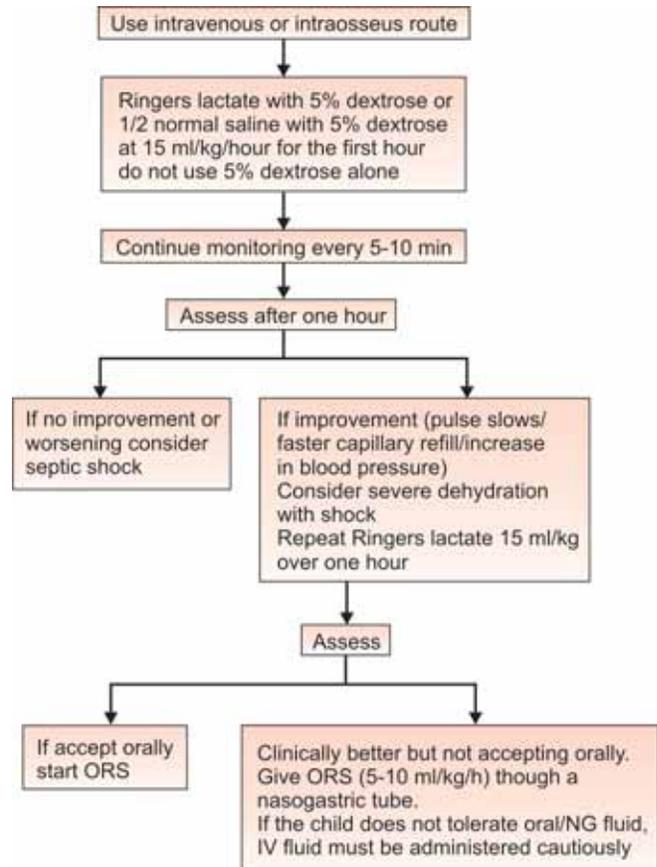
### Caution

Do not use 5% dextrose alone.

Add potassium to the IV fluids at the rate of 1.5 mL per 100 mL after the patient passes urine.

There must be frequent monitoring to look for features of overhydration and cardiac decompensation (see Appendix 34.1 for management of septic shock).

**Flow chart 34.1:** Fluid management for severe dehydration in severely malnourished children



### Step 4: Correct Electrolyte Imbalance

Excess body sodium exists even though the plasma sodium may be low in severely malnourished children. Giving high amounts of sodium could kill the child. In addition, all severely malnourished children have deficiencies of potassium and magnesium; these may take two weeks or more to correct. Edema may partly be due to these deficiencies. Do NOT treat edema with a diuretic.

### Treatment

- All severely malnourished children need to be given supplemental potassium at 3-4 mmol/kg/day for at least 2 weeks. Potassium can be given as syrup potassium chloride; the most common preparation available has 20 mmol/15 mL.

*Note:* Wherever it is possible to measure serum potassium and there is severe hypokalemia i.e., serum potassium is < 2 mmol/L or < 3.5 mmol/L with ECG changes, correct by starting at 0.3-0.5 mmol/kg/hour

infusion of potassium chloride in intravenous fluids, preferably with continuous monitoring of the ECG. For arrhythmia attributed to hypokalemia, give 1 mmol/kg/hour of potassium chloride till the rhythm normalizes; this has to be administered very carefully with controlled infusion and continuous ECG monitoring.

- On day 1, give 50% magnesium sulphate (equivalent to 2 mmol/mL). IM once (0.3 mL/kg up to a maximum of 2 mL) Thereafter, give extra magnesium (0.4-0.6 mmol/kg daily) orally. Injection magnesium sulphate can be given orally as a magnesium supplement mixed with feeds.
- Prepare food without adding salt.

Potassium and magnesium can also be supplemented daily by preparing a stock solution of the WHO electrolyte and mineral mix and adding 20 mL of this solution to 1 liter of feed (Appendix 34.2 for composition).

### Step 5: Treat/Prevent Infection

In severe malnutrition, multiple infections are common. However, the usual signs of infection such as fever are often absent. Review of literature identifies few studies, mainly from Africa, that have looked at the prevalence of infections in severely malnourished (Table 34.4).<sup>6-8</sup>

In a study from Egypt, 62% of the studied children had lower respiratory tract infection (33% pneumonia, 29% bronchitis). Signs and symptoms were few and mostly non specific in these children. The authors suggested that chest X-ray should be mandatory in evaluating patients with SMN whenever possible.<sup>9</sup>

Similarly, there are studies that have documented high rates of urinary tract infections in children with SMN (Table 34.5).

All these studies showed high rates of infection and majority of the bloodstream infections were due to gram negative bacteria. This provides the basis for the recommendation that all severely malnourished children should be assumed to have a serious infection on their arrival in hospital and treated with antibiotics. In addition, hypoglycemia and hypothermia are considered markers of severe infection in children.

### Investigations

In addition to complete clinical evaluation, following investigations may be done for identifying the infections in SMN children, whenever and wherever feasible/available.

- Hb, TLC, DLC, peripheral smear
- Urine analysis and urine culture
- Blood culture
- X-ray chest
- Mantoux test
- Gastric aspirate for AFB
- Peripheral smear for malaria (in endemic areas)
- CSF examination (if meningitis suspected).

### Treatment

All severely malnourished children should receive broad-spectrum antibiotics. Give parenteral antibiotics to all admitted children.

- Ampicillin 50 mg/kg/dose 6 hourly IM or IV for at least 2 days; followed by oral amoxicillin 15 mg/kg

**Table 34.4: Prevalence of infections in children with SMN**

Authors year published	Age	Children studied	Prevalence of infection	Bacterial isolates
Isaack H, et al. (1992) Tanzania <sup>6</sup>		164	92%	<i>Staphylococcus</i> , <i>E. coli</i> , <i>Klebsiella</i>
Shimeles D, et al. (1994) Ethiopia <sup>7</sup>	4-60 months	90	> 80%	Gram -ve enteric organism
Noorani N, et al. (2005) Kenya <sup>8</sup>	2-60 months	91	28.9%	Mostly Gram -ve

**Table 34.5: Prevalence of UTI in children with SMN**

Authors/Country	Children studied	Prevalence of UTI	Common bacterial isolates
Berkowitz, et al. (1983), Atlanta <sup>10</sup>	68	31%	<i>E. coli</i>
Caksen H, et al. (2000) <sup>11</sup>	103	30%	<i>E. coli</i>
Rabasa, et al. (2002), Nigeria <sup>12</sup>	194	11.3%	Gram negative bacteria; predominantly <i>E. coli</i>
Bagga, et al. (2003), India <sup>13</sup>	112	Bacteriuria in 17 (15.2%) SMN and 2 (1.8%) in control	

8 hourly for five days (once the child starts improving) and

- Gentamicin 7.5 mg/kg *or*  
Amikacin 15-20 mg/kg I.M or I.V once daily for seven days.

If the child fails to improve within 48 hours, change to IV Cefotaxime (100-150 mg/kg/day 6-8 hourly)/Ceftriaxone (50-75 mg/kg/day 12 hourly). However, depending on local resistance patterns, these regimens should be accordingly modified.

If meningitis is suspected, perform lumbar puncture for confirmation, where possible, and treat the child with IV Cefotaxime (200 mg/kg/day 6 hourly) and IV Amikacin (15 mg/kg/day 8 hourly) for 14-21 days. Moreover, if staphylococcal infection is suspected add IV Cloxacillin (100 mg/kg/day 6 hourly).

Besides the above, if other specific infections (such as pneumonia, dysentery, skin or soft-tissue infections) are identified, give appropriate antibiotics.

Add antimalarial treatment if the child has a positive blood film for malaria parasites.

Tuberculosis is common, but anti-tuberculosis treatment should only be given when tuberculosis is diagnosed.

Some experienced doctors routinely give metronidazole (7.5 mg/kg 8-hourly for 7 days) in addition to broad-spectrum antibiotics. However, the efficacy of this treatment has not been established by clinical trials.

### Monitoring

It is important to look for response to treatment. The response will be indicated by resolution of the initial symptoms and signs of infection, if any. The child's activity, interaction with parents and appetite should improve. If there is no improvement or deterioration of the symptoms/signs of infection, the child should be screened for infection with resistant bacterial pathogens, tuberculosis, HIV and unusual enteric pathogens.

### Prevention of Hospital Acquired Infections

The healthcare personnel should follow standard precautions. The effectiveness of hand hygiene should be emphasized to all health care providers, attendants and patients. It is essential that adequate safety measures are taken to prevent the spread of hospital acquired infections, since these children are at higher risk of acquiring infections due to their lowered/compromised immune status.

Give measles vaccine if the child is > 6 months and not immunized, or if the child is > 9 months and had

been vaccinated before the age of 9 months, but delay vaccination if the child is in shock.

### Step 6: Correct Micronutrient Deficiencies

All severely malnourished children have vitamin and mineral deficiencies. Micronutrients should be used as an adjunct to treatment in safe and effective doses. Up to twice the recommended daily allowance of various vitamins and minerals should be used. Although anemia is common, do not give iron initially. Wait until the child has a good appetite and starts gaining weight (usually by week 2). Giving iron may make infections worse.<sup>14</sup>

- Give vitamin A orally on day 1 (if age >1 year give 200,000 IU; age 6-12 m give 100,000 IU; age 0-5 m give 50,000 IU) unless there is definite evidence that a dose has been given in the last month.
- Give daily multivitamin supplement containing (mg/1000 cal): Thiamin 0.5, Riboflavin 0.6 and Nicotinic acid (niacin equivalents) 6.6. It is better to aim for a formulation that is truly multi (e.g., one that has vitamins A, C, D, E, and B<sub>12</sub>).
- Folic acid 1 mg/d (give 5 mg on day 1).
- Zinc 2 mg/kg/d (can be provided using zinc syrups/zinc dispersible tablets).
- Copper 0.2-0.3 mg/kg/d (will have to use a multivitamin/mineral commercial preparation).
- Iron 3 mg/kg/d, only once child starts gaining weight; after the stabilization phase.

### Step 7: Initiate re-feeding

Start feeding as soon as possible with a diet, which has:

- Osmolarity less than <350 mosm/L.
- Lactose not more than 2-3 g/kg/day.
- Appropriate renal solute load (urinary osmolarity <600 mosm/L).
- Initial percentage of calories from protein of 5%.
- Adequate bioavailability of micronutrients.
- Low viscosity, easy to prepare and socially acceptable.
- Adequate storage, cooking and refrigeration.

### Start Cautious Feeding

- Start feeding as soon as possible as frequent small feeds. Initiate nasogastric feeds if the child is not being able to take orally, or takes < 80% of the target intake.
- Recommended daily energy and protein intake from initial feeds is 100 kcal/kg and 1-1.5 g/kg respectively.

**Table 34.6: Starter diets**

Diets contents (per 100 mL)	F-75 Starter	F-75 Starter (Cereal based) Ex: 1	F-75 Starter (Cereal based) Ex: 2
Cows milk or equivalent (mL) (approximate measure of one katori)	30 (1/3)	30 (1/3)	25 (1/4)
Sugar (g) (approximate measure of one level teaspoon)	9 (1 + 1/2)	6 (1 )	3 (1/2)
Cereal: Powdered puffed rice* (g) (approximate measure of one level teaspoon)	–	2.5 (3/4)	6 (2)
Vegetable oil (g) (approximate measure of one level teaspoon)	2 (1/2)	2.5 (1/2+)	3 (3/4)
Water: make up to (mL)	100	100	100
Energy (kcal)	75	75	75
Protein (g)	0.9	1.1	1.2
Lactose (g)	1.2	1.2	1.0

\* Powdered puffed rice may be replaced by commercial pre-cooked rice preparations (in same amounts).

**Note:**

1. Wherever feasible, actual weighing of the constituents should be carried out. Household measure should be used only as an alternative, as they may not be standardized.
2. The above charts give the composition for 100 ml diet. Wherever there is a facility for refrigeration, 1 liter diet could be prepared by multiplying the requirement of each constituent by 10.

- Total fluid recommended is 130 mL/kg/day; reduce to 100 mL/kg/day if there is severe, generalized edema.
- Continue breastfeeding *ad libitum*.

#### Starter Diets (Adapted from WHO Guidelines) Recommended in Severe Malnutrition

The diets given below have been adapted for the hospital based Indian settings from the diets recommended in the WHO manual.<sup>3</sup> Some examples of diets are given, which could be used to initiate feeding in severely malnourished children. Of these diets, two use cereals in addition to sugar. In addition, older children could be started on cereal-based diets (Table 34.6). However, there is need for adapting diets using similar concepts in different regional settings in the country.

The cereal-based low lactose (lower osmolarity) diets are recommended as starter diets for those with persistent diarrhea.<sup>15</sup> Lactose free diets are rarely needed for persistent diarrhea as most children do well on the above mentioned, low lactose F-75 diets. Children with persistent diarrhea, who continue to have diarrhea on the low lactose diets, should be given lactose (milk) free diets.<sup>14</sup> Examples are shown in Appendix 34.3.

#### How to Prepare the Feeds?

Milk cereal diets do not need cooking, as powdered puffed rice is pre-cooked. Add the sugar and oil to powdered puffed rice. Add the milk and water to prepare the feed.

#### Feeding Pattern in the Initial Days of Rehabilitation

The volume of feeds should be increased gradually while decreasing the frequency of administration (Table 34.7). The calories should be increased only after the child is able to accept the increased volume of feeds.

**Table 34.7: Feeding pattern in the initial days of rehabilitation**

Days	Frequency	Vol/kg/feed	Vol/kg/day
1-2	2 hourly	11 mL	130 mL
3-5	3 hourly	16 mL	130 mL
6-	4 hourly	22 mL	130 mL

Source: WHO guidelines.<sup>3</sup> Please see Appendix 34.4 for the detailed charts on feeding volumes.

### Step 8: Achieve Catch-up Growth

Once appetite returns which usually happens in 2-3 days higher intakes should be encouraged. The

**Table 34.8: Catch-up diets**

Diets contents (per 100 mL)	F-100 Catch-up	F-100 Catch-up (cereal based)
Cows milk/toned dairy milk (ml) (approximate measure of one katori)	95 (3/4+)	75 (1/2)
Sugar (g) (approximate measure of one level teaspoon)	5 (1)	2.5 (1/2-)
Cereal: Puffed rice (g) (approximate measure of one level teaspoon)	–	7 (2)
Vegetable oil (g) (approximate measure of one level teaspoon)	2 (1/2)	2 (1/2)
Water to make (mL)	100	100
Energy (kcal)	101	100
Protein (g)	2.9	2.9
Lactose (g)	3.8	3

Given below are some examples of low lactose catch-up diets (Table 34.9).

frequency of feeds should be gradually decreased to 6 feeds/day and the volume offered at each feed should be increased. It is recommended that each successive feed is increased by 10 mL until some is left uneaten. Breastfeeding should be continued *ad libitum*.

Make a gradual transition from F-75 diet to F-100 diet. The starter F-75 diet should be replaced with F-100 diet in equal amount in 2 days.

These diets as shown below contain 100 kcal/100 mL with 2.5-3.0 g protein/100 mL. The calorie intake should be increased to 150-200 kcal/kg/day, and the proteins to 4-6 g/kg/day.

**Catch-up diets recommended in severe malnutrition:**  
The diets given below have been adapted for the Indian

settings from the diets recommended in the WHO manual (Table 34.8).<sup>2</sup>

For children with persistent diarrhea, who do not tolerate low lactose diets, lactose free diet can be started. In these diets, carbohydrates (rice, sugar and glucose) can be given in varying proportions according to the patients' individual level of carbohydrate to achieve optimal balance between osmolarity and digestibility<sup>15</sup> (see Appendix 34.5 for an example).

Complementary foods should be added as soon as possible to prepare the child for home foods at discharge. They should have comparable energy and protein concentrations once the catch-up diets are well tolerated. Khichri, dalia, banana, curd-rice and other

**Table 34.9: Low lactose catch-up diet**

Catch-up low lactose diets	Example 1	Example 2
Milk (cow's milk or toned dairy milk)	25 mL	25 mL
Egg white *(g) (approximate measure of one level teaspoon)	12 (2+)	–
Roasted powdered groundnut	–	5 g
Vegetable oil (g) (approximate measure of one level teaspoon)	4 (1)	
Cereal flour: Powdered puffed rice** (g) (approximate measure of one katori)	12 (4)	12 (4)
Energy (kcal)	100	–
Protein (g)	2.9	2.9
Lactose (g)	1	1

\* Egg white may be replaced by 3g of chicken or commercially available pure protein like casein.

\*\*Powdered puffed rice may be replaced by commercial pre-cooked rice preparations (in same amounts). Jaggery could be used instead of glucose/sugar.

culturally acceptable and locally available diets can also be offered liberally (see IMNCI Food Box).<sup>16</sup>

Emergency treatment for severe anemia is shown in Appendix 34.6, Treatment of associated conditions is shown in Appendix 34.7.

### Step 9: Provide Sensory Stimulation and Emotional Support

Delayed mental and behavioral development often occurs in severe malnutrition. In addition to the above management, try to stimulate and encourage:

- A cheerful, stimulating environment.
- Age appropriate structured play therapy for at least 15-30 min/day.
- Age appropriate physical activity as soon as the child is well enough.
- Tender loving care.

### Step 10: Prepare for Follow-up after Recovery

*Primary failure to respond is indicated by:*

- Failure to regain appetite by day 4.
- Failure to start losing edema by day 4.
- Presence of edema on day 10.
- Failure to gain at least 5 g/kg/day by day 10.

*Secondary failure to respond is indicated by:*

Failure to gain at least 5 g/kg/day for 3 consecutive days during the rehabilitation phase.

#### *What is Poor Weight Gain?*

- Good weight gain is >10 g/kg/day and indicates a good response. It is recommended to continue with the same treatment.
- Moderate weight gain is 5-10 g/kg/day; food intake should be checked and the children should be screened for systemic infection.
- Poor weight gain is < 5 g/kg/day and screening for inadequate feeding, untreated infection, tuberculosis and psychological problems is recommended.

#### *Possible Causes of Poor Weight Gain*

1. **Inadequate feeding:** It is recommended to check:
  - That night feeds have been given.
  - That target energy and protein intakes are achieved. Is actual intake (offered minus food left) correctly recorded? Is the quantity of feed recalculated as the child gains weight? Is the child vomiting or ruminating?
  - Feeding technique: Is the child fed frequently and offered unlimited amounts? What is the quality

of care? Are staff motivated/gentle/loving/patient?

- All aspects of feed preparation: Scales, measurement of ingredients, mixing, taste, hygienic storage, adequate stirring if separating out.
  - If giving family foods with catch-up F-100, that they are suitably modified to provide >100 kcal/100 g (if not, they need to be re-modified).
2. **Specific nutrient deficiencies:** It is recommended to check:
    - a. Adequacy and the shelf life of the multivitamin composition.
    - b. Preparation of electrolyte/mineral solution and whether they have been correctly prescribed and administered.
  3. **Untreated infection:** If feeding is adequate and there is no malabsorption, infection should be suspected. Urinary tract infections, otitis media, TB and giardiasis are often overlooked. It is therefore important to:
    - Re-examine carefully.
    - Repeat urinalysis for white blood cells.
    - Examine stool.
    - If possible, take chest X-ray.
 Antibiotic schedule is modified only if a specific infection is identified.
  4. **HIV/AIDS:** In children with HIV/AIDS, good recovery from malnutrition is possible though it may take longer and treatment failures may be common. Lactose intolerance occurs in severe HIV-related chronic diarrhea. Treatment should be the same as for HIV negative children.
  5. **Psychological problems:** It is recommended to check for:
 

Abnormal behavior such as stereotyped movements (rocking), rumination (self stimulation through regurgitation) and attention seeking. These should be treated by giving the child special love and attention.

#### *Criteria for Discharge*

Severely malnourished children are ready for discharge when the following criteria have been fulfilled:

- Absence of infection.
- The child is eating at least 120-130 cal/kg/day and receiving adequate micronutrients.
- There is consistent weight gain (of at least 5 g/kg/day for 3 consecutive days) on exclusive oral feeding.
- WFH is 90% of NCHS median; the child is still likely to have a low weight-for-age because of stunting.
- Absence of edema.

- Completed immunization appropriate for age.
- Caretakers are sensitized to home care.

Advise caregiver to:

- Bring child back for regular follow-up checks.
- Ensure booster immunizations are given.
- Ensure vitamin A is given every six months.
- Feed frequently with energy-and nutrient-dense foods.
- Give structured play therapy.

Criteria for discharge before recovery is complete is shown in Appendix 34.8.

### If the Patient is Considered to have Septic Shock

- Continue administration of oxygen.
- Give 10 mL/kg normal saline or Ringers' lactate bolus cautiously over 20-30 minutes. Repeat boluses till a total of 30 mL/kg of crystalloids. This fluid administration rate is much slower than what is currently recommended for children.<sup>4</sup>
- Consider colloids, i.e. high molecular weight dextran, degraded gelatin, hydroxyl-ethyl starch etc, when 30 mL/kg crystalloids have been used and more fluid infusion is required.
- Monitor vitals, urine output, sensorium, features of fluid overload and cardiorespiratory status during boluses to monitor the response to fluid therapy and then at least hourly (more frequently if required).
- Stop bolus and restrict fluids/colloids at first sign of fluid overload (appearance of crepitations or S3, worsening respiratory distress, increase in liver size).
- Consider central venous pressure (CVP) monitoring to guide fluid therapy in fluid refractory shock, wherever feasible.
- Consider mechanical ventilation in fluid refractory shock to decrease work of breathing (This may be feasible in only some health care settings).
- Start vasoactive agents, dopamine (10-20 µg/kg/min), dobutamine (10-20 µg/kg/min) as indicated (see Appendix 34.1). Adjust the dose according to the response.
- Consider 10 mL/kg packed red blood cells slowly over 4-6 hours if hemoglobin is <10 g/dL or the patient is actively bleeding.
- **Use appropriate and adequate antibiotics:** Third generation cephalosporins and aminoglycosides should be added within 1st hour of shock. Add antistaphylococcal cover if indicated.
- **Steroids:** Consider using hydrocortisone @ 100 mg/m<sup>2</sup>/d if adrenal insufficiency is suspected, i.e.

hypoglycemia, hyponatremia, hyperkalemia and acidosis is present.

If available, also add selenium (0.028 g of sodium selenate, NaSeO<sub>4</sub> 10H<sub>2</sub>O) and iodine (0.012 g potassium iodide, KI) per 2500 mL.

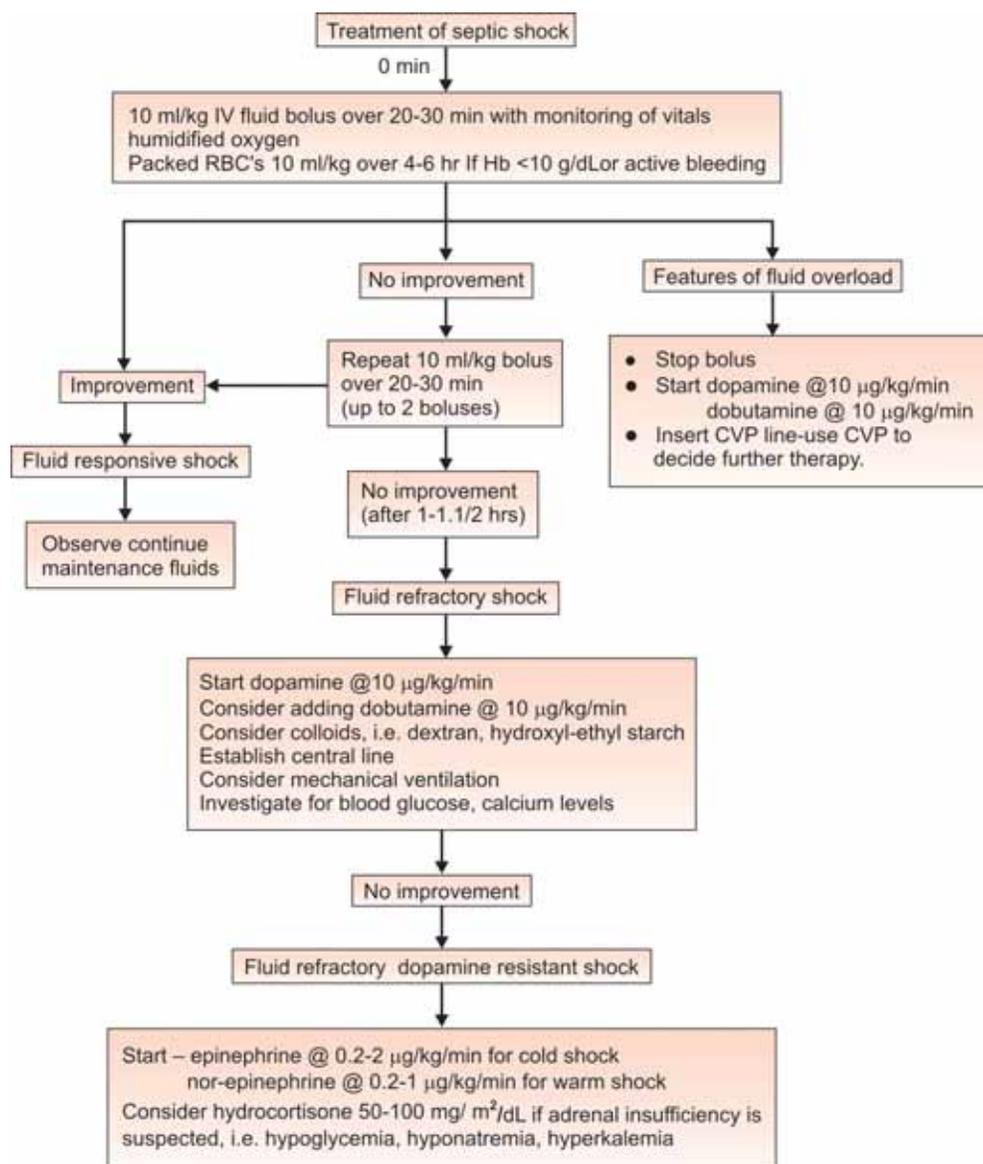
- Dissolve the ingredients in cooled boiled water.
- Store the solution in sterilized bottles in the fridge to retard deterioration. Discard if it turns cloudy. Make fresh each month.
- Add 20 mL of the concentrated electrolyte/mineral solution to each 1000 ml of milk feed. If it is not possible to prepare this electrolyte/mineral solution and pre-mixed sachets are not available, give K, Mg and Zn separately.

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#### Appendix 34.1: Treatment of septic shock



(Adapted from: Carcillo JA, Fields AI. American College of Critical Care Medicine Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002; 30: 1365-78).

**Appendix 34.2: Composition of concentrated electrolyte/mineral solution**

	<i>g</i>	<i>Molar content of 20 mL</i>
Potassium chloride: KCl	224	24 mmol
Tripotassium citrate: C <sub>6</sub> H <sub>5</sub> K <sub>3</sub> O <sub>7</sub> ·H <sub>2</sub> O	81	2 mmol
Magnesium chloride: MgCl <sub>2</sub> ·6H <sub>2</sub> O	76	3 mmol
Zinc acetate: Zn acetate, 2H <sub>2</sub> O	8.2	300 mmol
Copper sulphate: CoSO <sub>4</sub> ·5H <sub>2</sub> O	1.4	45 mmol
Water: Make up to		2500 mL

**Appendix 34.4: Volumes of F-75 per feed (approx 130 mL/kg/day)**

<i>Child's weight (kg)</i>	<i>2-hourly (mL/feed)</i>	<i>3-hourly (mL/feed)</i>	<i>4-hourly (mL/feed)</i>
2.0	20	30	45
2.2	25	35	50
2.4	25	40	55
2.6	30	45	55
2.8	30	45	60
3.0	35	50	65
3.2	35	55	70
3.4	35	55	75
3.6	40	60	80
3.8	40	60	85
4.0	45	65	90
4.2	45	70	90
4.4	50	70	95
4.6	50	75	100
4.8	55	80	105
5.0	55	80	110
5.2	55	85	115
5.4	60	90	120
5.6	60	90	125
5.8	65	95	130
6.0	65	100	130
6.2	70	100	135
6.4	70	105	140
6.6	75	110	145
6.8	75	110	150
7.0	75	115	155
7.2	80	120	160
7.4	80	120	160
7.6	85	125	165
7.8	85	130	170
8.0	90	130	175
8.2	90	135	180
8.4	90	140	185
8.6	95	140	190
8.8	95	145	195
9.0	100	145	200
9.2	100	150	200

**Appendix 34.3: Starter lactose free diet**

Lactose free diets are rarely needed as most children do well on the above mentioned, low lactose F-75 diets

Starter lactose free diets	Ex: 1
Egg white *(g)	5
(approximate measure of one level teaspoon)	(2)
Glucose (g)	3.5
(approximate measure of one level teaspoon)	(3/4+)
Cereal flour: Powdered puffed rice** (g)	7
(approximate measure of one level teaspoon)	(2+)
Vegetable oil (g)	4
(approximate measure of one level teaspoon)	(1)
Water to make (mL)	100
Energy (kcal)	75
Protein (g)	1
Lactose	-

\* Egg white may be replaced by 3g of chicken or commercially available pure protein like casein.

\*\* Powdered puffed rice may be replaced by commercial pre-cooked rice preparations (in same amounts).

**Appendix 34.5: Catch-up lactose free diet**

Catch-up lactose free diets	Ex: 1
Egg white *(g)	5
Egg white *(g)	20
(approximate measure of one level teaspoon)	(2+)
Glucose or sugar (g)	4
(approximate measure of one level teaspoon)	(1)
Cereal Flour: Puffed rice** (g)	12
(approximate measure of one level teaspoon)	(3 + 1/2)
Vegetable oil (g)	4
(approximate measure of one level teaspoon)	(1)
Water to make (mL)	100
(approximate measure of one katori)	(3/4)
Energy (kcal)	100
Protein (g)	3
Lactose (g)	-

\* Egg white may be replaced by 3g of chicken or commercially available pure protein like casein.

\*\* Powdered puffed rice may be replaced by commercial pre-cooked rice preparations (in same amounts).

**Appendix 34.6: Emergency treatment**

Severe anemia in malnourished children

A blood transfusion is required on admission if:

1. Hb is less than 4 g/dL or
2. If there is respiratory distress and Hb between 4 and 6 g/dL

(In mild or moderate anemia, iron should be given for two months to replete iron stores BUT this should not be started until after the initial stabilization phase has been completed).

Give:

1. Whole blood 10 mL/kg bodyweight slowly over 3 hours
2. Furosemide 1 mg/kg IV at the start of the transfusion.

It is particularly important that the volume of 10 ml/kg is not exceeded in severely malnourished children. If the severely anemic child has signs of cardiac failure, transfuse packed cells rather than whole blood.

Monitor for signs of transfusion reactions. If any of the following signs develop during the transfusion, stop the transfusion:

1. Fever
2. Itchy rash
3. Dark red urine
4. Confusion
5. Shock

Also, monitor the respiratory rate and pulse rate every 15 minutes. If either of them rise, transfuse more slowly.

Following the transfusion, if the Hb remains less than 4g/dL or between 4-6 g/dL in a child with continuing respiratory distress, DO NOT repeat the transfusion. The hemoglobin concentration may fall during the first week of treatment. This is normal and no transfusion should be given.

**Appendix 34.7: Treatment of associated conditions**

Treatment of conditions commonly associated with severe malnutrition:

**1. Vitamin A deficiency**

If the child has any eye signs of deficiency, give orally:

- a. Vitamin A on days 1, 2 and 14 (if aged >1 year give 200,000 iu; if aged 6-12 months give 100,000 iu, if aged 0-5 months give 50,000 iu). If first dose has been given in referring center, treat on days 1 and 14 only.

If there is inflammation or ulceration, give additional eye care to prevent extrusion of the lens:

- A. Instil chloramphenicol or tetracycline eyedrops, 2-3 hourly as required for 7-10 days in the affected eye.
- B. Instil atropine eyedrops, 1 drop three times daily for 3-5 days.
- C. Cover with saline-soaked eye pads and bandage.

**2. Dermatitis**

Signs

- A. Hypo- or hyper-pigmentation.
- B. Desquamation.
- C. Ulceration (spreading over limbs, thighs, genitalia, groin and behind the ears).
- D. Exudative lesions (resembling severe burns) often with secondary infection, including *Candida*.

Zinc deficiency is usual in affected children and the skin quickly improves with zinc supplementation. In addition:

- E. Dab affected areas with 0.01% potassium permanganate solution.
- F. Apply barrier cream (zinc and castor oil ointment, or petroleum jelly or tulle grass) to raw areas.
- G. Omit nappies/diapers so that the perineum can dry.

3. **Parasitic worms** If there is evidence of worm infestation, give mebendazole (100 mg orally twice a day) for 3 days. In areas where infestation is very prevalent, also add mebendazole to children with no evidence of infestation after day 7 of admission.

4. **Tuberculosis** If TB is strongly suspected (contacts, poor growth despite good intake, chronic cough, chest infection not responding to antibiotics): Catch-up

- a. Perform Mantoux test (NB false negatives are frequent).
- b. Chest X-ray if available. If positive test or strong suspicion of TB, treat according to national TB guidelines.

(NB: Children with vitamin A deficiency are likely to be photophobic and have closed eyes. It is important to examine the eyes very gently to prevent rupture).

**Appendix 34.8: Discharge before recovery is complete**

For some children, earlier discharge may be considered if effective alternative supervision is available. Domiciliary care should only be considered if the following criteria are met:

**The child**

1. Is aged >12 months.
2. Has completed antibiotic treatment.
3. Has good appetite and good weight gain.
4. Has taken 2-weeks of potassium/magnesium/mineral/vitamin supplement (or continuing supplementation at home is possible).

**The mother/care giver**

1. Is not employed outside the home.
2. Is specifically trained to give appropriate feeding (types, amount, frequency).
3. Has the financial resources to feed the child.
4. Lives within easy reach of the hospital for urgent readmission if child becomes ill.
5. Can be visited weekly.
6. Is trained to give structured play therapy.
7. Is motivated to follow advice given.

**Local health workers**

1. Are trained to support home care.
2. Are specifically trained to examine child clinically at home, when to refer back, to weigh child, give appropriate advice.
3. Are motivated.

For children being rehabilitated at home, it is essential to give frequent meals with a high energy and protein content. Aim at achieving at least 150 kcal/kg/day and adequate protein (at least 4 g/kg/day). This will require feeding the child at least 5 times per day with foods that contain approximately 100 kcal and 2-3 g protein per 100 g of food. A practical approach should be taken using simple modifications of usual home foods. Vitamin, iron and electrolyte/mineral supplements can be continued at home.

1. Give appropriate meals at least 5 times daily.
2. Give high energy snacks between meals (e.g., milk, banana, bread, biscuits).
3. Assist and encourage the child to complete each meal.
4. Give electrolyte and micronutrient supplements. Give 20 mL (4 teaspoons) of the electrolyte/mineral solution daily. Since it tastes unpleasant, it will probably need to be masked in porridge, or milk (one teaspoon/200 mL fluid).
5. Breastfeed as often as child wants.

Malaria is one of the leading cause of morbidity and mortality in developing countries. Nearly 2.48 million malaria cases are reported annually from South Asia of which 75% cases are contributed by India alone.<sup>1</sup> It is heartening to know the total number of laboratory confirmed cases have declined from 3 million reported in 1997 to 1.84 million in early 2000.<sup>3</sup> At the same time, it is perplexing that the number of falciparum cases is constantly on the rise and in recent years they contribute nearly 50% of the total cases.<sup>2</sup>

Falciparum malaria resistant to chloroquine (CQ) was identified in the districts of North East along the International border from 2003 onwards. According to National Vector Borne Disease Control Program, high treatment failure to CQ has been detected in 44 districts of 18 states in the country for which second line treatment with sulphadoxine – pyrimethamine (SP) was suggested.<sup>3</sup> Resistance to SP combination at various levels has also been reported in the districts of seven North Eastern States. It has been seen that the introduction of a single new drug leads to rapid development of resistance. To overcome this, WHO has recommended Artemisinin based combination therapy (ACT) for the treatment of uncomplicated falciparum malaria.<sup>4</sup>

The number of falciparum malaria as well as multidrug resistant falciparum malaria cases are constantly on the rise. So there was need to revise the existing treatment guidelines<sup>5</sup> for malaria with special reference to artemisinin based combination therapy. The need for artemisinin based combination therapy (ACT) is emphasized in chloroquine resistant falciparum malaria. Monotherapy with artesunate will further increase the resistance. Once malaria treatment is initiated it should be completed.<sup>6</sup> In severe malaria the maintenance dose of artesunate is revised.

#### ARTEMESININ COMBINATION THERAPY

Antimalarial combination therapy is simultaneous use of two or more blood schizontocidal drugs with different mode of action in unrelated biochemical

targets in the parasite. According to WHO, one of the partner in combination therapy should be an artemisinin derivative due to its high killing rate (reduces parasite number 10,000 fold per cycle whereas other antimalarial reduces 100 to 1000 fold per cycle), lack of serious side effects, relatively low level of resistance and rapid elimination rate, which ensures that the parasites are not exposed to subtherapeutic levels of the drug. When administered in combination with rapidly eliminated antimalarials (clindamycin, tetracycline), a seven days course of treatment is required and adherence to treatment is usually poor. If artemisinin derivatives are combined with slowly eliminated antimalarials [SP, mefloquine (MQ), lumefantrine], shorter courses of treatment (3 days) are effective which ensures better treatment adherence. These combinations also protect against emergence of drug resistance despite the fact that they do leave the slowly eliminated tail of long acting drugs unprotected. Resistance could arise within the residual parasite that have not yet been killed by the artemisinin derivative. However, number of parasites exposed to long acting drug alone is a tiny fraction (less than 0.00001%) of those present in the acute infection. Furthermore, these residual parasites are exposed to relatively high levels of long acting drugs and even if susceptibility was reduced, these levels may be sufficient to eradicate the infection.

#### UNCOMPLICATED MALARIA

Treatment regimes are to be tailored specifically according to the resistance pattern of the region under consideration (Tables 35.1A to D).

#### SEVERE AND COMPLICATED MALARIA

The main objective of treatment is to prevent death. Prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities are of secondary importance. Untreated severe malaria has a mortality of 100% but with proper treatment it can be reduced to 15-20%. As death due to severe malaria

**Table 35.1A: Recommended treatment in chloroquine sensitive malaria**

Drug sensitivity	Recommended treatment
<i>P. vivax</i> and chloroquine sensitive <i>P. falciparum</i>	*Chloroquine 10 mg base/kg stat followed by 5 mg/kg at 6, 24 and 48 hours. OR Chloroquine 10 mg base/kg stat followed by 10 mg/kg at 24 hours and 5 mg/kg at 48 hours (total dose 25 mg base/kg). **In case of vivax malaria, to prevent relapse, primaquine should be given in a dose of 0.25 mg/kg once daily for 14 days. In case of falciparum malaria, a single dose of primaquine (0.75 mg/kg) is given for gametocytocidal action.

\*Chloroquine should not be given on an empty stomach and in high fever. Bring down the temperature first. If vomiting occurs within 45 minutes of a dose of chloroquine, that particular dose is to be repeated after taking care of vomiting by using antiemetic (domperidone/ondansetron).

\*\*According to National Anti Malarial Program, a 5 days course of primaquine is advocated because of risk of toxicity and operational feasibility. Whereas other authorities advocate 14 days course of primaquine due to lack of evidence to support shorter courses.<sup>7</sup> As primaquine can cause hemolytic anemia in children with G6PD deficiency, they should be preferably screened for the same prior to starting treatment. As infants are relatively G6PD deficient, it is not recommended in this age group and children with 14 days regime should be under close supervision to detect any complication. In cases of borderline G6PD deficiency, once weekly dose of primaquine 0.6 - 0.8 mg/kg is given for 6 weeks.

**Table 35.1B: Recommended treatment in chloroquine resistant *P. falciparum***

Artesunate 4 mg/kg of body weight once daily for 3 days and a single administration of SP as 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine on day 1 or artesunate as above and mefloquine 25 mg/kg of body weight in two (15 + 10) divided doses on day 2 and day 3.

Or

Coformulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen twice a day for 3 days.

For 5-14 kg body weight 1 tablet at diagnosis, again after 8 hours and then twice daily on day 2 and day 3. For 15 to 24 kg body weight same schedule with 2 tablets. For 25-35 kg body weight and above same schedule with 3 and 4 tablets, respectively.

- i. Under the previous National Drug Policy, SP monotherapy in a single dose was used in areas of chloroquine resistance. Countries where SP was introduced following CQ resistance showed its rapid decline in efficacy within few years.
- ii. Currently, there are insufficient safety and tolerability data on mefloquine at its recommended dosage of 25 mg/kg body weight in children. Mefloquine shares cross resistance with quinine which is still a effective drug in our country. Health planners of our country do not advocate use of mefloquine.
- iii. Advantage of artemether lumefantrine combination is that lumefantrine is not available as monotherapy and has never been used by itself for the treatment of malaria. Lumefantrine absorption is enhanced by coadministration with fatty food like milk.

often occurs within hours of admission it is essential to ensure therapeutic concentration of antimalarial drugs as soon as possible. Hence, antimalarial drug should be given initially by intravenous infusion, which should be replaced by oral administration as soon as condition permits.

According to the National Anti Malaria Program (NAMPP), drug policy in all cases of severe malaria is either IV quinine or parenteral artemisinin derivatives

to be given irrespective of chloroquine resistance status.<sup>8</sup> Treatment Guidelines are summarized in Table 35.2.

### SUPPORTIVE MANAGEMENT

1. Rapid clinical assessment with respect to level of consciousness (use Blantyre coma scale), blood pressure, rate and depth of respiration, anemia, state of hydration and temperature.

**Table 35.1C: Recommended treatment of multidrug resistant *P. falciparum* (both to chloroquine and sulfadoxine-pyrimethamine)**

Quinine, 10 mg salt/kg/dose 3 times daily for 7 days.  
 +  
 Tetracycline (above 8 years) 4 mg/kg/dose 4 times daily for 7 days  
 Or  
 Doxycycline (above 8 years) 3.5 mg/kg once a day for 7 days  
 Or  
 Clindamycin 20 mg/kg/day in 2 divided doses for 7 days.  
 In case of cinchonism,  
 Quinine 10 mg salt/kg/dose 3 times daily for 3-5 days  
 +  
 Tetracycline (above 8 years) 4 mg/kg/dose 4 times daily for 7 days  
 Or  
 Doxycycline (above 8 years) 3.5 mg/kg once a day for 7 days  
 Or  
 Clindamycin 20 mg/kg/day in 2 divided doses for 7 days.  
 A single dose of primaquine above 1 year age (0.75 mg/kg) is given for gametocytocidal action.  
 Or  
 Artemether lumefantrine combination as in Table 35.1B

- i. Doxycycline is preferred to tetracycline as it can be given once daily and does not accumulate in renal failure.
- ii. One of the drawbacks of quinine therapy is its long course. Unsupervised and ambulatory setting may decrease patient's compliance and many patients might not complete the full course of prescribed therapy.
- iii. Fortunately children tolerate quinine better than adults.

**Table 35.1D: Recommended treatment in failure with artemisinin combination therapy (ACT)**

Quinine + Tetracycline or Doxycycline or Clindamycin for 7 days as in Table 35.1C.

- i. Treatment failure within 14 days of receiving an ACT is unusual. It should be confirmed parasitologically by blood slide examination. It is important to determine whether patient has omitted previous treatment or did not complete a full course.
  - ii. Failure after 14 days of treatment can be re-treated with first line ACT.
2. Thick and thin blood films should be made. Minimal investigation should include PCV (hematocrit), blood glucose and lumbar puncture specially in cerebral malaria. If lumbar puncture is delayed proper antibiotic cover for meningitis must be given. Antibiotics may also be considered if any secondary infection is suspected, which is common in severe malaria. Start intravenous antimalarial after drawing blood.
  3. Good nursing care with proper positioning, meticulous attention to airways, eyes, mucosa and skin should be done. Appropriate fluid therapy is to be given.
  4. For unconscious child nasogastric tube is to be inserted to reduce the risk of aspiration.
  5. Oxygen therapy and respiratory support should be given if necessary.
  6. In case of shock resuscitate with normal saline or Ringer lactate by bolus infusion. Avoid under or overhydration.
  7. Convulsion should be treated with diazepam.
  8. Hyperpyrexia should be treated with tepid sponging, fanning and paracetamol.
  9. Close monitoring of the vital signs preferably every 4 hours to be done till the patient is out of danger. Also maintain intake output chart and watch for hemoglobinuria.
  10. Monitoring of the response to treatment is essential. Detail clinical examination with particular emphasis on hydration status, temperature, pulse, respiratory rate, blood pressure and level of consciousness is to be given. Blood smear examination every 6 to 12 hours for parasitemia for first 48 hours is needed.

**Table 35.2: Drug and dosage of antimalarials in complicated and severe malaria**

Drug	Dosages <sup>4,9</sup>
Quinine salt	20 mg salt/kg (loading dose) diluted in 10 mL of isotonic fluid/kg by infusion over 4 hours. Then 12 hours after the start of loading dose give a maintenance dose of 10 mg salt/kg over 2 hours. This maintenance dose should be repeated every 8 hours, calculated from beginning of previous infusion, until the patient can swallow, then quinine tablets, 10 mg salt / kg 8 hourly to complete a 7 day course of treatment (including both parenteral and oral). Tetracycline or doxycycline or clindamycin is added to quinine as soon as the patient is able to swallow and should be continued for 7 days. Dosage as in Table 35.1C. If controlled IV infusion cannot be administered then quinine salt can be given in the same dosages by IM injection in the anterior thigh (not in buttock). The dose of quinine should be divided between two sites, half the dose in each anterior thigh. If possible IM quinine should be diluted in normal saline to a concentration of 60-100 mg salt/ml. (Quinine is usually available as 300 mg salt/ml). Tetracycline or doxycycline or clindamycin should be added as above.
Artesunate	2.4 mg/kg IV then at 12 and 24 hours, then once a day for total 7 days. If the patient is able to swallow, then the daily dose can be given orally. Tetracycline or doxycycline or clindamycin is added to artesunate as soon as the patient can swallow and should be continued for 7 days. Dosage as in Table 35.1C.
Or	
Artemether	3.2 mg/kg (loading dose) IM, followed by 1.6 mg/kg daily for 6 days. If the patient is able to swallow, then the daily dose can be given orally. Tetracycline or doxycycline or clindamycin is added to artemether as soon as the patient can swallow and should be continued for 7 days. Dosage as in Table 35.1C.

- i. Loading dose of quinine should not be used if the patient has received quinine, quinidine or mefloquine within the preceding 12 hours. Alternatively, loading dose can be administered as 7 mg salt/kg by IV infusion pump over 30 minutes, followed immediately by 10 mg salt/kg diluted in 10 ml isotonic fluid/kg by IV infusion over 4 hours.
- ii. Quinine should not be given by bolus or push injection. Infusion rate should not exceed 5 mg salt/kg/hour.
- iii. If there is no clinical improvement after 48 hours of parenteral therapy, the maintenance dose of quinine should be reduced by one third to one half i.e., 5-7 mg salt/kg.
- iv. Quinine should not be given subcutaneously as this may cause skin necrosis.
- v. Previous maintenance dose of parenteral artesunate of 1.2 mg/kg has been modified by WHO to 2.4 mg/kg.
- vi. Artesunate, 60 mg per ampoule is dissolved in 0.6 mL of 5% sodium bicarbonate diluted to 3-5 mL with 5% dextrose and given immediately by IV bolus (push injection).
- vii. Artemether is dispensed in 1 mL ampoule containing 80 mg of artemether in peanut oil.

**Key Messages**

- Malaria treatment, once initiated, should be completed.
- Artemisinin based combination therapy is recommended in chloroquin resistant falciparum malaria.

11. In case of quinine parasite count may remain unchanged or even rise in first 18-24 hours which should not be taken as an indicator of quinine resistance. However, parasite count should fall after 24 hours of quinine therapy and should disappear within 5 days.
12. In case of artemisinin derivatives parasite count usually comes down within 5 to 6 hours of starting therapy. Asexual parasitemia generally disappears after 72 hours of therapy.<sup>10</sup>
13. Poor prognosis is suggested by high parasite densities (above 5% RBC infected or parasite density >250000/µl). At any parasitemia prognosis worsens if there is predominance of more mature parasite stages. If more than 20% of the parasite contain visible pigment (mature trophozoites and schizonts) the prognosis worsens. Poor prognosis is also indicated if more than 5% of the peripheral blood polymorphonuclear leukocyte contain visible malaria pigment.
14. In follow-up cases, add iron and folic acid.

## MANAGEMENT OF COMPLICATIONS OF MALARIA

Of the various complications of falciparum malaria the common and important ones in children are as follows:

- a. Cerebral malaria
- b. Severe anemia
- c. Respiratory distress (acidosis)
- d. Hypoglycemia.

*Cerebral malaria:* Initial presentation is usually fever followed by inability to eat or drink. The progression to coma or convulsion is usually very rapid within one or two days. Convulsions may be very subtle with nystagmus, salivation or twitching of a isolated part of the body. Effort should be given to exclude other treatable causes of coma (e.g. bacterial meningitis, hypoglycemia). Patients should be given good nursing care, convulsions should be treated with diazepam/midazolam and avoid harmful adjuvant treatment like corticosteroids, mannitol, adrenaline and pheno-barbitone.

*Severe anemia:* Children with hyperparasitemia due to acute destruction of red cells may develop severe anemia. Packed red cell transfusion should be given cautiously when PCV is 12% or less, or hemoglobin is below 4 g%. Transfusion should also be considered in patients with less severe anemia in the presence of respiratory distress (acidosis), impaired consciousness or hyperparasitemia (>20% of RBCs infected).

*Lactic acidosis:* Deep breathing with indrawing of lower chest wall without any localizing chest signs suggest lactic acidosis. It usually accompanies cerebral malaria, anemia or dehydration. Correct hypovolemia, treat anemia and prevent seizures. Monitor acid base status, blood glucose and urea and electrolyte level.

*Hypoglycemia:* It is common in children below 3 years specially with hyperparasitemia or with convulsion. It also occurs in patients treated with quinine. Manifestations are similar to those of cerebral malaria so it can be easily overlooked. Monitor blood sugar every 4 to 6 hours. If facilities to monitor blood glucose is not available assume hypoglycemia in symptomatic patient and treat accordingly. Correct hypoglycemia with IV dextrose (25% dextrose 2 to 4 ml/kg by bolus) and it should be followed by slow infusion of 5% dextrose containing fluid to prevent recurrence.

*Hyperpyrexia:* High fever is common in children and may lead to convulsion and altered consciousness.

Tepid sponging, fanning and paracetamol 15 mg/kg should be given.

*Hyperparasitemia:* Specially seen in nonimmune children associated with severe disease. Consider exchange transfusion/cytapheresis if greater than 20% of RBCs are parasitised.

*Circulatory collapse (Algid malaria):* In case of circulatory collapse suspect gram negative septicemia, send blood for culture before starting antibiotics. Resuscitate with judicious use of fluids.

*Spontaneous bleeding and coagulopathy (DIC):* Usually seen in nonimmune children which should be treated with vitamin K, blood or blood products as required.

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Dengue infection has become endemic in most of the South-East Asian countries including India. In the last one-decade several minor and major outbreaks have been reported from various parts of India.<sup>1</sup> Dengue fever and dengue hemorrhagic fever (DHF) are caused by infection due to any of the four serotypes of dengue viruses (Den 1-4). *Aedes* mosquito transmits the infection. DHF and dengue shock syndrome (DSS) are serious clinical manifestations of the dengue infection. It is estimated that during outbreaks, about 150-200 mild to silent infections occur in the community for each case of DSS seen in the hospital.<sup>2</sup> It is believed that dengue infection occurs periodically and one out break is predominantly caused by one type of dengue virus. Evolution of dengue infection over last one decade<sup>3</sup> and report of all four strains of dengue virus in one season from Delhi suggests high endemicity of disease.<sup>4</sup>

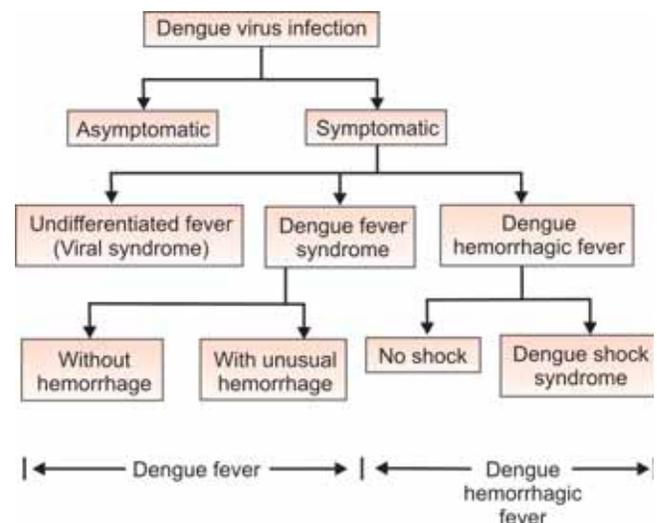
The major pathophysiologic changes that determine the severity of disease in DHF and differentiate it from dengue fever are plasma leakage and abnormal hemostasis leading to rising hematocrit values, moderate to marked thrombocytopenia and varying degrees of bleeding manifestations.<sup>5</sup> Despite our growing understanding of various facets of the infection, its pathogenesis still remains unclear, with the possibility of several mechanisms being involved simultaneously. The virus is taken up by dendritic cells, which, after antigen processing, presents it to T cells, leading to immune activation and release of a cascade of cytokines that are believed to mediate the systemic effects of plasma leakage and circulatory insufficiency. Thrombocytopenia develops due to the presence of cross-reacting antibodies to platelets and is responsible for the bleeding diathesis. The phenomenon of 'original antigenic sin' may explain the increased severity of illness during secondary infections, due to the presence of antibody to the previously infecting serotype. This leads to immune of dengue shock syndrome (DSS). In addition, there is evidence for increased apoptosis and endothelial cell dysfunction, which may also contribute to its pathogenesis.<sup>6</sup>

### CLINICAL MANIFESTATIONS

The clinical manifestations of dengue virus infection vary from asymptomatic to severe life-threatening illness in the form of DHF/DSS (Flow chart 36.1).<sup>2</sup> Most dengue infections in young children are mild and indistinguishable from other common causes of febrile illnesses. Fever, headache, myalgia, arthralgia, skin rashes and malaise characterize the illness.<sup>3</sup>

Some patients with dengue infection have varying degrees of mucosal and cutaneous bleeds with some degree of thrombocytopenia. These patients may not demonstrate other criteria for diagnosis of DHS/DSS, i.e. hemoconcentration or objective evidence of fluid leak, e.g. ascites or pleural effusion. These patients are classified as *dengue fever with unusual bleeding*. Patients falling in this category may be seen in significant numbers in epidemics.<sup>7-10</sup> Since hypovolemia and hypotension do not occur in this group of children, fluid requirement is lesser than in DHF.<sup>11</sup> It is, therefore, important to distinguish these children from classical DHF.

Flow chart 36.1: Manifestations of dengue virus infection



DHF can occur in all age groups including infants. Typically, after an incubation period of 4-6 days the patients may develop abrupt onset of high-grade fever, facial flushing and headache. Anorexia, vomiting, pain abdomen and tenderness over the right costal margin are common. There may be varying degrees of tender hepatomegaly. Spleen is less commonly enlarged. All patients have some hemorrhagic phenomena in form of positive tourniquet test, petechial spots, bruising at venipuncture sites, bleeding from gums, epistaxis, hematemesis, or melena. Occasionally, adolescent girls may have bleeding per vaginum that mimics menstrual bleeding. Rarely bleeding from ears, muscle hematoma, hematuria, or intracranial hemorrhage may occur. Fever may subside after 2-7 days. At this stage the child may show varying degrees of peripheral circulatory failure, characterized by excessive sweating, restlessness and cold extremities. Initially the pulse pressure is narrow; the blood pressure later starts falling, leading to unrecordable blood pressure and irreversible shock. Prior to the child becoming afebrile, thrombocytopenia and a rise in hemotocrit occurs; these features are characteristic of the disease. Patients with shock and bleeding manifestations, usually show increase in hematocrit and thrombocytopenia. Unusual manifestations DHF/DSS include hepatitis, encephalitis and glomerulonephritis.<sup>5</sup>

Cases of dengue infection with secondary hemophagocytosis,<sup>12</sup> acute respiratory distress syndrome (ARDS)<sup>13</sup> and prolonged thrombocytopenia mimicking idiopathic thrombocytopenia have been reported.<sup>14</sup>

Infants may develop dengue hemorrhagic fever. As compared to older children they develop more nervous system manifestations in form of seizures, encephalopathy, bleeding and hepatic dysfunction. They have less shock.<sup>15</sup>

### GRADING OF DHF

The presence of thrombocytopenia with concurrent hemoconcentration differentiates DHF from dengue fever. On the basis of clinical features, DHF is classified into four grades of severity and grades III and IV define DSS.<sup>2</sup>

1. *Grade I*—Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test and/or easy bruising.
2. *Grade II*—In addition to features of grade I, there may be spontaneous bleeding, usually in the skin or other hemorrhages.
3. *Grade III*—Circulatory failure manifested by a rapid weak pulse, narrowing of pulse pressure, or

hypotension, with cold clammy skin and restlessness.

4. *Grade IV*—Profound shock with undetectable blood pressure or peripheral pulse.

### DIAGNOSIS

Diseases, which may mimic DHF/DSS include infections due to gram-negative organisms such as meningococemia, typhoid and rarely plague. Infection due to chikungunya has also gained epidemic proportion in part of country and may mimic dengue infection. Clinical features are mild but needs to be differentiated from dengue infection.<sup>16</sup> Mixed infection of dengue and chikungunya may occur as both share same vector and are endemic in many part of country.<sup>17</sup> Falciparum malaria may manifest with fever and bleeding, but is distinguished by the presence of splenomegaly and significant pallor. The following features are useful for making a provisional diagnosis of DHF/DSS:<sup>3</sup>

*Clinical criteria:* Acute onset high fever, hemorrhagic manifestations (at least a positive tourniquet test), hepatomegaly and shock.

*Laboratory criteria:* Thrombocytopenia (less than 100,000 cells/mm<sup>3</sup>), hemoconcentration (hematocrit elevated at least 20 percent above the standard for age, sex and population baseline or baseline hematocrit).

Two clinical observations plus one laboratory finding (or at least a rising hematocrit) are sufficient to establish a provisional diagnosis of DHF.

A rise in hematocrit of 20 percent over the baseline can be documented if the hematocrit is monitored regularly from the early stages of illness. Since patients are likely to present with symptoms suggestive of DHF, a drop in hemoglobin or hematocrit of more than 20 percent following volume replacement therapy can be taken as an indication of previous hemoconcentration. A recent report suggests that hematocrit value of 36.3 percent had a sensitivity of 60 percent and specificity of 94 percent for identification of DHF.<sup>18</sup> Hematocrit can, however, be affected by various factors including baseline anemia, time of hematocrit estimation during illness and blood loss. In monitoring hematocrit one should bear in mind the possible effects of pre-existing anemia, severe hemorrhage or early volume replacement therapy.

Presence of pleural effusion on X-ray film of chest or hypoalbuminemia provide supportive evidence of plasma leakage, the distinguishing feature of DHF. In a patient with suspected DHF, the presence of shock suggests the diagnosis of DSS.

### LABORATORY INVESTIGATIONS

During the course of illness children with DHF/DSS show increasing hemotocrit, decreased platelet counts, increased white cell count with relative lymphocytosis. The peripheral smear may show transformed lymphocytes.<sup>19</sup> In severe illness with prolonged shock, there may be evidence of disseminated intravascular coagulation.

Blood chemistry may show reduced levels of total protein and albumin, which are more marked in patients with shock.<sup>20</sup> Levels of transaminases are raised. A higher increase in levels of SGOT than SGPT suggests the possibility of DHF rather than hepatitis due to other virus.<sup>21</sup> In severe cases there may be hyponatremia, acidosis, and increase in blood urea and creatinine.<sup>7</sup>

X-ray film of the chest may show varying degrees of pleural effusion, commonly on the right side, occasionally bilateral.<sup>22</sup> Ultrasonography of abdomen may show enlarged gallbladder due to wall edema.<sup>23</sup> Abnormal electrocardiogram<sup>24</sup> and myocardial dysfunction on echocardiogram<sup>25</sup> has also been reported.

Demonstration of dengue virus on culture or demonstration of antibodies against dengue virus are required for confirming dengue infection. Viral isolation is recommended if the blood sample is taken within 5 days of the onset of fever while serologic methods are used if blood samples are taken after defervescence or during convalescence.<sup>26</sup> Commonly used serologic tests to detect antibodies include MAC-ELISA test and hemagglutination inhibition test. MAC-ELISA test measures dengue specific IgM antibodies and suggests recent infection with dengue virus. The hemagglutination inhibition test measures IgG antibodies. It is a simple, sensitive and reproducible test but requires paired sera collected at interval of 1-2 weeks. Positive test result indicates a recent infection due to flavivirus. A strip test is commercially available, which requires a drop of serum and gives results within few minutes but the result will depend on presence of IgM and that may be evident only by day 4-5 in most cases. Comparison of various rapid diagnostic tests suggests low sensitivity, therefore in emergency room setting diagnosis is clinical.

### TREATMENT

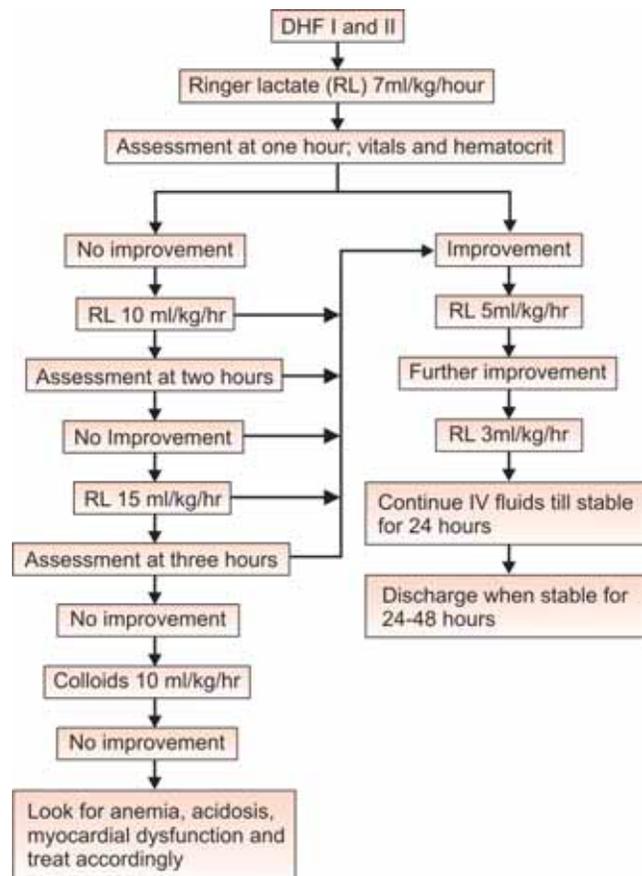
The treatment of dengue fever is symptomatic. Fever is treated with paracetamol. Salicylates and other non-steroidal anti-inflammatory drugs should be avoided as these may predispose a child to mucosal bleeds. In an epidemic setting all patients with dengue fever need

regular monitoring by a primary care physician for early detection of DHF. The primary care physician/health care worker should monitor the patient for clinical features of DHF/DSS along with hematocrit and platelet counts, if possible. Any patient developing cold extremities, restlessness, acute abdominal pain, decreased urine output, bleeding and hemoconcentration should be admitted in a hospital.<sup>5</sup> Children with rising hematocrit and thrombocytopenia without clinical symptoms should also be admitted.

In the hospital, all children without hypotension (DHF grades I and II) should be given Ringer's lactate infusion at the rate of 7 ml/kg over one hour. After one hour if hematocrit decreases and vital parameters improve, fluid infusion rate should be decreased to 5 ml/kg over next hour and to 3 ml/kg/hour for 24-48 hours. When the patient is stable as indicated by normal blood pressure, satisfactory oral intake and urine output, the child can be discharged (Flow chart 36.2).

If at one hour the hematocrit is rising and vital parameters do not show improvement, fluid infusion

**Flow chart 36.2:** Intravenous fluid infusion in DHF



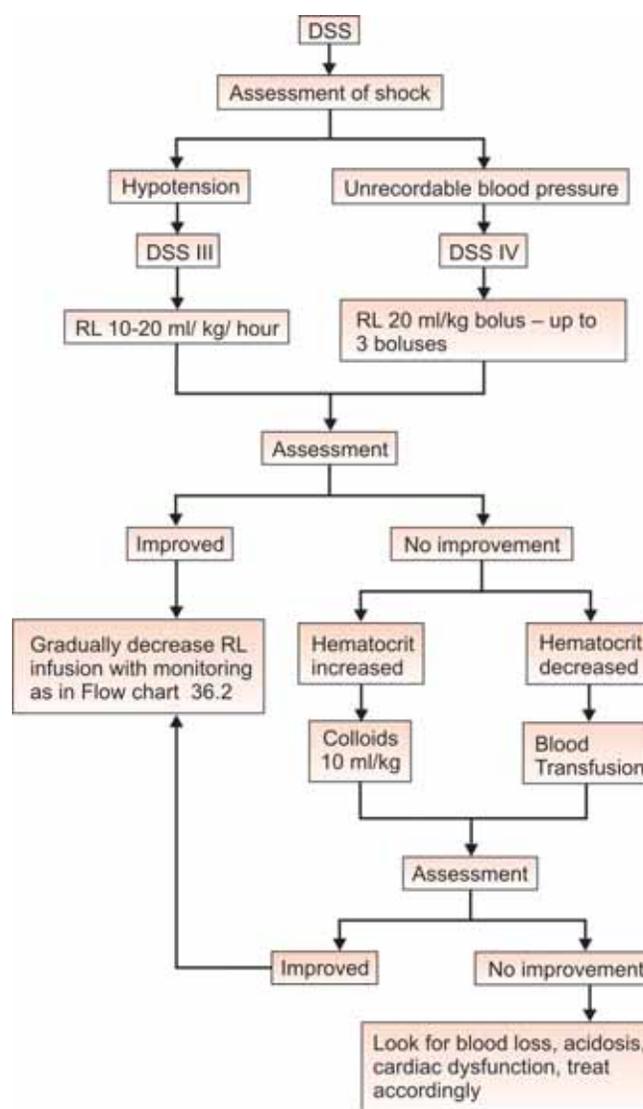
rate is increased to 10 ml/kg over next hour. In case of no improvement fluid infusion rate is further increased to 15 ml/kg over the third hour. If no improvement is observed in vital parameters and hematocrit at end of 3 hours, colloids or plasma infusion (10 ml/kg) is administered (Flow chart 36.2). Once the hematocrit and vital parameters are stable the infusion rate is gradually reduced and discontinued next 24-48 hours.

In children with hypotension (DSS grade III) Ringer's lactate solution, 10-20 ml/kg is infused over one hour or given as bolus if blood pressure is unrecordable (DSS grade IV). The bolus may be repeated twice if there is no improvement. If there is no improvement in vital parameters and hematocrit is rising, colloids 10 ml/kg are rapidly infused. If the hematocrit is falling without improvement in vital parameters, blood is transfused, presuming that lack of improvement is due to occult blood loss (Flow chart 36.3).<sup>27</sup> Once improvement starts then fluid infusion rate is gradually decreased. In addition to fluids, oxygen should be administered to all patients in shock.

There have been few studies that have evaluated the efficacy of different types of fluids in DHF/DSS. A randomized controlled trial four different types of fluid in 230 children in Vietnam suggested that 0.9% saline is the resuscitation fluid of choice for the majority of patients with dengue shock syndrome<sup>28</sup> Lactated Ringer's solution was not as effective as the other solutions, and allergic reactions occurred in five of the 56 children given 3% gelatin. Children given dextran 70 recovered more quickly, but they were not as ill as the children in the other treatment groups. None of the 230 children with dengue shock syndrome died, despite the fact that 51 children had a pulse pressure of  $\leq 10$  mm Hg at the time of presentation—although children with severe hemorrhagic manifestations were excluded. With early aggressive fluid therapy, the mortality rate should be very low, even in severe dengue.<sup>29</sup>

Wills et al reported on a double-blind, randomized comparison of three fluids for initial resuscitation of Vietnamese children with dengue shock syndrome.<sup>30</sup> 383 children with moderately severe shock were randomized to receive Ringer's lactate, 6 percent dextran 70 (a colloid), or 6 percent hydroxyethyl starch (a colloid). One hundred twenty nine children with severe shock were assigned to receive one of the colloids. The primary outcome measure was requirement for rescue colloid at any time after administration of the study fluid. The case fatality ratio was less than 0.2 percent. The primary outcome measure—requirement for rescue colloid—was similar for the different

**Flow chart 36.3:** Treatment of dengue shock syndrome (DSS)



fluids in the two severity groups. Treatment with Ringer's lactate resulted in less rapid improvement in the hematocrit and a marginally longer time to initial recovery than did treatment with either of the colloid solutions; however, there were no differences in all other measures of treatment response. Significantly more recipients of dextran than of starch had adverse reactions. Bleeding manifestations, coagulation derangements, and severity of fluid overload were similar for all fluid-treatment groups. In this study, the authors concluded that initial resuscitation with Ringer's lactate is acceptable for children with moderately severe dengue shock syndrome. Six percent

hydroxyethyl starch may be preferred in children with severe shock, the use of dextran is associated with various adverse reactions. However a recent randomized controlled trial suggest no difference in outcome with different colloid solutions.<sup>31</sup> In view of non availability of dextran solutions and no unequivocal support for particular colloid, it is suggested that when indicated, one can use any colloid solution till more studies are available. It is important to treat shock aggressively with fluid management and to avoid fluid overload, judicious use of frusemide infusion has been reported in one study.<sup>32</sup> However patients with aggressive fluid therapy needs very careful monitoring. In absence of adequate monitoring facility it is advised to use WHO protocol (as suggested above). During recovery the extravasated fluid is mobilized and gets in to intravascular space leading to fluid overload. In presence of clinical evidence of fluid overload, an intravenous dose of frusemide (1-2 mg/kg) may be given.

For uncontrolled bleeding in DHF or DSS, the role of plasma or platelet infusion remains unclear. In a small study in which children with severe thrombocytopenia were included, platelet infusion did not alter the outcome.<sup>33</sup> Infusion of fresh frozen plasma and platelet concentrates may be beneficial in patient with disseminated intravascular coagulation.<sup>34</sup> Treatment with methylprednisolone did not show any benefit in a double blind placebo controlled trial in patients with DSS.<sup>35</sup>

### MONITORING

In view of the rapid course in DHF and DSS, close monitoring of the patient is crucial in the first few hours of illness. Heart rate, respiratory rate, blood pressure and pulse pressure should be measured every 30 minutes till the patient is stable and thereafter every 2-4 hours. Central venous pressure monitoring is desirable in all children who develop hypotension. Difficulties are often encountered in insertion of central lines in critically ill small children.

Laboratory monitoring includes hematocrit measurement every 2 hours for the first 6 hours or till stable. Absolute platelet counts may be carried out once a day till it shows a rising trend. Platelet counts are repeated and coagulation studies performed if there is uncontrolled bleeding. If insertion of a central line is not feasible, clinical and hematocrit monitoring every 30 minutes may guide the rate of fluid infusion. It is emphasized that infusion rates decrease rapidly in the first 6 hours following intervention in most uncomplicated cases of DSS and DHF.<sup>33</sup>

*Criteria for discharge:* Children should be kept in hospital for 24-48 hours after they are hemodynamically stable off intravenous fluid, accepting well orally, have good urine output and no evidence of fluid overload. It is desirable that platelet counts are more than 50000/mm<sup>3</sup>. However in outbreak situation, if a patient is well and does not have bleeding and platelets are showing rising trend; patients could be considered for discharge even with platelet counts of less than 50000/mm<sup>3</sup>.

### PROGNOSIS

If left untreated, the mortality in patients with DHF or DSS may be as high as 40-50 percent. Early recognition of illness, careful monitoring and appropriate fluid therapy alone has resulted in reduction in mortality to 1-5 percent.<sup>36</sup> Early recognition of shock is of paramount importance as the outcome in DSS depends on the duration of shock. If shock is identified when pulse pressure starts getting narrow and intravenous fluid are administered, the outcome is excellent. Recovery is fast and majority of the patients recover in 24-48 hours without any sequelae. The outcome may not be as good once patient develops cold extremities. The prognosis is grave in patients with prolonged shock and when blood pressure is not recordable.

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Fever is merely a symptom with diverse causes resulting from varieties of pyrogenic stimuli. Though infection is a common cause of fever in clinical practice, other conditions such as immune mediated inflammatory diseases and malignant disorders are not uncommon. Miscellaneous conditions such as heatstroke, drug fever, central neurogenic lesions, thyrotoxicosis and factitious fever are rare.

Fever *per se* may not be life-threatening except in case of hyperthermia or hyperpyrexia.<sup>1</sup> In hyperthermia, hypothalamic set point is not elevated and this results in excessively high body temperature as a result of failure of thermoregulation. Such patients present with *fever without a focus* and need emergency cooling measures as antipyretics alone do not work in such patients. Hyperthermia is caused by some of the miscellaneous conditions mentioned above. Hyperpyrexia is defined as fever  $> 41.5^{\circ}\text{C}$  ( $106^{\circ}\text{F}$ ) and differs from hyperthermia in that hypothalamic set point is elevated. This may result from serious infections and may also endanger life, if not treated promptly. However, fever due to infection rarely exceeds  $40^{\circ}\text{C}$  because of 'thermal cooling' mediated through neuropeptides functioning as central antipyretics. Antipyretics are useful in such patients though these patients may also need cooling measures. Difference between hyperthermia and hyperpyrexia is not easily made out on clinical examination. Skin is hot and dry in hyperthermia. However, in case of doubt, empirical therapy for infection is justified along with emergency cooling measures.

In most of the situations, it is the cause of fever that determines the outcome in a given patient and not just the degree of fever. Therefore, it is important to diagnose the cause of fever as early as possible. Clinical approach to fever should first consider anatomical diagnosis and then only the pathology and etiology may be guessed. Thus, it is mandatory to define the focus of disease causing fever. Disease causing fever may be localized by analysis of symptoms and signs. At times, symptoms may be non-specific such as

vomiting, irritability, and headache and may not help in correct localization. However, fever may often present without any obvious clue to a focus.

*Fever without a focus is almost a rule in early stages of the disease.* Thus accurate diagnosis in a child with fever is often not possible during first couple of days, except in case of acute tonsillitis, cervical lymphadenitis or bacillary dysentery. These are the infections that are caused by direct local invasion and not through bloodstream. Systemic blood borne infections evolve a focus over few days. In such cases, it is necessary to anticipate the probable cause based on age and relevant epidemiology and predict the risk of serious bacterial infection, which if not treated promptly may be fatal. Timely relevant laboratory tests prior to administration of antibiotic and thereafter empirical antibiotic therapy may be justified in such situations even without proper diagnosis. However, in absence of adverse factors, physicians may observe further course of illness and act accordingly. Pattern of fever is a useful indicator of probable cause of fever (Table 37.1).<sup>2</sup> However, it does not offer any clue if fever is greatly modified with use of powerful antipyretic such as nimesulide. Paracetamol is a trusted antipyretic, which prevents body temperature from rising to very high levels and may not modify natural course of fever. Especially in case of fever without a focus, undue suppression of fever by nimesulide, at times has led to missing a serious illness during early stage of the disease. Bacteremia and toxemia result in high fever often poorly responding to paracetamol. Viral infections and mild bacterial infections

**Table 37.1: Useful clinical clue to probable etiology of infection**

History	Viral	Bacterial	Malaria
Onset	High	Mild to moderate	High
Rhythm	Rhythmic	Rhythmic	Non-rhythmic
Day 3-4	Better	Peak	Erratic
Interfebrile period	Normal	Sick looking	Normal

often respond to paracetamol, though temporarily for few hours and the child is near normal during intervening period between two spikes of fever. Biphasic fever is seen in many viral infections and also in infections which evoke immune response such as leptospirosis.

### RULE OUT SERIOUS ILLNESS

In a child with fever without a focus, primary concern is to rule out serious illness. Infections of vital systems leading to organ dysfunction and immune mediated response to infections such as sepsis, shock and multiorgan failure endanger life.<sup>3,4</sup> These conditions have to be diagnosed early enough, even without a focus, for successful outcome and antibiotics alone do not save life. Early diagnosis of pneumonia and meningitis is not easy. Careful evaluation of increased respiratory rate and effort may point to the possibility of pneumonia. Suspicious meningeal signs, boggy fontanelle or drowsiness should prompt spinal tap to rule out intracranial infection. Cerebral malaria is difficult to diagnose and should be suspected based on local epidemiology, especially when fever is erratic. If such a child is sick looking, he must be treated even empirically. It is important to examine throat of every child for serious disease such as diphtheria. Sepsis is a systemic inflammatory response to infection and is clinically recognized by disproportionate tachycardia and tachypnea in a febrile child. Close observation of blood pressure, capillary refill, core-skin temperature difference, urine output and mental status is necessary to monitor progress. Fluid resuscitation is the mainstay of treatment in such patients. In every child with fever, skin surface should be examined for presence of rash. Purpuric spots suggest either disseminated intravascular coagulopathy or vasculitis as in case of meningococemia. Once the possibility of serious illness is ruled out, attempt is made to diagnose the cause of fever.

### Fever with Skin Rash

Though often non-specific, type and distribution of skin rash offers clue to the probable etiology. Centrally distributed maculopapular rash is seen in infections such as measles, Epstein-Barr and other viral infections including HIV, leptospirosis, typhoid, Lyme disease and also in autoimmune disorders such as chronic juvenile arthritis and systemic lupus. Peripheral rash is typical of meningococemia, subacute bacterial endocarditis and erythema multiforme. Confluent desquamating erythema is characteristic of scarlet fever, streptococcal/staphylococcal infections and Kawasaki syndrome.

Vesicobullous rash is seen in varicella, herpes and rickettsial infection. Urticarial rash may be caused by varieties of infections and drugs. Nodular rash represents erythema nodosum or fungal infections. Purpura may result from disseminated intravascular coagulopathy or due to leukemia and bone marrow suppression.

### Fever with Nonspecific Physical Signs

Hepatomegaly, splenomegaly or both may not suggest etiology of fever but offer clinical clues and lead to relevant investigations. Such findings may suggest infections involving reticuloendothelial system as in case of typhoid fever, tuberculosis, leptospirosis, brucellosis, malaria, chronic viral infection like viral hepatitis or Epstein-Barr virus infection or fungal infection. These findings may also be seen in infiltrative disorders such as leukemia or histiocytosis or in autoimmune disorders. Generalized lymphadenopathy may also be indicative of similar diseases. Histopathological diagnosis is often possible in such situations in addition to hematological and liver function tests.

### Fever without Focus Beyond Seven Days

Most of the time, either focus evolves over first 4-5 days or fever subsides as in case of self-limiting viral infection. Repeated physical examination is mandatory that often unfolds the diagnosis. However if fever persists without focus beyond 7 days, typhoid and tuberculosis must be ruled out by proper investigations. Blood culture for *S. typhi* is the gold standard of diagnosis of typhoid fever and it is easy to grow *S. typhi* in blood culture. Widal test may not be easy to interpret and is not diagnostic. Mantoux test and chest X-ray needs proper evaluation and if possible, gastric lavage should be sent for definitive diagnosis. Serological tests for tuberculosis are not helpful and PCR though sensitive and specific is highly technical test and results are dependable only if done at specialized laboratory. At this juncture, therapeutic trial for typhoid may be justified but anti-TB trial is not recommended.

### Fever without Focus Beyond Two Weeks

By now, most of the common infections would have been ruled out and therapeutic trial with antibiotic and antimalarial drugs would have failed. Tuberculosis even if ruled out still is a possibility as focus may not be visible even on routine chest X-ray. As mentioned above, there is no substitute to repeated physical examination.

**Table 37.2: Broad investigational plan**

Time frame	Laboratory tests
First 3-4 days	No tests except in suspected serious conditions
4-7 days	CBC/urinalysis/chest X-ray (CSF in special situations)
8-14 days	Repeat CBC/blood culture
Beyond 2 weeks	Repeat CBC/ESR/Abd USG/specific serology
Beyond 4 weeks	Repeat CBC/ESR/CT chest and abd bone marrow

At this juncture, repeat hemogram and ESR may offer some clue to autoimmune disorders or malignancy. Increasing neutrophilic leukocytosis and thrombocytosis with high ESR may suggest juvenile chronic arthritis and very high lymphocytosis may suggest lymphatic leukemia. ANA – antinuclear antibody test is non-specific and must be properly analyzed. It is positive in many autoimmune diseases but also in infections and may be drug induced. RA factor – Rheumatoid factor test is reserved only for older female children with pauciarticular arthritis and is negative in more than 95% of juvenile chronic arthritis. Abdominal USG and CT scan of chest may be considered if routine hemogram does not offer any clue.

Table 37.2 gives a broad investigational plan for fever.

### AGEWISE DIAGNOSTIC APPROACH

Evaluation of risk factors based on age related epidemiology demands variable approach in different age groups.

#### Young Infant (<3-6 months)

This is a vulnerable age group where cause of fever may be considered as acute bacterial infection till proved otherwise, especially in bottle fed and/or undernourished infants. Diseases considered even without a focus include meningitis, pneumonia, urinary tract infection and malaria. Complete blood count with peripheral smear, routine urinalysis and chest X-ray should be the minimum tests performed and if indicated, blood and urine culture. In case of doubt of intracranial infection, spinal tap must be considered. Empirical treatment should begin before the test results are available and choice of antibiotics is decided by epidemiological information. Therapy may be modified further depending upon the results of laboratory tests. This is the age group where safety margin is so small that liberal use of antibiotics is justified and not

considered irrational. Fever without a focus in an exclusively breastfed infant who otherwise is stable and does not look sick, may be observed closely without any specific therapy and attempt may be made to diagnose the cause of fever by appropriate laboratory tests. Several studies have tried to evolve strategies to decide hospitalization and antibiotic therapy in young infants with fever without a focus. Until further large prospective studies are available, use of the Rochester criteria including spinal puncture has been shown to provide the best screening method for selecting a low risk subset of febrile infants.<sup>5-8</sup>

#### Older Infant and Toddler (6 months to 5 years)

Infections predominate in this group, as autoimmune and malignant disorders are not so common. Infections are often localized to a system but during first few days, localization is not evident clinically and hence they present without any obvious focus of infection. In most of these situations, it is safe to observe the child closely for first couple of days and in majority, localization becomes apparent. However, if focus is not seen within 2-3 days, complete blood count with peripheral smear examination, urinalysis and chest X-ray are imperative. Urinary tract infection often lacks any symptoms referable to urinary tract and pneumonia presents with little or no cough and physical signs may not be easy to obtain. Malaria is always a possibility, and is difficult to prove each time on peripheral smear examination.

#### School Going Child (>5 years)

This is the age group wherein fever may go on for long time without demonstrable focus. Predominant amongst the infections are typhoid fever, leptospirosis, dengue fever, tuberculosis, malaria and deep-seated abscesses. Noninfectious diseases are also common in this age group and they include autoimmune disorders including systemic vasculitis and malignancy such as leukemia, lymphoma and neuroblastoma. Many of these diseases unfold their characteristic clinical picture over few days and till then pose a diagnostic dilemma. It is safe to observe these patients for first few days and then plan relevant investigations.<sup>9</sup> If fever continues beyond 4-5 days without any clue to the diagnosis, routine investigations should be ordered such as complete blood count with peripheral smear examination and if relevant other tests such as urinalysis, spinal tap and chest X-ray. These tests may offer some clues to the probable diagnosis. Based on the interpretation of these tests, empirical therapy may be planned. It is rational to send

out blood culture before starting empirical antibiotic in these patients so that action can be planned logically. In case of failure of empirical therapy and persistence of fever without a focus for > 8-10 days, further tests may have to be planned. Repeat blood counts are useful to follow the course of illness. Other commonly required tests at this stage include ESR, CRP, Widal test and abdominal USG. Repeat chest X-ray or CT scan, tuberculin test and contact study may help to establish the diagnosis of tuberculosis. Attempt must be made to look for bacteriological or histological proof of tuberculosis. Isolated focus of tuberculosis in liver or spleen is difficult to diagnose; fine needle biopsy may prove the diagnosis.<sup>10,11</sup> It is not rational to try empirical therapy for tuberculosis because improvement on such a treatment may not signify correct diagnosis as anti-tubercular drugs also act against many other bacterial infections. Once common infections are ruled out, tests for uncommon infections must be carried out. Choice of these tests would depend upon the prevailing epidemiology and may include tests for dengue, leptospirosis, CMV and brucellosis. Bone marrow examination is helpful and should always be undertaken especially before considering steroid therapy. Diagnosis of autoimmune disorders is not easy especially in case of fever without a focus. Skin rash, however, transient, may offer clue to such a diagnosis. Estimation of various autoantibodies can at best suggest the possibility of the diagnosis and accurate label often eludes the clinician for many months. With no obvious manifestations of the disease evident on physical examination or extensive laboratory tests, special tests may have to be considered such as CT or MRI of abdomen/chest/brain and radionuclide scans.<sup>12-14</sup>

### Fever without a Focus in Special Situations

Fever in an immunocompromized host such as malignancy or neutropenia deserves special consideration to plan therapy. These patients are highly vulnerable to all types of infections and may easily succumb, especially if not treated aggressively. While there should not be a delay in starting broad-spectrum combination antibiotics, attempt must be made to define source of fever by various tests.<sup>15,16</sup>

An individualized approach, based on clinical evaluation supplemented with screening and definitive laboratory tests to determine the need for empiric antibiotic therapy and hospitalization, seems to be the best approach to fever without a focus. The place of laboratory tests, empiric antibiotic therapy and hospitalization are important issues that are likely to remain debatable.<sup>17,18</sup>

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# 38 Dermatologic Emergencies

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Several skin problems require a quick diagnosis and appropriate and timely management and the situation can be especially serious if a dermatologist is not available at hand and the patient is a child. Since in the present curriculum of undergraduate training, the exposure of the students to the dermatologic problems and their management is far from satisfactory,<sup>1</sup> it is often a challenge for a primary care provider to differentiate mundane skin ailments from more serious, life-threatening conditions that require immediate intervention.

Children with serious skin diseases require not only specialized skin care but aggressive supportive therapy including balanced nutrition, intravenous rehydration with maintenance of electrolyte balance, continuous monitoring of the vital signs like body temperature and cardiopulmonary function, maintenance of good oral hygiene and eye care. Moreover, since the barrier function of the skin is impaired in patients with several skin diseases, it is essential to prevent opportunistic infections. And all this requires a close interaction between the pediatrician and dermatologist. In this chapter we will deal with the more frequently occurring serious dermatological problems when they occur in children.

## ACUTE URTICARIA AND ANGIOEDEMA

Urticaria and angioedema are classical signs of cutaneous anaphylaxis. Incidence is 0.5 percent. Urticaria is due to edema of dermis and angioedema is due to edema of dermis and subcutis.

### Etiology

Acute urticaria usually occurs frequently in children with an atopic diathesis and the triggers in children are no different from adults (Table 38.1).

### Clinical Features

#### *Urticaria*

Urticaria begins as itchy (some times intense) erythematous macules which rapidly evolve into pale pink

**Table 38.1: Causes of urticaria**

Idiopathic	
Hypersensitivity urticaria	Food, inhalants, insect stings, infestations, infections
Physical urticaria	Cold, solar, heat, cholinergic, dermographic
Drugs	Salicylates, penicillin, sera
Inherited	Hereditary angioedema
Others	Cutaneous mastocytosis

edematous wheals with a surrounding flare. The number and size of the wheals is variable. They can be annular, circular, serpiginous and even bizarre shaped and are linear in dermographic urticaria. Lesions usually last a few (always within 24-48) hours and resolve to leave behind normal skin.

#### *Angioedema*

Angioedema is more frequently (50-60%) associated with urticaria in infants and young children and a hemorrhagic pattern has been reported.<sup>2</sup> Pale pink swellings occur mostly on face, especially eyelids and lips (Fig. 38.1). It may also be associated with swelling of tongue, pharynx and larynx. Swelling may last for several days. Unlike urticaria, angioedema is usually not very itchy.

#### *Systemic Associations of Urticaria and Angioedema*

Urticaria and angioedema may be associated with systemic symptoms of fever, bodyaches, vomiting, abdominal pain, diarrhea, hypotension, tachycardia, cardiovascular collapse and anaphylaxis.

### Course

About 20-30 percent of children with urticaria experience recurrent attacks or develop chronic urticaria.<sup>2</sup>



**Fig. 38.1:** Angioedema: Pale pink swellings on lips. May also be associated with swelling of tongue, pharynx and larynx (For color version see plate 1)

## Treatment

### In the Acute Stage

- **Antihistamines:** All cases of urticaria must be treated with antihistamines, at a dose which controls the wheals within 24 hours. The choice of the antihistamine is largely personal, but generally a combination of a short-acting and a long-acting medication is very effective. In moderately severe cases, oral antihistaminic drugs may suffice but in severe cases, parenteral drugs need to be given to provide rapid relief.
  - *Conventional (sedating):* Pheniramine, chlorpheniramine and hydroxyzine.
  - *Newer (non-sedating):* Cetrizine, levocetirizine, fexofenadine and loratene.
- **Vasopressors:** Children with severe anaphylactic reaction should be treated with subcutaneous administration of aqueous epinephrine (1:1000, 0.01 ml/kg body weight), long with parenteral antihistamine drugs and systemic corticosteroids.
- **Supportive measures:** Children with laryngeal edema require prompt intervention and vigorous supportive measures such as oxygen, intravenous fluids and vasopressors (Table 38.2).<sup>3</sup>
- As antipyretic drugs, especially salicylates, cause direct mast cell degranulation (and so aggravation of wheals), they are best avoided even if the child is febrile. The fever generally responds to antihistamines alone.<sup>3</sup>

**Table 38.2: Management of anaphylaxis**

- Stop all drugs
- Give subcutaneous epinephrine (1:1000, 0.01 ml/kg) immediately
- Monitor blood pressure
- Maintain airway; administer oxygen
- Intravenous fluids
- **Antihistamines:** Pheniramine maleate intramuscular, 1 mg/kg
- **Corticosteroids:** Hydrocortisone intravenously, loading dose 10 mg/kg and then 5 mg/kg every 6 hours
- Nebulized salbutamol, 0.15 mg/kg/dose if bronchospasm present

### After the Acute Phase

- Once the acute phase has subsided, oral antihistamines form the mainstay of therapy. These should be continued for 1-2 weeks and then tapered. Systemic corticosteroids are usually not required (and ofcourse are best avoided).
- Search should be made to establish and eliminate the cause of urticaria to prevent recurrences, but this is seldom useful.
- And what is best not used:
  - Specific desensitization is not necessary.
  - Disodium cromoglycate does not act on cutaneous mast cells and so it is not recommended for prevention of urticaria.

## EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome-toxic epidermal necrolysis complex (SJS-TEN complex) is an acute life-threatening mucocutaneous reaction pattern characterized by extensive necrosis and detachment of epidermis. Though commoner in adults, it can occur in children.

### Etiology

EN is generally precipitated by drugs (Table 38.3). More than 100 drugs have been implicated but the importance of one medication can be established in 70 percent cases.

### Clinical Features

#### Prodromal Symptoms

Most children have prodromal symptoms in the form of high fever, cough, sore throat and malaise.

**Table 38.3: Causes of epidermal necrolysis**

• Anticonvulsants	Carbamazepine, hydantoin, barbiturates, lamotrigine <sup>4</sup>
• Antituberculous drugs	Isoniazid, thiacetazone
• Antimicrobials	Sulphonamides, penicillins
• Vaccinations	Measles
• Graft vs host reaction	
• Infections	
– Viral infections:	Herpes simplex, hepatitis A and B
– Bacterial infections:	<i>Mycoplasma</i> , <i>Streptococcus</i>
• Lymphoreticular malignancies	
• Idiopathic	

**Fig. 38.2:** SJS/TEN complex: Targetoid lesions (For color version see plate 1)

### Cutaneous Lesions

EN is characterized by appearance of generalized, symmetrical tender, ill defined erythematous macules, initial lesions may be targetoid (Fig. 38.2). The lesions rapidly coalesce, become brownish black, and denude in sheets to leave behind moist eroded areas. Occasionally, small flaccid bullae appear, prior to denudation of skin. If neglected, the lesions often get secondarily infected. Scarring then may cause cosmetic and functional complications.<sup>5</sup> Lesions initially appear on the face, upper trunk and proximal parts of the extremities and may eventually involve other parts.

### Mucosal Lesions

Involvement of mucosa is universal and usually precedes the skin eruption. Oral mucosal involvement is frequent (90%) and manifests as edema, erythema and blisters which rupture to form extensive hemorrhagic erosions with greyish white pseudomembrane or hemorrhagic crusts especially on lips (Fig. 38.3). Oral lesions may slough to cause problems in feeding. Eye

**Fig. 38.3:** SJS/TEN complex: Hemorrhagic crusts on lips and purulent conjunctivitis. Dehydration, electrolyte imbalance, pneumonia, renal failure and septicemia are the causes of high mortality (For color version see plate 2)

involvement is common (85%) manifesting as purulent conjunctivitis and may result in corneal opacities. Genital and nasal mucosa involvement is characterized by hemorrhagic crusting.

### Classification

Based on percentage of body surface area, patients are classified into:

- SJS: < 10% BSA involved.
- SJS/TEN overlap: 10-30% BSA involved.
- TEN: > 30% BSA involved.

### Course

Mortality is high (25-70%), chiefly due to dehydration, electrolyte imbalance, pneumonia, renal failure and septicemia. The value of SCORTEN in predicting mortality in children has not been reproducibly evaluated.

### Differential Diagnosis

SJS-TEN in children needs to be differentiated from staphylococcal scalded skin syndrome.

### Treatment

#### Supportive Care

Immediate hospitalization is necessary as extensive skin loss is analogous to partial thickness burns and needs aggressive supportive care (Table 38.4).

**Table 38.4: Supportive care in patients with SJS-TEN**

- Proper maintenance of fluid, electrolyte and nutrition balance
- Proper maintenance of body temperature
- Proper maintenance of indwelling catheters and intravenous lines
- Barrier nursing. Frequent blood cultures and skin cultures
- Care of skin:
  - 0.5% silver nitrate soaks or saline washes
  - Frequent wound debridement of necrotic tissue
- Prompt treatment of complications

### Specific Treatment

- *Withdrawal of all drugs:* It is essential.<sup>5,6</sup> In case the group of drug which the child is taking cannot be withdrawn, it definitely needs to be substituted with chemically unrelated drug with similar therapeutic effect.
- *Systemic steroids:* Use of steroids in SJS-TEN is debated:
  - Several studies have shown that systemic steroids do not reduce mortality or duration of hospital stay, and may even promote and mask infections.
  - Some studies have shown benefit of systemic corticosteroids in the condition. For benefit, steroids need to be instituted early and at an adequate dose (2 mg/kg/day of prednisolone equivalent). If the perilesional erythema does not reduce and/or new lesions continue to appear 48 hours after starting therapy with corticosteroids, the steroid dose should be increased. Once the new lesions stop appearing and old ones start healing, the corticosteroids dosage is tapered and withdrawn in the next 7-10 days.<sup>2</sup>
- *Other medications:* Several other medications have been used with success in SJS-TEN:
  - Intravenous immunoglobulin
  - Cyclosporine A
  - Plasmapheresis or hemodialysis
  - Anti-tumor necrosis factor.

## STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

### Etiology

SSSS is caused by circulating exfoliatin produced by Group II phage 71 *Staphylococcus aureus* present at distant sites (usually an occult upper respiratory infection, occasionally purulent conjunctivitis or otitis media and rarely impetigo).<sup>7</sup> The skin lesions by themselves are sterile.

### Clinical Features

SSSS is seen in children younger than 5 years. Lesions begin with cutaneous tenderness followed by widespread blistering and superficial denudation or desquamation. Periorificial and flexural accentuation may be conspicuous. Lesions resolve within 5-7 days of therapy, with superficial desquamation (and no scarring). Mucous membranes are spared and constitutional symptoms are minimal.

### Diagnosis

SSSS needs to be differentiated from SJS-TEN. Apart from clinical differences, a bed-side cytopathological smear may be helpful:

- In SSSS, since the split is intraepidermal, so epithelial cells with small nuclei are seen.
  - In TEN, split is at dermoepidermal junction, so cuboidal cells are seen.
- A new rapid diagnostic test has been devised to detect circulating toxin.<sup>8</sup>

### Treatment

#### Specific Treatment

- Systemic antibiotics: Aggressive treatment with antibiotics, preferably with intravenous beta-lactamase resistant, anti-staphylococcal antibiotics, should be instituted immediately.<sup>9</sup>
- Utility of specific antitoxins to prevent exfoliation is being examined.<sup>8</sup>
- Topical antibiotics are not helpful.

#### Supportive Treatment

Attention should be given to maintenance of an adequate fluid and electrolyte balance and appropriate supportive care.

## ERYTHRODERMA

### Etiology<sup>11,12</sup>

Common causes of erythroderma in children include bullous and non-bullous varieties of ichthyosiform erythroderma and drugs. Less frequently, erythroderma may occur as a complication of infantile seborrheic dermatitis, atopic dermatitis, psoriasis and even immunodeficiency disorders. Erythroderma occurring at birth is usually due to ichthyosis or immunodeficiency.

### Clinical Features

Erythroderma is characterized by extremely itchy (not in infants younger than 3 months) erythema and scaling



**Fig. 38.4:** Erythroderma: Erythema and scaling involving almost the entire body. Complications are fluid and electrolyte imbalance, impaired regulation of body temperature, high-output cardiac failure, hypoalbuminemia and secondary infections (For color version see *plate 2*)

involving almost the entire body (Fig. 38.4). There may be generalized lymphadenopathy. In addition clinical clues to the underlying disease, (such as bullae in bullous ichthyosiform erythroderma, psoriatic plaques in psoriatic erythroderma) may be present. Often, however, the etiological diagnosis is difficult to ascertain due to poor specificity of clinical and histological signs. In immunodeficiency the erythrodermic skin is infiltrated and failure to thrive, frequent infections, alopecia and diarrhea may be associated.<sup>13</sup>

### Complications

Erythroderma may be associated with fluid and electrolyte imbalance and with hypothermia or hyperthermia due to impaired regulation of body temperature. Extensive peripheral vasodilation can lead to a high-output cardiac failure. Hypoalbuminemia is common due to loss of protein in the scales and secondary infections are not infrequent due to impaired immune functions. Erythroderma, if not managed appropriately, may be associated with a high morbidity and mortality.

### Treatment

In case of erythroderma caused by drugs, withdrawal of the causative drug along with a short course of corticosteroids is usually adequate.

- Ichthyosiform erythroderma requires long-term treatment with keratoplastic and keratolytic agents such as 3 percent salicylic acid or 10-12 percent urea in glycerine or propylene glycol.
- Topical retinoic acid may be useful at a later stage of treatment.
- Synthetic retinoids, though potentially toxic, are useful in the management of severe forms of ichthyosiform erythroderma, collodion baby and Harlequin ichthyosis.<sup>1</sup>

## COLLODION BABY

### Etiology

A morphological diagnosis, which could be the result of several ichthyosiform dermatoses (but never epidermolytic hyperkeratosis) most notably non bullous ichthyosiform erythroderma, lamellar ichthyosis and rarely X-linked ichthyosis. In 10% of collodion babies, there is no underlying disorder.

### Clinical Features

Baby is born with generalized glistening, yellowish parchment like membrane and the skin markings are obliterated (Fig. 38.5). The membrane usually sheds in first 2 weeks, to reveal the underlying ichthyosis in 90% of infants. In 10%, the underlying skin is normal. There



**Fig. 38.5:** Collodion baby: Newborn ensheathed in generalized glistening, yellowish parchment like membrane and associated with ectropion, eclabium, flattened pinnae and restricted limb mobility. High mortality is due to temperature dysregulation, renal failure, and sepsis or electrolyte imbalance (For color version see *plate 2*)

may be associated ectropion, eclabium, flattened pinnae and restricted limb mobility.

### Complications

Mortality (about 10%) is due to temperature dysregulation, renal failure, sepsis or electrolyte imbalance.

### Variants

#### *Harlequin Fetus*

Harlequin fetus is a premature infant who is born encased in a rigid coat of armour composed of firmly adherent, dense plaques which develop fissures (so resembling a harlequin costume). There is severe ectropion, conjunctival edema and eclabium; the nose and external ears appear rudimentary. The hands are encased in mitten like casts. Mortality is high due to respiratory insufficiency (due to restricted chest movement), nutritional imbalance (absence of sucking), dehydration, temperature instability, sepsis and renal failure.

### Treatment

#### *Supportive Treatment*

- Child needs to be managed in thermoneutral environment with appropriate management of nutrition, electrolytes and hydration.

- Soothing applications, in the form of emollients (vegetable oils, petrolatum) are used.

#### *Specific Treatment*

Retinoids (acitretin) may hasten shedding of the membrane, thus reducing morbidity and mortality.<sup>10,12,13</sup>

### DRUG ERUPTIONS

A variety of drug eruptions can be serious (Table 38.5).

#### Treatment

- All drugs being taken by the child should be stopped. Essential drugs need to be substituted with chemically unrelated drugs.
- *Mild reactions:* Calamine lotion and systemic antihistamine medications are enough for milder cases.
- *Severe reactions:* Severe reactions should be treated with a short course of oral corticosteroids along with symptomatic therapy.<sup>1</sup>

### PEMPHIGUS

#### Etiology

Pemphigus is an autoimmune disorder<sup>14</sup> caused by the deposition of autoantibodies in the intercellular spaces

**Table 38.5: Common drug eruptions**

<i>Pattern</i>	<i>Morphology</i>	<i>Drugs implicated</i>
Exanthematous eruptions	Commonest. Symmetric erythematous macules and papules surmounted by scales	Pencillins, sulphonamides, anti-convulsants, antitubercular drugs
Erythroderma (exfoliative dermatitis)	Erythema, scaling and edema	Pencillins, sulphonamides, barbiturates, isoniazid, gold
Stevens Johnson syndrome-toxic epidermal necrolysis (SJS-TEN) complex	Initial lesions targetoid, followed by diffuse, intense erythema. Flaccid blisters, followed by large areas skin denudation. Mucosae always involved	Sulphonamides, pencillin, quinolones, barbiturates phenytoin, frusemide, hydralazine, NSAIDs
Fixed drug eruption	Well demarcated, erythematous plaques, recurring at same site each time implicated drug is taken. Subside with hyperpigmentation	Phenolphthalein, barbiturates, sulphonamides, tetracyclines, salicylates
Photosensitive eruption	Pruritic papules and plaques on sun-exposed areas	Thiazides, sulphonamides, tetracyclines, quinolones, phenothiazines, psoralens
Vasculitis	Can manifest as palpable purpura, urticarial vasculitis, necrotic ulcers, nodular vasculitis	NSAIDs, phenytoin, sulphonamides, tetracyclines, ampicillin
Urticaria and angioedema	Can occur independently or as apart of a severe generalized reaction with bronchospasm and circulatory collapse (anaphylaxis)	Aspirin, indomethacin, opiates, sulphonamides, pencillin



**Fig. 38.6:** Pemphigus vulgaris: Flaccid bullae on normal looking skin. Secondary sepsis, dehydration, or secondary biochemical abnormalities caused by corticosteroid therapy are the frequent complications (For color version see plate 2)

of the epidermal cells leading to cell separation (acantholysis) and formation of intraepidermal bullae. Though considered uncommon in children, cases of pemphigus in childhood have been reported.<sup>2</sup> Neonatal cases are due to transplacental transmission of antibodies from an affected mother.<sup>15</sup>

### Clinical Features

Pemphigus is a potentially fatal disease and severe cases often present as emergencies.

### Morphology

Though there are several clinical variants, pemphigus vulgaris is the commonest. In pemphigus vulgaris, flaccid bullae arise on normal looking skin (Fig. 38.6) and quickly evolve into painful denuded areas. Healing is slow and recurrence is the rule. Oral ulcers are frequently present and may herald the onset of the disease in 50% patients.

### Variants

*Pemphigus foliaceus*: It is a benign but relatively less common condition.

- It presents as scaly and crusted lesions in a seborrhoeic distribution, or in a generalized distribution-closely simulating exfoliative dermatitis. Bullae and ulcers are rare and oral lesions are absent.
- *Pemphigus vegetans*
- *Pemphigus erythematousus*

### Complications

Pemphigus is a chronic problem, associated with considerable morbidity and mortality. Death results from secondary sepsis, dehydration, or secondary biochemical abnormalities caused by corticosteroid therapy.

### Treatment

#### Supportive Care

If the lesions are extensive, immediate hospitalization is necessary for aggressive supportive care (Table 38.4).

#### Specific Treatment

- *Corticosteroids*: They form the mainstay of therapy. After initial control with a combination of daily steroids (1 mg/kg daily of prednisolone equivalent) and suprapharmacological doses at monthly intervals (pulse therapy), the patient can often be maintained on pulse therapy given under supervision. The preparation recommended is methylprednisolone,<sup>16</sup> but the availability and low cost of dexamethasone and betamethasone (the latter may be given orally) has prompted their preferential use in India.<sup>17</sup> Cushing's syndrome, growth retardation and infection are the most common side effects seen in children.
- *Adjuvants*: Several adjuvants have been used in children:
  - *Azathioprine*: It has been best studied. It is given in a dose of 2 mg/kg/day to be used initially in two divided doses followed by maintenance dose of 1 mg/kg/day. Due to relatively lower toxicity, lower risk of sterility and lower life time risk of malignancy especially as compared to cyclophosphamide, it is well recommended in children.
  - Other adjuvants that can be used are cyclosporine, methotrexate, dapsone, cyclophosphamide, mycophenolate mofetil, plasmapheresis.

### EPIDERMOLYSIS BULLOSA (EB)

This is a heterogeneous group of heritable mechanobullous disorders characterized by formation of bullae at sites of trivial trauma.

### Classification

- Autosomal dominant
  - Simplex or epidermolytic variant
  - Dominant dystrophic

**Table 38.6: Clinical features of epidermolysis bullosa**

	<i>EB simplex</i>	<i>Junctional EB</i>	<i>Autosomal dominant dystrophic EB</i>	<i>Autosomal recessive dystrophic EB</i>
<b>Age of onset</b>	Early childhood	Birth	Birth/early infancy	Birth
<b>Skin lesions</b>	Non-hemorrhagic bullae develop on normal skin	Large flaccid bullae which heal slowly	Hemorrhagic blisters which heal with scarring and milia	Hemorrhagic blisters which heal with severe scarring
<b>Sites</b>	Sites of repeated trauma (hands and feet)	Perioral and perianal areas and sites of trauma	Sites of friction (knees, elbows, fingers)	Generalized
<b>Mucosal lesions and nail involvement</b>	–	+	+	++
<b>Complications</b>	Heal without scarring	One variant is lethal	Scarring and milia formation	Severe scarring: • Webbing of digits (mitten hands) • Esophageal strictures

- Autosomal recessive
  - Atrophic or junctional variant
  - Dystrophic or dermolytic variant

### Clinical Features (Table 38.6)

EB is characterized by development of bullae at sites of trivial trauma and variable mucosal and nail involvement, depending on the variant.

The epidermolytic variety is relatively benign because it is limited to the skin only and there are no scars, while the atrophic and the dystrophic varieties are serious and can be life-threatening. In the atrophic variety, bullae and mucosal ulcers appear at birth and many infants succumb to secondary infections. Nail changes, dysplastic teeth, refractory anemia and secondary growth retardation appear in those who survive. In the dystrophic variety, blistering of the skin and mucosal ulcers begin in infancy and bullae heal with severe scarring. Anemia, secondary infections, deformities, ocular complications and esophageal stricture cause considerable morbidity.

### Treatment

#### Supportive Care

This forms the cornerstone of treatment

- In most cases the triad of wound management, nutritional support and infection control is the key to management. Survival in the acute phase depends on skilled nursing and supportive care.

- Child must always be handled gently and protected from trauma.
- Though systemic corticosteroids have been used in the acute phase to prevent deformities, they do not alter the course of the disease.

#### Specific Treatment

- There is yet no specific treatment for EB. Future potential therapies for epidermolysis bullosa include protein and gene therapy.
- Diphenylhydantoin and tetracyclines have been used in the past for dystrophic variety but do not significantly alter disease progression. Other drugs, which have been tried with variable results, include antimalarials and retinoids.

#### Other Measures

- Surgical treatment of contractures and strictures may be necessary.
- Genetic counseling and prenatal diagnosis: Families at risk must be given adequate genetic counseling. Since prenatal diagnosis has become possible, pregnancies in these families can be screened for the disease.<sup>18</sup> Prenatal diagnosis is of considerable importance to the families who have had an affected child, or in which one of the parents is affected. The prenatal diagnosis is performed by either chorionic villous sampling at 8-10 weeks or amniocentesis in second trimester. Fetoscopy and fetal skin biopsy with

their increased loss of pregnancy are now avoidable.

### HERPES VIRUS SIMPLEX INFECTIONS

Two clinical conditions caused by infection due to the herpes simplex virus (HSV), neonatal herpes infection and eczema herpeticum are likely to prove serious.

#### Neonatal Herpes Infection

##### Factors which Promote Infection

- Neonates might be infected during delivery or due to ascending infection after prolonged rupture of membranes.<sup>19</sup>
- The risk of neonatal infection is much greater during the primary episode of maternal infection than during recurrent episodes, because of higher viral load shed during the primary infection and absence of maternal antibodies.

#### Clinical Features

Intrauterine infection results in skin vesicles and scarring, chorioretinitis, keratoconjunctivitis and microcephaly. Infection of neonates during birth results in single or grouped vesicles and pustules on the scalp or buttocks during the first few days of life. Petechiae, ecchymoses, jaundice, hepatomegaly and involvement of the eye and the brain are common.

#### Complications

Infection in the newborn is associated with 60% mortality primarily due to herpes encephalitis, pneumonitis or disseminated intravascular coagulation and a high morbidity due to severe neurological and ocular sequelae.<sup>20</sup>

#### Management

##### Prevention

Since, the risk of infection of the infant from a primary herpetic vulvovaginitis in the mother at the time of vaginal delivery is very high, the neonate should be delivered by cesarean section preferably within 24 hours of the rupture of membranes. Acyclovir is administered following birth, to prevent infection.

##### Treatment

Once herpes infection has occurred, it is treated with intravenous acyclovir (20 mg/kg) 8 hourly for 10-14 days.<sup>21</sup>

### Eczema Herpeticum

#### Pathogenesis

This is caused by dissemination of the HSV infection in children having a pre-existing inflammatory dermatoses or immunodeficiency. It is common in patients having atopic dermatitis and less frequently other dermatoses such as ichthyosiform erythroderma or burns. Recurrences may occur, especially following recurrent herpes labialis.

#### Clinical Features

The condition is characterized by a sudden and explosive onset of vesicles, which may become pustular and hemorrhagic and spread all over the body. Cutaneous edema, fever and lymphadenopathy are frequently present and there may be progression to potentially fatal systemic infection.

#### Treatment

Acyclovir, vidarabine and interferon greatly reduce the morbidity and mortality of the disease.<sup>20</sup> Acyclovir is given intravenous, 40-80 mg/kg/day in 3-4 divided doses. Valacyclovir and famciclovir are not approved for use in children.

### ERYSIPELAS AND CELLULITIS

#### Etiology

Both these conditions are nearly always caused by *Streptococcus pyogenes*.<sup>22</sup> In erysipelas, the infection is localized to the dermis, while in cellulitis the infection involves the subcutaneous tissue as well. Trauma, insect bites or surgical wounds may initiate the infection, but the increased susceptibility to infection is usually due to malnutrition, systemic illness or pre-existing lymphedema.

#### Clinical Features

Both conditions are characterized by an acute onset of intensely red and tender swelling with an advancing edge, high fever and constitutional symptoms. Lymphangitis and lymphadenopathy may also be present. Lesions are usually located on the abdomen, face or extremities. Without prompt treatment, these lesions may end up in local suppuration, necrosis and gangrene. In infants, the mortality is often high (50%). In those with facial lesions, hospitalization is required due to increased risk of *Haemophilus influenzae* infection and septicemia.<sup>23</sup>

## Treatment

- Therapy with appropriate systemic antibiotics leads to rapid regression of the lesions.
- Topical antibiotics have no role.
- Symptomatic treatment with analgesics should be given.
- The underlying cause, if any, should be treated.

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# 39 Gynecologic Emergencies

Reva Tripathi, Pooja Pundhir

The pediatric age group presents with certain unique gynecological problems. The impact of first gynecological examination must not be underestimated. Extreme sensitivity and gentleness is imperative in handling these patients. The most common complaints with which young girls present to the emergency are excessive vaginal bleeding (or blood stained vaginal discharge) or acute abdominal pain.

## Common Gynecologic Emergencies and their Causes

1. Excessive vaginal bleeding
  - a. Foreign body in genital tract
  - b. Genital trauma
    - i. Accidents
    - ii. Sexual abuse and postcoital injuries
  - c. Puberty menorrhagia
2. Acute abdominal pain
  - a. Imperforate hymen, transverse vaginal septum
  - b. Twisted ovarian cyst
3. Teenage pregnancy and its complications
4. Unprotected intercourse: need for emergency contraception

The gynecologic emergencies can further be classified into two groups: (a) Those seen in children below 8 years, and (b) Those in children 8 years and above. In children below 8 years of age the commonest problem is likely to be due to a foreign body unless there is a history of trauma.

## FOREIGN BODY IN GENITAL TRACT

Foreign body in vagina is most frequently seen in children between 3-7 years of age. Usually no history of insertion is forthcoming and virtually any kind of object may be found in the vagina.<sup>1,2</sup> The clinical picture is frequently of a chronic nature but could become acute either in the presence of secondary infection or repeated handling that provokes bleeding. Alternatively, parents or guardians may suddenly become aware of the problem and present in the emergency department.

## Presentation

The effect of any foreign body depends on its nature. Articles made of rubber are very irritant, while those made of inert materials such as plastic or porcelain may cause little trouble. Cotton and woolen fabrics quickly lead to local infection and foul smelling discharge. In all cases, the predominant symptom is an offensive discharge, which is often blood stained.

Sharp objects may cause abrasions or ulceration and can involve neighboring structures to cause urinary or fecal fistulae. In a long standing case, infection may spread to produce salpingitis and peritonitis when it may present as an emergency.

Sometimes the foreign body may become embedded with the vaginal wall partially or completely closing over it, thus further confusing the picture.

## Treatment

The foreign body must be removed. This usually requires examination under anesthesia followed by removal. During removal it has to be ensured that the entire foreign body has been removed and no part left, otherwise problems will continue. This is especially important for foreign bodies of breakable material. Once the foreign body is completely removed, the vaginal infection clears and any minor injury to the wall heals by itself.

## DIRECT TRAUMA TO VAGINA—TEARS AND LACERATIONS

Trauma to the female genital tract is not unusual. This may be localized and minor, or accompanied by life-threatening injuries. Genital injuries may be accidental, self inflicted or as a result of sexual assault.<sup>3,4</sup>

## Accidents

Cuts and lacerations of the vulva and vagina are sustained in accidents involving fractures of the pelvis or falling or sitting on sharp objects. Adjacent structures

such as the urethra, rectum, urinary bladder and pouch of Douglas may also be involved as the distance between the perineal skin and peritoneal cavity is short in small children.

*Treatment* involves examination under anesthesia, cleansing the damaged tissues and assessing the extent of injury. Prophylactic antibiotics are usually required. If the vagina is bleeding severely, packing the area tightly with sterile gauze or clean cloth can be undertaken as a first aid measure till the patient is able to be hospitalized and shifted to the operation theater so that final evaluation and treatment can be undertaken. As with all injuries, an early complete primary repair will give the best results.

### Coital Injuries

Forceful or violent coitus may be followed by catastrophic events such as severe hemorrhage and consequently shock, especially if tears extend to the vestibule or clitoris on account of their rich vascularity. Rape is defined as sexual assault accompanied by penile penetration either without consent or by threat of force or compulsion. The age at which a person can grant consent for sexual intercourse varies with state law, which defines *statutory rape*. India's age of consent for heterosexual sex is 16, except in the state of Manipur, where it is 14. If the partners are married to each other they may legally engage in sexual activity at a lower age (13 in Manipur and 15 elsewhere). Thus, statutory rape has occurred even in "consensual intercourse" when one party is not of "legal age" according to the state law. Coital injuries may be seen at any age and generally present as an emergency.

### Sexual Abuse and Rape

In 2007 the Ministry of Women and Child Development found that about 20% of adolescent girls reported having faced sexual abuse. Of these, 21% faced severe forms of sexual abuse.<sup>5</sup> Depending on the age and size

of the child, and the degree of force used, child sexual abuse may cause internal lacerations and bleeding. In severe cases, damage to internal organs may occur, which, in some cases, may cause death. Causes of death include trauma to the genitalia or rectum and sexual mutilation.

### History

A standardized approach to the initial management of the young female who has been raped is warranted. Pertinent historical information should include general demographic information; the name of the alleged perpetrator and relationship to the victim; the circumstances of the assault, such as location, particular sexual acts, physical violence, ejaculation, and physical and behavioural symptoms. Any relevant medical history, such as menarche, last menstrual period, previous consensual sexual activity, possibility of preexisting pregnancy, previous history of sexually transmitted diseases (STDs); and the use of alcohol or drugs by the patient or the assailant before the assault. Other components of the medical history, such as history of chronic illnesses, immunization history, current medications, and allergies, should not be overlooked.

### *Physical Examination and Collection of Forensic Evidence (Table 39.1)*

The seriously injured child should be referred to the closest tertiary care center capable of dealing with this situation and providing holistic care. This includes resuscitation, medical, surgical, psychological, social and rehabilitation components of care. Any concerns with the patient's airway, breathing or circulation should be immediately addressed. Five percent or more of rape victims have major nongenital injuries. Signs of shock, such as tachycardia, pallor, poor peripheral perfusion and hypotension, should be sought. Life threatening bleeding can occur in the abdominal cavity.

**Table 39.1: Physician's role in the care of the adolescent rape victim<sup>6</sup>**

<i>Medical</i>	<i>Legal</i>
Obtain and document medical history	Record events accurately
Recognize and stabilize any emergent conditions	Document injuries
Evaluate and treat physical injuries	Collect forensic evidence
Obtain cultures	Fulfil reporting requirements according to state law
Offer STD prophylaxis	Notify proper authorities
Offer postcoital contraception	
Provide counseling	
Arrange follow-up	

Any source of external bleeding should be controlled by the application of a gauze dressing and local pressure. Plugging the vagina, rectum or any wound is not advisable as evidence can be altered, and it creates the opportunity for lost swabs and foreign bodies. The following should be kept in mind:<sup>7</sup>

- A forensic evaluation should be performed within 72 hours of the assault.
- Examination of the genitourinary tract should first document the method of visualization (e.g. direct, hand-held magnifying lens, speculum, or colposcope) and Tanner staging. It is important to use only saline for lubrication for insertion of the speculum because other lubricants may alter evidence.
- Identify edema, ecchymoses, abrasions, bite marks, and lacerations on the face, neck, torso, buttocks, and extremities.
- Vaginal aspirates should be evaluated for spermatozoa, seminal contents and ABO antigens by the forensic laboratory.
- The central portion of all bite marks should be swabbed with swabs moistened with sterile saline. An outline drawing of the injuries on the body is helpful for documentation.

Definitive genital examination should be deferred until the patient is stable. Infants are best examined in the knee chest supine position and older children in the lateral knee-chest position. If there are extensive perineal tears, ongoing unexplained bleeding, a suspicion of a foreign body or abnormal abdominal signs, examination under general anaesthesia may be necessary and treatment as described for perineal tears in the above section. It is widely recommended that emergency contraception and antibiotics directed towards *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are administered after a sexual assault. Prophylaxis against HIV and Hepatitis B virus infection is not recommended but screening for HIV positivity is recommended for all rape victims.<sup>8</sup>

### Postcoital Injuries

Severe coital injuries are more likely to occur following rape, use of objects as sexual tools, violent or hurried sex and intercourse under the influence of drugs and alcohol. These may also occur following consensual sexual intercourse in older girls. Size disparity between the genital organs, young age, certain positions during intercourse, and congenital anomalies of the vagina are also risk factors. In teenage girls an accurate diagnosis is usually more difficult to achieve as there may be failure to volunteer a history of sexual intercourse and examination can be more difficult because of resistance.

### Grading of Perineal Injuries

First degree	Skin lacerations involving the introitus, anus or perineal skin
Second degree	Lacerations extending onto perirectal or vaginal tissues, sparing anal sphincters
Third degree	Compound lacerations involving anal and/or vaginal walls and sphincter

The most common types of genital injury are abrasions in the posterior fourchette, labia minora, hymen, and the fossa navicularis. In older children, in whom there is less disproportion between the size of the assailant's penis and the child's genital structures, minor injuries usually result. It is important that in females who present with an acute abdomen, with or without vaginal bleeding following coitus, the differential diagnosis should include severe upper vaginal injury. There may be complete disruption of the posterior fourchette, perineal body and anal sphincters. Once these muscular defences are breached there is a serious risk of vaginal vault, proximal rectal and intra-abdominal injuries. Bleeding from posterior vaginal fornix rupture as a result of coital injury may be revealed or concealed. Although vaginal lacerations following sexual intercourse are common, posterior vaginal fornix rupture communicating with the peritoneal cavity, causing massive hemoperitoneum, pneumoperitoneum, or hemopneumoperitoneum can rarely occur. Bowel or omentum may prolapse through a posterior vaginal wall tear. Rectal injury, resulting in rectovaginal fistula may result. A rectal examination should routinely be performed in the presence of a posterior vaginal wall tear following coitus.

A proper gynecological history and examination by a senior gynecologist should be performed. Examination under anesthesia has to be considered. Accessibility to the injured area is often a frequent issue of concern and availability of pediatric gynecologic instruments and good light are essential prerequisites. Most first-degree tears will heal satisfactorily without the need for suture. In selected circumstances, definitive primary suture will provide quicker and superior healing and is probably warranted. Primary repair of second and third degree tears under anesthesia must be performed. Colostomy may be indicated in complete perineal disruption with a common rectovaginal channel.

### PUBERTY MENORRHAGIA

This is the most common reason a teenager presents to the gynecology clinic. It is arbitrarily defined as excessive bleeding occurring between menarche and the

age of 20 years.<sup>9</sup> The first one or two periods after menarche are commonly profuse, prolonged and irregular but such disturbance generally cures itself quickly and medical advice is frequently not sought.

Sometimes, however, the bleeding may be so heavy as to produce anemia and even threaten life. Pubertal menorrhagia is a form of dysfunctional uterine bleeding and is usually anovular in type.<sup>10</sup> Although, the most frequent cause of bleeding is functional, abnormalities of coagulopathy or underlying hepatic or renal disease may be present in up to 20 percent of patients.

A detailed history should be taken giving attention to amount, duration and frequency of hemorrhage and its relationship to puberty. The background, environment and the presence of emotional upheavals deserve to be studied. A history of bleeding tendency, epistaxis, bruising and similar symptoms provide clues to the presence of a bleeding disorder. This should be followed by a detailed examination of all systems to assess the cause of bleeding. There is no place of bimanual vaginal examination in these girls. Though it is unlikely that there will be any pelvic pathology causing these problems, it is advisable to arrange for a trans-abdominal ultrasound for these patients as it is a non invasive procedure and can provide valuable information.

*Investigations* include a complete hemogram with platelet count and assessment of bleeding and coagulation times. Pregnancy related bleeding must be ruled out through history and sensitive pregnancy test. Kidney and liver function tests must be done. An ultrasound examination is required to rule out any organic lesions. Tuberculous endometritis must be excluded especially in developing countries such as India. Thyroid function tests should be assessed if there are features in history or examination suggestive of thyroid dysfunction.

### *Management*

General measures include management of severe anemia. Very often, these adolescent girls are already cases of borderline nutritional insufficiency, which becomes manifest after these episodes of blood loss and it may not be uncommon to see cases of puberty menorrhagia presenting with hemoglobin levels below 5 g/dL. Such cases are likely to require blood transfusion followed by further correction of anemia by iron supplementation and improved dietary intake.

Medical management can treat almost all patients. Girls with regular heavy periods should be treated with tranexamic acid 1 g 6 hourly and mefenamic acid

500 mg 8 hourly. These drugs reduce blood loss by up to 50%. In girls with irregular periods, treatment should be with cyclical progestones—norethisterone, medroxyprogesterone acetate or combined oral contraceptive pills. The hormonal medication should be continued for 4–6 months with information that the medication is not curing a disease but only controlling symptoms till ovulatory cycles occur.

### **IMPERFORATE HYMEN, TRANSVERSE VAGINAL SEPTUM**

Congenital abnormalities in the development of the genital tract are generally diagnosed at puberty.<sup>11</sup> Though many varieties of abnormalities may be seen, the presence of imperforate hymen and transverse vaginal septum occurs more frequently.

Imperforate hymen occurs due to failure of disintegration of the central cells of the mullerian eminence which projects into the urogenital sinus whereas a transverse vaginal septum results due to faulty fusion of the urogenital sinus and mullerian ducts. Patients usually present in the emergency room with acute abdominal pain, urinary retention or dysuria in the presence of amenorrhea and normally developed secondary sexual characteristics. On further investigation, a history of not having achieved menarche and cyclical abdominal pain is elicited. Abdominal examination reveals a cystic mass in the suprapubic region which is generally due to a full bladder or may sometimes be due to a large hematocolpos. Local examination reveals a tense translucent thin bulging membrane of bluish discoloration between labia majora. On rectal examination, the distended vagina with the collected menstrual blood can be palpated and this may be continuous with the abdominal mass depending on the amount of collected blood.

Emergency surgical hymenectomy is the treatment of choice. Excision of the hymen is done followed by hemostatic sutures at the cut edges. No drain is required as this introduces infection in a sterile compartment and the hematocolpos drains spontaneously. It is important to keep the diagnosis of cryptomenorrhea in the differential diagnosis of adolescents presenting with pain abdomen. There are instances when such patients have been misdiagnosed and laparotomy performed with a suspicion of ovarian tumor, whereas a minor corrective surgery was all that was required.

Transverse vaginal septum is a more difficult situation as the problem is above the level of hymen and hence not amenable to clinical examination. It is advisable that these patients are electively treated by a

gynecologist after detailed investigations as in a few cases of a high transverse vaginal septum, differentiation between the mass of accumulated blood, bladder and rectum may be difficult through the vaginal route and an exploratory laparotomy may be required.

### TWISTED OVARIAN CYST

Adnexal torsion is more frequent in young females with adnexal pathology such as an ovarian cyst.<sup>12</sup> Patients present with features of acute abdomen, with a tender mass arising out of the pelvis. In some cases, the mass may not be clearly identifiable due to abdominal guarding and rigidity. Differential diagnosis of acute abdomen due to other causes such as acute appendicitis would also need to be considered. Pelvic ultrasonography with color Doppler examination is usually helpful in establishing the diagnosis.

#### Management

Surgery is the primary management. Conservative surgery by laparoscopy is gaining increasing preference as the surgical procedure of choice. Conventional surgery involves laparotomy followed by correction of torsion and cystectomy, if the torsion has not affected the vascularity of the rest of the ovary. It is preferable to do only cystectomy and leave functioning ovarian tissue so as not to compromise subsequent hormonal production. If features of ischemia and necrosis of ovarian tissue are evident, then oophorectomy will be required. These tumors are almost invariably benign but nevertheless need histopathological confirmation. Malignant ovarian tumors are well described during adolescence, but present as acute abdomen only when complicated by rupture and intraperitoneal hemorrhage.

### TEENAGE PREGNANCY COMPLICATIONS

Teenage pregnancy rate in India varies from 8-14 percent.<sup>13</sup> Various social factors such as early marriage, ignorance regarding contraception, failure to provide sex education, failure to provide supportive services to adolescents and taboo over discussing sexuality leads to the problem of teenage pregnancy.

Any pregnancy complication may be seen in these young girls and may include abortions, ectopic pregnancy, nutritional deficiencies, pregnancy induced hypertension, abruptio placenta, preterm labor, sexually transmitted diseases, prolonged labor, cephalopelvic disproportion and a higher incidence of operative delivery. There is an increased incidence of sepsis, emotional and psychological sequelae in the postpartum period. Management aims at imparting sex education,

counseling pertaining to prevention of HIV infection and other STDs, and contraceptive knowledge to adolescents, free and easy access to emergency contraception, meeting the nutritional needs of teenagers, and treating these pregnancies as high-risk.

Acute abdominal pain can be due to ruptured ectopic pregnancy, a diagnosis which is difficult to arrive at in young unmarried girls especially when one fails to elicit a history of coitus which is usually not forthcoming. Ectopic pregnancy may present as any other surgical emergency and a high degree of suspicion should be kept in mind otherwise the diagnosis may be missed.

### Emergency Contraception

As the numbers of teenage pregnancies and termination rates are increasing, combating the high rates of adolescent pregnancy has become a challenge for clinicians. Emergency contraception (EC) has the potential to prevent 75 to 85% of unintended pregnancies and to eliminate approximately 50,000 elective abortions per year. In an adolescent patient population where contraception compliance is a serious issue, EC can be supported as an essential component to pregnancy prevention.

EC is effective in preventing an unwanted pregnancy when administered in a proper manner at the proper time, i.e. within 72 hours of unprotected coitus. The various methods of EC available include:

- a. *Levonorgestrel (LNG) only pill*:<sup>14</sup> Recently pills containing 750 µg of LNG have been introduced in the Indian market. The dosage of this regime is 2 tablets each of 750 µg of LNG at 12 hours interval. Apart from being more effective, this regimen is associated with significantly fewer side effects, particularly nausea and vomiting. About 85% of pregnancies are prevented.
- b. *Yuzpe regime*:<sup>15</sup> consists of 100 µg ethinyl estradiol and 500 µg levonorgestrel in 2 doses 12 hours apart. This is a well-established regime for emergency contraception and is to be used within 24 hours of unprotected coitus for maximum efficacy. It prevents 75% of pregnancies.
- c. *Intrauterine contraceptive device (IUCD)*: Copper containing IUCD inserted up to 5 days of unprotected intercourse is still considered to be the most effective emergency contraception. It is however, not the preferred method for adolescents because of its potential to cause pelvic inflammatory disease and its attendant complications though it is almost 100% successful.

While advising emergency contraception, it is important to avail the opportunity to counsel these

youngsters. They should be made aware of the fact that emergency contraception should be used only as an emergency measure and it should not replace regular contraceptive use. In case the girl is likely to be exposed to subsequent risk of pregnancy it is preferable for her to use combined oral contraceptive pills or other methods as may be considered appropriate.

### Acute Pelvic Inflammatory Disease (PID)

Sexually active adolescents are at risk for acute PID, which may manifest as severe acute abdominal pain. A high index of suspicion coupled with appropriate history is important. Abdominal examination could reveal guarding and rigidity. Local examination revealing presence of purulent cervicovaginal discharge almost clinches the diagnosis. Vaginal swab, which isolates *N. gonorrhoeae*, will be confirmatory. Treatment includes administration of injectable antibiotics and supportive measures.

The occurrence of gynecological problems leading to emergency room visit for pediatric and adolescent girls is not very uncommon. These situations need sensitive handling by an expert. Having a person sensitized to these problems would go a long way in appropriately managing these cases.

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A *child psychiatric emergency* is any unusual behavior, mood, thought, or physiological state, which if not rapidly attended to may result in harm to the patient, others or both. The philosophy of management of these emergencies in pediatric emergency department (PED) has shifted from the traditional *triage model* to the *treatment models*.<sup>1-5</sup>

This chapter discusses the common psychiatric emergencies that presents at PED.

### BASIC PRINCIPLES AND DECISION MAKING IN EMERGENCY PSYCHIATRY

Some of the principles in child and adolescent psychiatric emergencies are distinct from that of pediatric emergencies. Firstly, a child is brought to PED when an adult figure (e.g. parent, school teacher) interprets the child's thought and behavior as inappropriate or unmanageable in the current environment, when the child infact has a developmentally appropriate behavior (e.g. hallucinations in phobias among prepubertal children). Secondly, multiple sources of collateral information are needed to assess children in different areas of their lives (e.g. home, school, play) before the diagnosis is confirmed and treatment started since the request for an emergency consult might be to settle scores among adults (e.g. alleged child abuse in marital disharmony). It is good practice to reduce the stimulation of a busy emergency department that can escalate the patient's symptoms. It is also necessary to, determine the risk of danger to the patient, clinician and others as about 50 percent of mental health care providers are assaulted at work. The patients characteristics predictive of assault, prevention of assault, and strategies for handling assaultive patients have been elaborated elsewhere.<sup>6</sup> Following medical and mental status examination,<sup>7</sup> working diagnosis is established and appropriate therapy initiated.

If the child presents at the PED (e.g. abnormal vital signs in substance abuse or delirium), medical support is given first. If residual abnormal behaviors are noted appropriate psychiatric care is given. In case of

threatening behaviors (e.g. suicidal, homicidal), the patient should be isolated; physical restraints are used if necessary. In cases of acute non-threatening situations (e.g. panic, grief) the focus is on amelioration of the distressing but not life-threatening symptoms with medication and psychological techniques. The patient should not leave the PED unnoticed before the medical as well as mental status examination is complete.

### EPIDEMIOLOGY

About 75-80 percent of the population attending the PED with a psychiatric emergency are 13 years or older. Despite the increased prevalence of psychiatric syndromes among boys, more girls seek emergency treatment. Also, children from upper socioeconomic suburbs make use of PED more often.<sup>3</sup> Epidemiological data on childhood and adolescent psychiatric illnesses are not readily available.<sup>8</sup>

### CLASSIFICATION OF PSYCHIATRIC EMERGENCIES IN INFANTS AND TODDLERS, CHILDREN AND ADOLESCENTS

Child and adolescent psychiatric emergencies arise in the context of psychiatric illness, severe physical or emotional trauma, substance abuse, as the consequence of medical illness, psychiatric illness presenting as medical illness or as a result of an adverse drug reaction. There are also differences in the profile of psychiatric emergencies in infants, prepubertal children and adolescents. Based on age (infant-prepubertal-adolescent), etiology (primary-secondary to medical problems-stress related) and lethality (emergency – threatening—acute) one can classify childhood and adolescent psychiatric emergencies (Table 40.1).

#### Primary Psychiatric Emergencies

##### *Psychiatric Emergencies in Infants and Toddlers*

The psychiatric emergencies in infants and toddlers are mostly because of problems in physiological processes

**Table 40.1: Clinical classification of psychiatric emergencies**

- I. *Primary psychiatric emergencies*
  - A. Emergency
    - Infants and toddlers (e.g. self-injurious behavior)
    - Prepubertal children (e.g. child abuse)
    - Adolescent (e.g. suicidal, homicidal)
  - B. Threatening
    - Infants and toddlers (e.g. defiant behavior)
    - Prepubertal children (e.g. negativistic)
    - Adolescent (e.g. destructive)
  - C. Acute
    - Infants and toddlers (e.g. feeding disorders)
    - Prepubertal children (e.g. sleep disorders)
    - Adolescent (e.g. panic disorder)
- II. Psychiatric disorders that present with somatic symptoms
- III. Medical illness that presents with psychiatric symptoms
- IV. Adverse action or interaction of medication

like sleep wake rhythm, deviant communicative processes like repetition of words, self-stimulatory behaviors like masturbation and temperamental predisposition.

*Sleep disorders:* Sleep disorders cause substantial problems in infants and toddlers.<sup>9</sup> The common problems encountered are inability to initiate and maintain sleep, co-sleeping, conditioned night feeding, colic, food allergy, insomnia, night waking and separation anxiety.

*Inability to initiate sleep:* It is the most common problem in the first 3 years of life, resulting in disrupted sleep for family members, negative parent-toddler interactions, and child abuse. This disorder could be because of the lack of training, failure to teach self-comfort, lack of associated materials or activities (conditioned to fall asleep only while being nursed, rocked or held), and inadequately enforced bedtime schedule. The management would be accordingly exposure to bright light in the mornings, teaching self-comfort, where the child learns to fall asleep with minimal parental interaction and parent's ability to enforce sleep schedule respectively.

*Inability to maintain sleep:* The goal here is to convert a bad sleeper who needs parental intervention (signal for nursing, rocking) to a good sleeper who puts himself back to sleep (hugging a stuffed animal, twirling a strand of hair or thumb sucking) and thereby avoiding parent-child struggle.

*Nocturnal eating syndrome (or drinking):* Syndrome affecting infants and children presents as an inability to get back to sleep after awakening unless the individual has something to eat or drink. The problem is mainly associated with breast nursing, bottle-feeding, or both and the infant drinks about 4 to 8 ounces or more at each awakening. The sleep problem is managed by unmodified systematic ignoring, minimal check with systematic ignoring, parental presence with systematic ignoring, gradual systematic ignoring and medication.<sup>10</sup> Although, medication could be used to break the cycle of sleep related problem it should be complimented by behavioral techniques.

*Feeding disorders:* *Feed refusal* is characterized by near-total rejection of edible substances and *food selectivity* is displayed by preference for certain types of food (based on the texture, taste, composition, etc.). Limited food intake presents as willingness to eat a variety of food but in small amounts. Self-feeding deficits exhibit as difficulty in locating, transporting and inserting food into the mouth. Improper pacing involves excessively slow or rapid feeding without chewing. Mealtime problem behaviors includes crying, screaming, throwing utensils, spilling food and tipping furniture by the child during mealtime. The management of these problems is more behavioral than pharmacological.<sup>11</sup>

*Self-injurious behavior:* The prevalence of self-injurious behavior is about 17.4 percent in individuals with developmental disabilities and 1.7 percent have life-threatening self-mutilatory behavior.<sup>12</sup> The cause of self-injurious behavior is biopsychosocial in nature.<sup>13</sup> Biologic conditions predispose the child to self-injurious behavior and psychological factors precipitate and well as perpetuate the self-injurious behavior through environmental responses.

The emergent management includes, sedation or physical restraint for immediate control, protective aids (e.g. soft helmet for head banging), controlling of psychological factors like positive or negative reinforcement, and appropriate psychotropic medication (Table 40.2).<sup>13</sup>

*Other disorders:* Hallucinations are uncommonly encountered in toddlers. Central nervous system tumors, encephalitis, temporal lobe epilepsy, frontal lobe injury, hypoglycemia, drug intoxication, and ingestion of high doses of sympathomimetics.<sup>14</sup> An other problem in infants and toddlers with a psychological component is incessant crying and colic.<sup>15</sup>

**Table 40.2: Biological classification of self-injurious behavior (SIB) and treatment**

<i>Biological subtypes of SIB</i>	<i>Neurotransmitter implicated and medication</i>
<p>1. <i>Extreme self-inflicted tissue damage</i> Past or present evidence of SIB (cauliflower ear, laceration with area &gt; 3 × 3 cm, auto-amputation) and 1 or more of the following:</p> <ol style="list-style-type: none"> <li>Lack of distress (<i>i.e.</i>, crying) when inflicting injury.</li> <li>Predilection for the head as injury site</li> </ol>	<p><i>Opioid excess</i> Naltrexone initially at 0.5 mg/kg daily, increased to 1 mg/kg/day after 10 days, increased to maximum of 2 mg/kg/day, or until a clinical endpoint is reached</p>
<p>2. <i>Stereotypic SIB</i> The topography of SIB is similar, and 2 or more of the following:</p> <ol style="list-style-type: none"> <li>Duration of 1-10 sec between movement</li> <li>Tissue damage after repeated responses</li> <li>Co-occurring non-injurious stereotypes</li> <li>Diagnosis of pervasive development disorder (Autism)</li> </ol>	<p><i>Dopamine excess</i> Haloperidol started at 0.25 mg twice daily or 0.025 mg/kg/day. This dosage is increased by 0.25 to 0.5 mg/day every 4 days, as SIB rates indicate, to a maximum of 4 mg/day or 0.1 mg/kg/day</p>
<p>3. <i>High rate SIB and agitation if interrupted:</i> Agitation or distress occurs when SIB is interrupted (e.g. crying, hyperventilation, aggression, pacing) and 1 or more of the following</p> <ol style="list-style-type: none"> <li>Mean SIB rate &gt; 100/hour</li> <li>SIB stops during an activity, resumes within 30 seconds of its completion</li> </ol>	<p><i>Serotonergic dysfunction</i> Fluoxetine started at 10 mg/day in children less than 8 years, and 20 mg daily in those older</p>
<p>4. <i>SIB co-occurring with agitation</i> SIB co-occurs with agitation or aggression (e.g. pacing, screaming, tachycardia) and 1 or more of the following:</p> <ol style="list-style-type: none"> <li>SIB rates vary by &gt; 50% per session</li> <li>Topographies consist of self-hitting</li> <li>Evidence of sleep or appetite disturbance</li> </ol>	<p><i>Nor-epinephrine dysfunction</i> Propranolol started at 10 mg thrice daily for children under the age of 8 years. For older children, the starting dose 20 mg thrice daily increased by the same amount every 3 days to a maximum daily dose of 250 mg Lithium carbonate may be used in those intolerant to propranolol</p>
<p>5. <i>Multiple features</i> A child meets inclusion criteria for two or more clinical subtypes</p>	

### *Psychiatric Emergencies in Prepubertal Children*

Prepubertal children have few life-threatening psychiatric emergencies. Invariably when it happens, the acute event has been preceded by a period of marginal adjustment on part of the child, and the school or clinic may not have answers to the impending crisis. Thus a prepubertal child in crisis typically reflects a family in crisis. Crises often presents with a brief window of opportunity during which rigid ways of relating within a family becomes more flexible and this should be therapeutically used.<sup>3</sup>

*Child abuse and neglect:* Physical and sexual abuse can present with acute or delayed emergency symptoms, in both boys and girls. *Physical abuse* is suspected when a child has multiple injuries at various stages of healing, burns, bruises, ruptured viscera, spiral fractures, head

and eye injury. *Sexual abuse* is under-reported; when incestual in nature is usually kept secret and abuse by a stranger precipitates an evaluation and management. *Neglect* includes ignoring the medical care, lack of supervision and compromised safety standards, physical neglect (lack of food and shelter) and emotional and educational neglect. Risk factors that predict recurrent abuse include younger age of victim, disability in the child, caretaker characteristics such as emotional impairment, substance abuse, lack of social support, presence of domestic violence, and history of childhood abuse.<sup>16</sup>

The diagnostic presentation of abuse can take the form of post-traumatic stress disorder, conduct disorder, depressive disorder, dissociative disorder, reactive attachment disorder, substance abuse, aggressiveness, sexually inappropriate and promiscuous

behavior, running away, sleep disturbance, academic failure, gender identity disorder, self-destructive behavior and difficulty trusting others.

The emergent management includes safety of the child prevention of further traumatization as a result of evaluation, collecting legal evidence and informing appropriate external agencies.<sup>17</sup> An attempt is made to identify if the child would require pediatric or psychiatric hospitalization, placement in respite care, foster care, or could return home safely.<sup>17</sup>

*Fire setting child:* Fire setters, because of the potential for injury and destruction reach emergency facilities often, though these adolescents rarely present with symptoms of acute psychiatric disorder. Differentiate *fire interest* (3-5 years) and *fire play* (5-9 years), which are normal developmental stages from fire setting. The former groups set fire accidentally and call for adult help, whereas fire setting is deliberate, planned, to specific targets and involvement is denied. Prevention of further incidents of fire setting while treating any underlying psychopathology (e.g. conduct disorder) is critical as part of emergency intervention.

Hospitalization is indicated if there is a continued direct threat that the child will set another fire. Fire setting being a complex problem, the therapy should emphasize differential reinforcement for alternate behavior (where the child is rewarded when he does not get involved in fire setting and is involved in an alternative socially acceptable activity), in addition to an overall risk assessment.<sup>3</sup>

*Runaway child:* Runaway children are usually brought by an agency or distraught parents to the pediatric emergency. Typically these children are suspicious of adults and engaging them in the interview is the key to a useful assessment and management. These individuals are frequently victims of abuse as well as neglect and frequently have significant psychiatric illness intelligence deficits. The immediate management is to provide solution to their concerns and improve the communication between them and parents. Management of abuse or underlying psychopathology should be initiated.<sup>3,8</sup>

*Sleep disorders:* About 20-30 percent of prepubertal children have complaints related to sleep that are regarded as significant problems by their families.<sup>18</sup> *Parasomnias* are most common group of sleep disorders in children between 3-10 years of age. The parasomnias are behavioral or physiological phenomena that are potentiated by sleep and occur during that period. Seizure disorder has to be ruled out before a definitive

diagnosis of parasomnia is made. *Nightmares*, experienced by 10-50 percent of children, are experienced as anxiety provoking dreams that occur during REM sleep, become increasingly frightening toward the end, culminating in an awakening and on awakening the child recollects the content. The treatment includes low dose benzodiazepines (diazepam 2 mg), tricyclic antidepressants (imipramine 25 mg) or haloperidol (0.5 mg) given at bedtime.

*Night terrors:* These occur in 3 percent of children and are characterized by sudden awakening from non-REM sleep with a piercing scream or cry, accompanied by autonomic arousal and behavioral manifestations of intense fear. After awakening, children have no memory of the content and are usually unresponsive to stimuli, confused or disoriented.

*Sleepwalking disorder:* It is another non-REM phenomenon. In its most extreme form, it consists of ambulating during sleep (somnambulism) and as it arises during non-REM sleep, the patient is difficult to awaken, confused, and amnesic.

Other sleep disorders like sleep talk, bruxism, restless leg syndrome, REM sleep behavioral disorders might also warrant treatment. Chloral hydrate, barbiturates, zopiclone tricyclic antidepressants (imipramine 25 mg at bedtime) and benzodiazepines have been effectively used.<sup>19</sup>

### *Psychiatric Emergencies in Adolescents*

Adolescents often seek emergency help on their own especially when the parents are non-supportive, unapproachable, and abusive or absent.

*Agitated adolescents:* Agitation is a state of increased mental excitement and motor activity. The reason for agitation may or may not be obvious, depending on the level of agitation. A safe environment for adolescent should be provided. When the cause of agitation can be rapidly addressed (e.g. relieving pain or correcting metabolic disturbances), psychotropic should be deferred. Agitation is managed with verbal redirection towards harmless activities, provision of less stimulating environment and initiation of physical restraints. Pharmacological interventions should be considered when agitation impairs a person's capacity to tolerate diagnostic or therapeutic procedures. Rapidly sedating medications like antihistamines, benzodiazepines or low potency antipsychotics are most commonly used. When agitation is the result of simple anxiety or sleep deprivation, lorazepam may be given at a dose of 1 to

2 mg orally or IM. Where delirium, delusions, or hallucinations are present, risperidone (1 to 2 mg PO), or low-dose haloperidol (2.5 to 5 mg IM or PO) is preferred.<sup>20</sup>

*Aggressive and violent adolescents:* This is seen in nearly 25 percent of adolescent emergency psychiatric evaluation.<sup>3</sup> The aggressive behavior may not be observable till it happens and hence when an adolescent with history of violence visits the emergency it should be ensured that he is free of weapons and the interviewer has access to an exit. The room should be free of objects that could be used as weapons and a family or friend should be available to intervene, if required. Once organic causes (e.g. delirium), medication side effect (e.g. akathisia) or substance abuse are excluded, it is evaluated if the aggression is in response to psychotic symptoms (auditory hallucination, paranoia), conduct disorder, mood disorder or anxiety disorder; whether it is impulsive or precipitated; response to limit setting; lethality and if the patient is already on antiaggressive medication. Use of verbal and behavioral therapy, seclusion and restraints has been summarized elsewhere.<sup>21</sup> Non-specific sedation is frequently used in containing violent patients. Rapid tranquilization is required in acutely violent adolescents. The choice of medication is between haloperidol (5-10 mg), thiothixene, loxapine or a benzodiazepine, e.g. lorazepam (1 to 2 mg) and clonazepam (1 to 2 mg) administered intramuscularly.<sup>22</sup> Lorazepam has the advantage of short half-life and also could be used if there is suspected alcohol or sedative withdrawal related violent behavior.

*Substance abuse:* Adolescents of increasingly younger age are using alcohol as well as illegal substances. When an adolescent presents in the emergency with a history of substance abuse, assess first if it is acute intoxication or withdrawal, maintaining patient and staff safety as well as medical stability.

Treatment for acute intoxication involves the management of respiratory and cardiac depression or neurological abnormalities, control of acute agitation and antagonists, wherever indicated. The treatment for withdrawal includes detoxification in the form of controlling the withdrawal (decreasing quantity of the same substance, medication with cross-tolerance), improving hydration, controlling intercurrent infections and adding vitamin supplements. An emergency psychiatric assessment to identify any mental illness personality disorders should be carried out. Admission should be recommended if there is history of

polysubstance abuse, repeated attempts to stop have failed or there are life-threatening withdrawal episodes. After deciding the setting for the long-term care, the process of de-addiction starts involving a multidisciplinary team.<sup>23</sup>

*Suicidal behavior:* Suicidal behavior includes suicidal ideation, plans, attempts, and completed suicides. About 20 percent of school children seriously consider attempting suicide, 15 percent had made a plan to attempt suicide, 7.7 percent make a suicidal attempt, and 0.01 percent complete their suicide. Completed suicide is the third leading cause of death among children and adolescents. Identifying and managing this group of patients by pediatricians becomes important as an increasing numbers of children and adolescents now present to hospital with self-destructive behavior.<sup>4</sup>

The clinical prediction of suicide is nearly impossible.<sup>24</sup> Assessment of risk factors should include intentionality, lethality and state of mind. Intentionality includes expression of intent, duration of desire, duration of plan, intensity of thoughts, specific plan, availability of plan, preparation for death, past attempts and secrecy of the plan. Lethality of the method as well as the state of mind should be probed. It is important to assess for a paradoxical calmness as decision to die is made and patient is at peace.

Acute management in the emergency includes non-specific and specific efforts to tip the balance away from suicide as an option and establishing an alliance with the adolescent as this improves the likelihood of continuing the treatment. The reasons for suicide (50% escape from stress, 20% manipulation of others, 30% combination of escape and manipulation) are explored. The disadvantages of dying, and advantages of living are emphasized.

Suicide attempters who express a persistent wish to die or who have a clearly abnormal mental state should be hospitalized.

Psychotherapy and pharmacotherapy should be tailored to the patient's particular need. Tricyclic antidepressants should not be prescribed for the suicidal child or adolescent as a first-line of treatment. They are potentially lethal, because of the small difference between therapeutic and toxic levels of the drug, and have not been proven effective in children or adolescents. Caution must be taken to prescribe a very limited supply of tricyclic antidepressants medication if indicated. Selective serotonin re-uptake inhibitors will be the medication of choice and could

be started as tab. fluoxetine 10 mg after breakfast and increased to 20 mg after 2 weeks if the therapeutic effect is not significant. Other medications used to control anxiety associated with suicidal ideations, such as the benzodiazepines, may increase disinhibition or impulsivity and should be prescribed with caution or monitored by parents.<sup>25</sup>

*Psychotic disorders:* A dramatic increase in the incidence of psychotic syndromes occur in the adolescents and sometimes presents to the emergency.<sup>3</sup> Hallucinations are present in about 80 percent of cases, predominantly auditory, and delusions are present in about 50 percent of the adolescents. Medications that might be used include atypical antipsychotic medications including chlorpromazine (100 to 800 mg a day, orally) and haloperidol (2.5 to 10 mg a day, orally). Other medications like risperidone (1 to 3 mg a day, orally) and olanzapine (2.5 to 10 mg a day, orally) are popular because of their relatively lesser side effects. For acute psychotic disturbance rapid tranquilization should be resorted.<sup>26</sup>

*Mood disorders:* Mood syndromes present in the emergency because of potentially lethal consequences like self-neglect, self-destructive behavior and concern for public safety. The mood disorder may be primary, due to a stressful event, caused by physical illness, medication use or substance abuse, or coexist with other psychiatric disorders. Patients with a primary depressive disorder are treated with appropriate drugs. A selective serotonin reuptake inhibitor (e.g. fluoxetine 10 mg is given orally with breakfast, to a maximum of 60 mg). Psychological management starts with the use of supportive interviewing techniques and later could be tailored to the individual's need.

*Anxiety disorders:* Panic disorder and post-traumatic stress disorder (PTSD) may present in the emergency. Often the initial presentation of panic disorders may be repeated visits for shortness of breath and palpitations. After a medical or substance related etiology is ruled out, appropriate counseling is done. A benzodiazepine (e.g. lorazepam, 1-2 mg oral or IM) may be used if anxiety persists.

PTSD might present with explosive outbursts, poor impulse control, or insomnia requiring treatment with a benzodiazepine (lorazepam 1-2 mg single dose). Antidepressants are used for long-term treatment. Anxiety control with breathing techniques, muscle relaxation, thought stopping, guided self-dialogue, and stress inoculation training may be advocated.<sup>27</sup> Specific and social phobia can be treated with low doses of

benzodiazepine or  $\beta$ -blocker when contact with a phobic situation is unavoidable. More specific cognitive-behavioral techniques could be used for all the anxiety disorders but are generally reserved for definitive treatment. Grief and disaster related stress needs grief work and crises management, respectively.

Refusal to attend school because of separation anxiety may occur, particularly when a child is forced to go to school. The goal here is the rapid return of the child to the school setting.

*Anorexia nervosa:* This disorder, with an incidence of 14.6 percent in girls and 1.8 percent in boys, confers a significant risk for morbidity and mortality (20%). When an adolescent presents to the emergency with anorexia nervosa, significant medical complications are often present. Complications include dehydration, electrolyte imbalance, impaired cardiovascular functioning, neuroendocrine abnormalities and oral esophageal and gastric damage because of vomiting. Hospitalization is required if there is co-morbid depression, suicidality, medical complications and weight loss of 20 percent or more of ideal body mass. Initial goals are to restore body weight and refeeding. Medications that have been most frequently used include antidepressants and low-dose antipsychotics. Bulimia nervosa, psychogenic vomiting and other eating disorders have been presented in detail elsewhere.<sup>28</sup>

### Psychiatric Disorders that Present with Somatic Symptoms

These are psychological disorders that mimic a physical disorder.

#### *Somatoform Disorders*

Somatoform disorders refer to a variety of psychiatric conditions that lead to seek medical help for physical symptoms, which are misattributed to physical disease. Headache is reported by 10 to 30 percent of school children, recurrent abdominal pain by 10 to 25 percent, limb pain in 5 to 20 percent, fatigue in 15 percent and polysymptomatic somatization in 11 percent.<sup>29</sup> This is more common among girls and peaks between 9 to 12 years of age.

The management will cover symptom removal encouragement (with suggestion, placebo, physical therapy and exercise), and discouragement of "sick role". If total symptom removal is not possible then coping strategies for the symptoms should be taught. Reducing the secondary gains the child has been achieving (e.g. stabilizing effect the symptom has in

the family dynamics) should be addressed as soon as possible.

### *Dissociative Disorders*

The essential features of dissociative disorders is a disruption in the normal integrative functions of consciousness, memory, identity or perception of the environment. Although, dissociative symptoms may present in children of any age and sex, these symptoms most commonly occur in teenage girls.<sup>3</sup> The history from the child, parents, and other collateral sources might provide clues to precipitants for the dissociative symptoms.

Children and adolescents manifest the same core dissociative symptoms and secondary clinical phenomena as adults. However, age-related differences in autonomy and lifestyle influences the clinical expression of dissociative symptoms in this population (e.g. dissociative amnesias and perplexing forgetfulness are more apparent in school situations rather than family life). A number of normal childhood phenomena, such as imaginary companionship and elaborated daydreams, must be carefully differentiated from pathological dissociation in younger children. Ongoing severe trauma, sexual abuse, and violence among family members are often causal in the development of these disorders. The treatment is similar to that for somatoform disorders.

### **Medical Illness that Presents with Psychiatric Symptoms**

The list of potential medical illnesses that presents with psychiatric symptoms is exhaustive (brain tumors, congenital malformations, head trauma, neurodegenerative disorders, metabolic disorders, toxic encephalopathies, infectious diseases).

### *Delirium*

Delirium is often mistaken for psychosis and often not recognized. The symptoms include inability to maintain attention to external stimuli or shift attention to new stimuli, disorganized thinking reflected by rambling and incoherent speech, reduced level of consciousness, perceptual disturbances, disturbance of sleep-wake cycle, increased or decreased psychomotor functioning, disorientation, impaired immediate recall and behavior changes (e.g. aggressive, oppositional, anxiety and phobias).

The essential phase in the treatment of children with delirium is supportive care while specific therapy for

the underlying cause (stimulus deprivation as in ICU, side effects or toxicity of medication, metabolic causes, infections, fever, seizure) is given. Treatment includes stabilizing the vital signs, keeping the patient safe, supervised physical restraint as last resort (but preferred over medication especially if the cause of delirium is unclear), frequent reorientation and reassurance by parent or nurse, and dampening noise and light levels. High potency antipsychotics, such as haloperidol (2 to 5 mg intramuscularly every 30 to 60 minutes), are the treatment of choice. Benzodiazepines like oxazepam and lorazepam (0.5 to 2 mg sublingually or intramuscularly) are also used.<sup>30</sup>

### *Seizure Disorder*

The prevalence of epilepsy in the child and adolescent population is 0.1 to 0.5 percent and approximately 45 percent of them have complex partial seizures. The symptoms of complex partial seizures (CPS) might encompass mood, anxiety, psychotic, personality, and cognitive as well as disruptive behavioral domains.<sup>31</sup>

Non-convulsive status epilepticus (NCSE) with its pleomorphic clinic presentation in the form of acute waxing and waning confusional states associated with agitation, bizarre behavior, staring, increased tone, mutism, or subtle myoclonus is often mistaken for behavioral or psychiatric disturbance. EEG and a therapeutic trial of antiepileptic drugs afford the best diagnostic and treatment measures in these cases in an emergency.<sup>32</sup>

### **Adverse Action or Interaction of Medication**

Adverse effects vary with the psychotropic used. With low potency antipsychotics non-CNS side effects are more common and CNS side effects are more common with high potency antipsychotics. Cardiac arrhythmias and sudden death are reported with imipramine and Stevens-Johnson syndrome has been reported with carbamazepine. The neurological side effects are briefly discussed.

### *Neuroleptic Malignant Syndrome*

This condition develops in about 1 percent of patients on antipsychotic medication and is characterized by hyperpyrexia, diaphoresis, mutism, autonomic instability, extrapyramidal symptoms, and delirium, with the laboratory finding of increased creatine phosphokinase, leukocytosis, myoglobinuria, as well as elevated liver enzymes. Patients with neuroleptic malignant syndrome are at risk for serious medical complications

including renal failure, pneumonia, respiratory arrest, and cardiovascular collapse. The mortality rate is 10 to 30 percent but with prompt withdrawal of antipsychotic medication and supportive care, the survival rate is more than 95 percent. Amantadine (100 mg twice a day, maximum 400 mg a day, orally), bromocriptine (2.5 to 5 mg, maximum 60 mg per day, orally) and dantrolene (0.8 to 2.5 mg/kg every 6 hours, maximum 10 mg/kg daily, intravenously) are used. The syndrome usually lasts 5 to 10 days after discontinuation of antipsychotic medication. Two weeks after the resolution of neuroleptic malignant syndrome, rechallenge with an antipsychotic medication may be considered.<sup>33</sup>

### *Dystonia*

Acute dystonia induced by antipsychotic drugs is described as sustained abnormal postures or muscle spasms (torticollis, grimacing, oculogyric crises, trismus and opisthotonos) that develop within seven days (95% of cases within the first 96 hours) of starting or rapidly raising the dose of the antipsychotic medication, or of reducing the medication used to treat (or prevent) acute extrapyramidal symptoms (e.g. anticholinergic agents). Risk factors include age (highest between 10-19 years), male gender and taking large doses of parenteral, high-potency antipsychotics. Symptoms of potentially fatal laryngeal dystonia include dyspnea and gestures indicating respiratory distress, such as pointing to or clutching the throat. Intramuscular administration of anticholinergic drugs (biperiden 5 mg or procyclidine 5 mg) or antihistamines (promethazine 50 mg) is usually effective. This may be followed by oral antiparkinsonian treatment (trihexyphenidyl at 0.5 to 1 mg orally, twice a day, with a daily maximum of 6 mg). In oculogyric crisis that does not respond to anticholinergic drugs, treatment with clonazepam 0.5 to 4 mg may be beneficial.<sup>34</sup>

### *Extrapyramidal Symptoms*

In children, extrapyramidal side effects are common even with standard doses of typical antipsychotics. The common signs are tremors, cogwheel rigidity and motor retardation. The dosage of the antipsychotic should be reduced, an antiparkinsonism medication (trihexyphenidyl 1 to 4 mg per day) added, or the medication is changed to an atypical antipsychotic (risperidone, olanzapine, clozapine, etc.), which cause less extrapyramidal effects.<sup>35</sup>

### *Akathisia*

Akathisia is a common adverse effect of treatment with antipsychotics or selective serotonin reuptake inhibitors,

and presents with a subjective (feeling of inner restlessness, urge to move and dysphoria) and objective components (rocking while standing or sitting, lifting feet as if marching on the spot and crossing and uncrossing the legs while sitting) of restlessness. Severe akathisia results in poor medication compliance, aggressive and suicidal behavior resulting in increasing doses of the psychotropic. Emergent treatment is to give lorazepam 2 mg intramuscularly. As further treatment, dosage adjustment of the psychotropic,  $\beta$ -adrenergic receptor antagonists (propranolol 10 mg, three times a day, orally) provides considerable relief. Cyproheptadine, clonidine and buspirone, amantadine, clonidine, ritanserin, piracetam, valproic acid and tricyclic antidepressants have also been used beneficially.<sup>36</sup>

### *Tardive Dyskinesia*

Tardive dyskinesia (TD) is characterized by waxing and waning periods of involuntary choreiform, athetoid, or rhythmic movements (lasting at least a few weeks) of the jaw or extremities developing in association with the use of neuroleptic medication for at least a few months. In children, prevalence of TD ranges from a mean of 1 to 4.8 percent. Treatment options include stopping or reducing the antipsychotic drug or changing to an atypical antipsychotic drug. Administration of an anticholinergic medication, a calcium channel blocker or benzodiazepine is useful.<sup>37</sup>

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## INTRODUCTION

Though emergencies are relatively infrequent in pediatric rheumatic diseases, rapid diagnosis and treatment can have significant positive impact on future growth and development of the child and may minimize morbidity and mortality. Whether involving one organ system or many, the spectrum of rheumatic disease in children ranges from limited and indolent to rapidly progressive and life-threatening and often benefits from a multidisciplinary approach.

A large majority of acute medical problems in pediatric rheumatology fall into the category of “medical urgencies” and need specialist medical attention within 72 hours. Some present as true medical emergencies, may be life threatening, and need appropriate care. A recent survey in the U.K. has elegantly shown that emergency medical services are needed for this field, and are in fact cost effective.<sup>1</sup>

Common rheumatological conditions encountered are: Juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, systemic vasculitides commonly Henoch-Schönlein purpura and Kawasaki disease. This chapter deals with medical “urgencies” and emergencies in these diseases. Rare disorders such as sarcoidosis, Behcets, polyarteritis nodosa, and periodic fevers are not being dealt with here.

## JUVENILE IDIOPATHIC ARTHRITIS (JIA)

JIA is the umbrella term for a group of chronic childhood arthritides of unknown cause, in children below sixteen years of age, and persisting for at least six weeks. This is the new term proposed by the International League of Associations of Rheumatologists (ILAR) whose taskforce met twice to propose a unified classification in 1995 in Santiago, Chile and revised in Durban in 1997.<sup>2,3</sup>

This classification proposes seven subtypes, with specific inclusion and exclusion criteria. The subtypes are-Oligoarthritis, polyarthritis, (rheumatoid factor positive and negative).

Systemic onset JIA (SOJIA), enthesitis related arthritis, psoriatic arthritis, and “other” category. Important medical problems presenting emergently in this group of conditions are as follows:

### Acute Monoarthritis

This is a challenging problem to manage, especially in the febrile unwell child. It may sometimes complicate the course of JIA. Septic arthritis needs to be ruled out urgently in order to prevent destructive disease in the short term and morbidity in the long term. Physical findings characteristic of infection of a joint are extreme pain, tenderness, erythema and warmth over a joint. There is usually extreme limitation of movement of the joint. These signs are subtle in JIA, erythema is not a feature and range of movement is usually possible though may be limited. Management of a suspected septic joint is a medical emergency and needs aspiration of the joint by a skilled person, with blood cultures, and a C- reactive protein to support the diagnosis. Once the diagnosis is confirmed appropriate antibiotics should be started, and continued for 4-6 weeks. If the flare is as a result of JIA the joint should be aspirated and injected with a long acting crystalline steroid.<sup>4</sup>

There is no substitute for a detailed history and clinical examination, keeping in mind that other important causes of a single inflamed joint are infective endocarditis, osteo-articular tuberculosis, acute rheumatic fever, reactive arthritis and finally an acute hemarthroses. Up to 15% of patients with infective endocarditis have been reported to have peripheral arthritis. A tubercular joint can mimic oligoarticular disease. Rheumatologic manifestations of tuberculosis are many, and range from infection (Pott’s disease, septic or infectious arthritis, subcutaneous abscesses), immunologic reactions (Poncet’s disease, i.e. reactive arthritis, erythema nodosum) through to drug induced syndromes such as isoniazid induced systemic lupus erythematosus. In our country acute rheumatic fever is not an uncommon clinical diagnosis. The Jones criteria are helpful in diagnosing rheumatic fever. The joint in this condition

is erythematous, and very painful, in addition to the classic “flitting” pattern. Most postinfectious/reactive arthritides are self-limiting. A specific diagnosis is needed only in a few circumstances: when an antibiotic is required (Lyme disease, rat bite fever, brucellosis), when extraarticular involvement can be serious (hepatitis) when duration is prolonged (parvovirus) or finally when communicability is important (*Salmonella* infection to younger siblings, and parvovirus to pregnant women). An accurate diagnosis of the cause of monoarthritis is thus important, as urgent treatment is needed in some varieties.<sup>5-9</sup> Another important differential for an acutely swollen joint, usually a knee or an elbow in a male infant is hemophilic arthropathy. Nearly all patients with severe hemophilia A or B (<1% activity of the deficient factor) and half of patients with moderate disease activity experience hemarthrosis. Acute hemarthroses generally first occur when a child begins to walk and continue, usually cyclically, into adulthood, when the frequency diminishes. Joint pain responds rapidly to replacement of the deficient clotting factor. If hemostasis is achieved early after onset of hemarthrosis, full joint function may be regained within 12 to 24 hours. If the hemorrhage is more advanced, however, blood is resorbed slowly over 5 to 7 days, and full joint function is regained within 10 to 14 days. MRI is now routinely used to stage hemophilic arthritis accurately to determine optimal treatment and to follow response to therapy. Additionally, MRI and ultrasonography are useful in the detection and the quantitation of soft tissue bleeding, cysts, and pseudotumors. Prompt diagnosis and management help to prevent damage to the joint which occurs due to deposition of hemosiderin in the synovium.<sup>10</sup>

### Fever and Macrophage Activation Syndrome (MAS)

Fever is a manifestation of SOJIA, but may herald the onset of an infective complication or MAS. SOJIA is defined by the ILAR as spiking quotidian fever with a characteristic evanescent rash, polyarthritis often with lymphadenopathy, hepatosplenomegaly and serositis. Classically a child with a flare of SOJIA per se maintains the fever pattern and has a flare of the arthritis as well. Between the fever spikes this child looks well and remains active. A systemic infection on the other hand presents with an altered fever pattern probably persistent, with localizing signs. MAS is a complication of systemic rheumatic disorders. The clinical findings of MAS are dramatic. Typically patients with a chronic rheumatic disease become acutely ill at presentation with persistent fever, lymphadenopathy, and hepatospleno-

megaly. Significant depression of one or more blood cell lines, low ESR, elevated liver cell enzymes and abnormalities of the clotting profile are common. The pathognomonic feature of this syndrome is seen on bone marrow examination: numerous well-differentiated macrophages actively phagocytosing hematopoietic elements. Such cells may be found in various organs and may be responsible for many of the systemic features in this condition. The diagnosis may be delayed because the presentation mimics an acute exacerbation of SOJIA or severe infection. Precipitating factors that have been implicated include a flare-up of the underlying disease, aspirin or other nonsteroidal anti-inflammatory drug toxicity, viral infections, methotrexate, and sulfasalazine therapy. The presentation of MAS is a result of an ineffective immune response to an endogenous or exogenous stimulus leading to an exaggerated inflammatory state produced by a release of high levels of cytokines. These proinflammatory cytokines include tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL) 6, IL-8, IL-12, IL-18, macrophage inflammatory protein (MIP 1- $\alpha$ ), and interferon gamma (INF- $\gamma$ ) released by stimulated lymphocytes and histiocytes. Defective NK cell function and cytotoxic T-cell activity has been documented in patients with MAS as well as HLH and may be the common pathway leading to the clinical presentation.<sup>11</sup>

The hemoglobin scavenger receptor (CD163) is a newly described macrophage differentiation antigen with expression restricted exclusively to cells of the monocyte-macrophage lineage.<sup>12</sup>

It is important to define the cause of fever in patients with JIA as the treatment is different in each of the three groups described above: Appropriate antibiotics for infection, NSAID + steroids/DMARD's for a flare and IV steroids +/-cyclosporin for MAS.<sup>13,14</sup>

### Atlantoaxial Instability

This is well described in JIA and needs early and prompt detection. The usual symptoms are of parasthesia of the fingers and tingling, especially on the arms. Occasionally this is picked up on a routine lateral neck X-ray. The condition is diagnosed by appropriate imaging of the spine (common modalities used are plain X-ray, CT scan, and MRI). Measuring the atlanto-odontoid distance makes the diagnosis—less than 4 mm being normal. Defining the degree and site of cord impingement usually needs detailed imaging. Most children with atlantoaxial instability do not have evidence of cord compression, and require measures to reduce excessive movement for example: care during intubation, or the use of a cervical collar during a car

journey to prevent excessive anterior flexion. Surgical stabilization is needed in the presence of spinal cord compression.<sup>4,15</sup>

### Cardiac Complications

The common cardiac emergencies are pericarditis and valvular insufficiencies.

The overall incidence of pericarditis in JIA is 3-9%, and this occurs only in SOJIA. Episodes generally persist for 1-8 weeks, and are managed with systemic corticosteroids.

Tamponade is rare, presents with venous distention, hepatomegaly and peripheral edema. Pulsus paradoxus can often be demonstrated. Treatment is with urgent pericardiocentesis and IV pulsed methyl prednisolone.<sup>4,16</sup>

Cardiac valvular insufficiencies: Acute valvular insufficiencies are rare in children with JIA, but have been described in juvenile ankylosing spondylitis. In this condition acute aortic insufficiency needing emergency valve replacement may occur. This is usually as a result of aortic root dilatation.<sup>16</sup>

### Uveitis

This occurs in 10-20% of all children with JIA. It is usually chronic, silent and needs regular screening with a slit lamp for early diagnosis. Appropriate management with mydriatics, topical steroids and occasionally DMARD's are vital if long-term morbidity is to be avoided. Acute onset uveitis, (which occurs in the group "Enthesitis related arthritis") on the other hand is characterized by sudden pain, redness, photophobia and increased lacrimation. The treatment is as detailed above and in some patients medication needs to be instilled locally every 15-30 minutes.<sup>4,17</sup>

### Neurological Complications

Neurologic disease in systemic or polyarticular JRA is rare and may be primary or arise from complications of acute vasculitis, cerebral infarction, seizures, metabolic derangements, hemorrhage, disseminated coagulopathy, or fat embolism in the child who sustains a fracture or major trauma.<sup>18</sup>

### Complications due to Chronic Steroid Use

In poorly treated or unidentified cases of JIA, severely osteopenic bones are prone for fractures and can present in emergency with excruciating pain. Vertebral fractures are more common in a bed ridden child due to compression.

### ANTIPHOSPHOLIPID ANTIBODY SYNDROME

This is a thrombotic disorder characterized by association of arterial and venous thrombosis with antibodies directed against phospholipids. Clinical features include stroke, livedoreticularis, thrombocytopenia, chorea and recurrent fetal loss. An increasingly reported, devastating CNS emergency is stroke in young children caused by the antiphospholipid antibody syndrome. Strokes occur more often in the region supplied by the middle cerebral artery. Cerebral infarction may be silent, however, and when multiple events occur, patients may develop seizures or dementia secondary to widespread cerebral damage. Notably, a high prevalence of aPL has been reported in children with idiopathic cerebral ischemia, suggesting that these antibodies may play a major pathogenetic role in children who lack the other prothrombotic factors. Thrombosis of the cerebral sinus has been observed in both primary and SLE-associated APS. Ocular ischemic events, including anterior ischemic optic neuropathy, central retinal artery occlusion, amaurosis fugax, and occlusion of retinal veins, and sensorineural hearing loss, often presenting as sudden deafness, have been described in patients with APS. Several other neurologic abnormalities have been linked to aPL but are not clearly related to thrombosis. They include chorea, transverse myelopathy, Guillain-Barre' syndrome, psychosis, and migraine headaches. It has been suggested that these complications may result from direct interaction between aPL and the nervous tissue, or from immune complex deposition in cerebral or spinal cord vessels.

The syndrome can be primary when it occurs in the absence of an underlying rheumatic disease and secondary when there is an underlying rheumatic disease, most commonly lupus. The most useful tests are lupus anticoagulant and anticardiolipin antibodies both IgG and IgM. Although the antiphospholipid antibodies do prolong clotting in vitro, hemorrhage is rare in these patients. When hemorrhage occurs it is important to exclude other causes such as severe thrombocytopenia or clotting factor inhibitors. Acute onset arterial or venous thrombosis may present as an emergency and need anticoagulation with intravenous heparin to save the involved limb/organ. Acute hemorrhage needs support with IV glucocorticoids, fresh frozen plasma and vitamin K.<sup>19,20</sup>

### Systemic Lupus Erythematosus

This is a multisystem disease, which is pleomorphic in its presentation and course. Three challenging problems faced in this disease are—diagnosis and management

of the febrile child with lupus, dealing with a lupus crisis, and treatment of congenital heart block.

#### *Fever/Infection in a Child with Lupus*

Infection is a major cause of mortality in children with lupus. Patients with lupus who are on immunosuppressive treatment are at risk of developing viral, mycotic or opportunistic infections. Children not on immunosuppressive treatment on the other hand, are at risk of developing infection with encapsulated organisms such as *Pneumococcus* and *hemophilus influenzae*. Abnormal splenic function places them at an increased risk of developing bacteremia and overwhelming sepsis. Acutely ill children with pneumonia or meningitis should be admitted for IV antibiotics awaiting culture reports. A useful laboratory marker for infection in lupus patients is following a serial C-reactive protein, which is elevated with sepsis but usually normal when fever is a result of lupus flare.

#### *Lupus Crisis*

Acute clinical deterioration of a child with lupus can be challenging, has a high mortality and needs management in an intensive care facility. Almost any organ system may be involved. Important emergencies include

- *Renal*: In the presence of progressive renal failure the patient should be admitted for aggressive medical therapy with pulsed cyclophosphamide and methylprednisolone, failing which plasmapheresis may be tried.
- Severe thrombocytopenia/Coombs positive hemolytic anemia will need acute supportive care including platelet concentrate and/or blood. IVIG may have a role in this clinical setting.
- *Pulmonary complications*: Include pleural effusion, interstitial pneumonitis, and pulmonary hemorrhage. The pleural effusion is usually small, but may occasionally be massive and need an urgent pleural tap, along with pulsed IV methylprednisolone at 30mg/kg, for three consecutive days. Pulmonary hemorrhage is a potentially catastrophic complication. Early recognition is critical to outcome. The intra pulmonary bleeding can be related to vasculitis, infection or thrombocytopenia. Clinical features include hemoptysis, tachypnea, tachycardia, and dyspnea. Management includes transfusion and high doses of steroids. If there is progression of disease, intubation and positive pressure ventilation may be needed. Acute lupus interstitial pneumonitis may be the presenting manifestation of SLE. Such patients

are very sick with high fever, dyspnea and cough. Chest X-ray shows a diffuse alveolar infiltrate. In addition to supportive measures, corticosteroids and IV cyclophosphamide can lead to a dramatic improvement.

- *Acute abdomen*: It can be a life threatening complication in lupus patients. Important reasons for an acute abdomen are peritonitis, pancreatitis, and bowel vasculitis including perforation. Care of these patients is often done jointly with a pediatric surgeon and a skilled intensive care team. It is often difficult to determine the exact cause for the intra abdominal catastrophe. Detailed imaging, peritoneal aspiration and sometimes surgical exploration are needed to guide specific therapy.
- *Raynaud's*: The best treatment for Raynaud's is preventive-avoidance of cold exposure, and use of topical or systemic vasodilators. Impending gangrene is a medical emergency and is treated with IV prostacyclin. It is important to rule out a secondary antiphospholipid antibody syndrome in these patients.
- *CNS complications*: Seizures, altered state of consciousness and psychosis are well-recognized acute neurological presentations of lupus. The basic pathology underlying these problems is often CNS vasculitis. Hypertension, uremia, hemorrhage and CNS infection should be ruled out in these patients. Treatment is directed to treating the cause: antibiotics for infection, blood and fresh frozen plasma for hemorrhage, and increased immunosuppression for vasculitis usually with I.V. methylprednisolone and pulsed cyclophosphamide.<sup>4,21</sup>

#### *Congenital Complete Heart Block (CCHB)*

This is a rare entity affecting 1:20000 livebirths. A major cause of neonatal heart block is the presence of autoantibodies in the mother and the child, usually SSA (Ro), SSB (La), or anticardiolipin antibodies. The complete heart block is only one manifestation of neonatal lupus, in which the other features are a skin rash, hepatitis, and thrombocytopenia. Damage to the fetal cardiac conducting tissue usually takes place by the 22nd week of gestation, and may thus be manifest *in utero* as well. Despite early and frequent monitoring of pregnant women at risk, attempts to salvage the fetus with heart block have been variable. The presence of hydrops fetalis is almost universally fatal. It is estimated that up to 50% of pregnancies complicated by complete heart block result in fetal death, and that most mothers do not have an autoimmune disease. Elective screening of pregnant women with previous

second trimester abortion thus assumes importance. The birth of a neonate with CCHB can present an emergency and needs urgent pacing with appropriate supportive treatment for hypotension, and cardiac failure. The lower the heart rate, the more the chance that the patient will need emergent pacing.<sup>15,22</sup>

### JUVENILE DERMATOMYOSITIS (JDM)

It is a systemic vasculopathy with primary involvement of the skin and the muscles. Emergencies in this disease can involve many organ systems.

#### Respiratory Emergencies

Acute respiratory failure consequent to profound weakness of the respiratory muscles is perhaps the commonest emergency in this condition. Other life threatening problems include progressive interstitial lung disease, infection, and aspiration pneumonia especially in the presence of palatopharyngeal incompetence. Pneumothorax is another complication known to occur in JDM, and presents with sudden onset chest pain and dyspnea. Intensive care support with ventilation and treatment of the etiology of the acute event are critical to outcome in these children. If the acute deterioration is secondary to infection broad-spectrum antibiotics are needed. This often occurs in the setting of acute respiratory muscle weakness, where aggressive immunosuppression with pulsed methyl prednisolone, cyclophosphamide and plasmapheresis are used in addition to antibiotic support.<sup>4</sup>

#### Gastrointestinal Emergencies

Gut vasculitis, pancreatitis and upper GI ulceration are well-described emergencies in this condition. Vasculitis can involve any site-esophagus to colon. Signs and symptoms depend on the site of involvement. These patients are best managed in an intensive care setting, jointly with a surgeon. The management includes hemodynamic support, antibiotics for sepsis and aggressive immunosuppression. Rarely surgery may be indicated.<sup>4</sup>

#### CNS Emergencies

Commonly present as seizures, secondary to cerebral vasculitis. In addition to supportive measures, specific aggressive immunosuppression as detailed above can be lifesaving. Appropriate imaging and investigation should always exclude meningitis, hypo or hypertension, drug toxicity and intracranial hemorrhage.<sup>23</sup>

### Henoch-Schönlein Purpura (HSP)

It is the most common vasculitis syndrome of childhood. It is usually benign and self-limiting and often follows an intercurrent illness. It is diagnosed with the classical triad of a palpable purpuric rash, cramping abdominal pain and hematuria. The spectrum is variable and ranges from a very mild rash to acute emergencies.

#### Acute Abdomen

Acute abdominal pain may be secondary to a number of causes: bowel infarct, intussusception, perforation, pancreatitis or hydrops of the gallbladder. Intussusception is seen in 2% of patients with HSP, other causes being very rare. Management of acute abdomen in HSP includes: supportive care, exclusion of any treatable surgical cause (perforation, intussusception), and treatment with oral/pulsed methylprednisolone at 30 mg/kg.

#### Genitourinary Emergencies

Acute scrotal swelling due to inflammation and swelling of the scrotal vessels has been reported in 2 to 35% of children. The major differential diagnosis in this condition is torsion of the testis, which is a surgical emergency as vascular insufficiency may lead to infarction and death of Leydig cells within 10 hours, unless blood supply is restored. The best investigation in this scenario is a radionuclide scan which demonstrates increased vascularity in HSP, and decreased uptake in torsion.

#### Miscellaneous

Seizures and acute pulmonary hemorrhage are rare complications of this disease, and are treated with adequate supportive measures and pulsed methyl prednisolone as detailed above.<sup>24,25</sup>

### Kawasaki Disease (KD)

This is an idiopathic vasculitis of small and medium sized vessels and the leading cause of acquired heart disease in children in the United States. Characteristically the child with KD has persistent high-grade fever, conjunctivitis, rash, lymphadenopathy, mucosal inflammation, and changes involving the extremities. In KD extreme irritability is a disease hallmark, commonly caused by aseptic meningitis, although focal neurologic involvement and acute hemiplegia rarely may occur. The major morbidity occurs in the heart: coronary artery aneurysms in 20-25% of untreated children, which in

turn can lead to myocardial infarction, sudden death or chronic coronary insufficiency. Use of intravenous immunoglobulin (within ten days of onset) has reduced the risks of coronary aneurysms to fewer than 2%. Hence recognition and treatment of KD in this time frame constitutes a medical “urgency”. Treatment of myocardial infarction (a medical emergency) which can infrequently complicate this condition is with thrombolytic agents, mainly streptokinase and urokinase. The use of these agents has shown variable results. The thrombolytic therapy is most effective when begun within the first 3-4 hours of symptom onset, and is followed up by systemic heparin in combination with aspirin. Persistent fever after institution of IVIG is a challenge and may be managed with a repeat dose of IVIG or with pulsed methylprednisolone. Recently there are reports that suggest the use of Infliximab in IVIG resistant patients.<sup>26-28</sup>

### Conclusion

This chapter is not intended to be an exhaustive review of the clinical presentation, investigations and management of all pediatric rheumatological emergencies. The aim has been to generate awareness amongst practicing clinicians that though rare, emergencies do occur in rheumatology and can indeed be life threatening. Rapid diagnosis and treatment often has a significant positive impact on the growth and development of the child and minimizes immediate morbidity and mortality. It is hoped that this information will assist clinicians in this challenging task.

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S e c t i o n

4



Injury due to burns is the second most important cause of trauma-related deaths in children, ranking behind motor vehicular accidents only. A severe burn is, undoubtedly, the most devastating injury a person can sustain and yet hope to survive. In addition to the fatally burnt children, a large number survive the burns and have disfigurement, loss of function and physical deformity leading to psychological sequelae. A burn injury not only leaves the scars on the skin but also on the mind. Returning to school and relating to their peers and teachers requires a major psychological adjustment on the part of the child. The parents suffer not only monetary loss because of costly and lengthy treatment involving extended time away from work but also psychologically because they encounter great difficulty in finding a suitable 'match' for their child at the time of marriage. Burnt children account for almost 15 percent of all burn patients admitted to a large burn center.

#### MODE OF INJURY

Although, as in adults, burns may be thermal, electrical, chemical or through exposure to radiation, the mode of getting injured from these agents differs from them. The vast majority of burns in children occur in child's own home. The characteristics of the child and his environment are intertwined with the burn event and suggest subgroups of children at risk for burn injury.<sup>1</sup> The infants and toddlers (0-2 yr) are frequently burnt. An important factor leading to burns even in neonates is overcrowding in a small house in our country where a small room serves as a kitchen (with floor level cooking), a bedroom and even a bathroom. The victim is looked after by his/her siblings who are themselves no more than 5-6 years old when the mother is away at work to earn. Infants and small children are also the only victims when clusters of hundreds of 'jhuggis' (huts) catch fire specially in very hot summer months and they are either sleeping alone or unable to rescue themselves and get charred to death.

Very young children, just learning to locomote and explore, actively search and manipulate their physical environment. They usually suffer scalds by pulling down or knocking hot liquid onto themselves and sometimes stumbling onto a burning agent. Kitchen burns in toddlers can be reduced either by excluding them from the kitchen (almost an impossible task in majority of Indian homes) or by avoiding easy access to pans, bright colored pottery and by avoiding the use of table cloth or placemats at meal time. Immersion scalds are also common in a toddler. These burns occur when a child steps into a tub of hot water or stumbles into a container of hot milk or cooked food. Such cases have a higher morbidity and mortality as a larger surface area is involved.

Young children are fascinated by fire and if match boxes are accessible they are naturally curious to experiment. In this manner they may sustain flame burns which may be extensive and very serious. Fireworks during Diwali or other festivals is one such potential hazard which is highly preventable. Although burns from fire crackers seldom cause deaths, they often cause serious injury to the eyes, face and hands. In winter season, it is a common practice to collect wooden sticks, worn out tyres, etc. and ignite them to keep warm. Small children often imitate adults and get burnt.

Electrical burns in children are generally caused by domestic voltage electric current (220-250 volts). Typically, a child bites an electric cord sustaining a disfiguring third degree burn of the lips.<sup>2</sup> He may introduce a finger or a metallic object such as a hair pin, into an electric socket and suffer an electrical injury (Fig. 42.1). Chemical burns are caused by strong acids and alkalies used for cleaning toilets and drains and quite commonly stored carelessly in the house (Fig. 42.2).

Almost all burn injuries in children are accidental, although a very small percentage can be attributed to homicide and child abuse in India.<sup>3</sup>



Fig. 42.1: Electric burn (For color version see plate 3)



Fig. 42.2: Acid burn (For color version see plate 3)

## PREVENTION

It is the carelessness of the adults, which is to be blamed for almost all cases of pediatric burns. Hence, the incidence of childhood burns can be greatly reduced only if we, the adults, become a bit more careful and do not leave the child unattended/unobserved for even a very short period of time. In addition, we should teach them about being careful of hot liquids, fire and electricity from a very young age (perhaps 2 years onwards). Firecrackers should be burst only under adult supervision. The electrical sockets in the household should be at a higher level and out of reach of small

children. Also covers can be used on electrical outlets. The electrical appliances should be modified so as to be safe for children, e.g. use of hot blowers rather than heating rods during winters. Keep matches, lighters and inflammable materials out of reach of children. Schools, television and other media may help in spreading awareness at community level.

## FIRST AID

At the scene of the accident, the objectives are to extinguish the flames (by rolling on the ground/covering the child with a blanket) and to bring down the skin temperature to normal, in as short a time as possible. Damage due to heat is directly proportional to the temperature of the burning agent and the duration of contact.<sup>4</sup> All clothing and jewelry must be removed to prevent constriction and vascular compromise during the edema phase (first 24 hr) of burn injury. However, adherent synthetic clothing and tar may be left in place and can be cooled with water to be removed later by formal debridement. Tap water, instead of cold water or ice, should be used to bring down the temperature as it is easily available and the latter can lead to hypothermia in a small child. Chemical burns require prolonged washing (half to one hour) with copious amounts of tap water. No household remedy or topical agent should be applied to the burnt site lest evaluation of depth of burns become difficult. Moreover, removal of this agent may be a painful experience. The burnt area is covered with a clean sheet to prevent contamination and hypothermia and the child transported to the medical facility at the earliest. The victim is not given anything orally on the way as it may induce vomiting.

## HOSPITAL MANAGEMENT

In a child with major burns airway, breathing and circulation should be assessed and managed before assessing the extent of burn injury. Airway and breathing may be compromised due to inhalation injury as well as secondary to circulatory shock caused by burns.

## Assessment of Burn Injury

The burn wound has to be evaluated for (a) Its extent in relation to the total body surface area and (b) For the depth of skin burnt. This is important: (i) To establish criteria for admission to a specialized burn care facility, (ii) To classify the wounds as minor, moderate or critical for the purpose of management, (iii) For calculating the initial fluid requirements during

resuscitation, and (iv) To enable the surgeon to answer prognosis-related queries from the parents, e.g. with regard to survival, expected time of healing, need for surgical interventions, rehabilitation, scarring, etc.

### Estimating Burn Size

An accurate estimate of the surface area involved can be made by referring to detailed surface area charts prepared by Lund and Browder.<sup>5</sup> This is because the surface area of head and lower limbs, as a proportion of total body surface area (TBSA), is variable, depending on the age. However, in an emergency room, the following formulae are considered reasonably accurate.

- i. *Wallace's Rule of nine*: In children over 15 years, burn wounds are estimated by this formula which is also used in adults.<sup>6</sup> According to this, the head and neck constitute 9 percent of TBSA, each upper extremity is 9 percent, each lower extremity is 18 percent, the anterior and posterior trunk are 18 percent each, and the genitalia is 1 percent (Fig. 42.3). This formula is not useful for children <15 years.
- ii. *Rule of five*: Lynch and Blocker developed a formula for estimating the extent of burns in children.<sup>7</sup> This

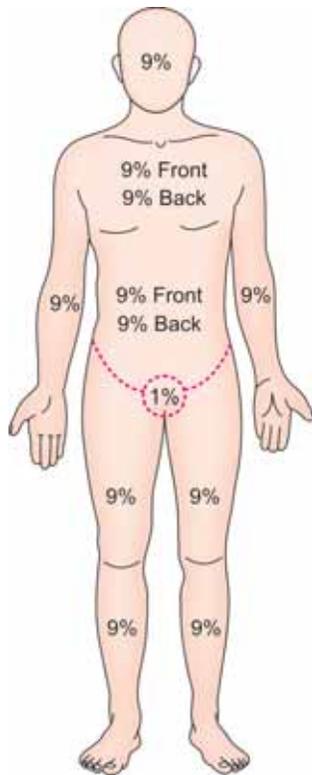


Fig. 42.3: Rule of nine for estimating extent of burns in adults

works very well in infant where head and neck, anterior and posterior aspects of trunk are 20 percent each and each limb constitutes 10 percent. For older children, this is slightly modified. The head, posterior trunk and lower limbs are 15 percent each, anterior trunk is 20 percent, and each upper limb is 10 percent (Fig. 42.4).

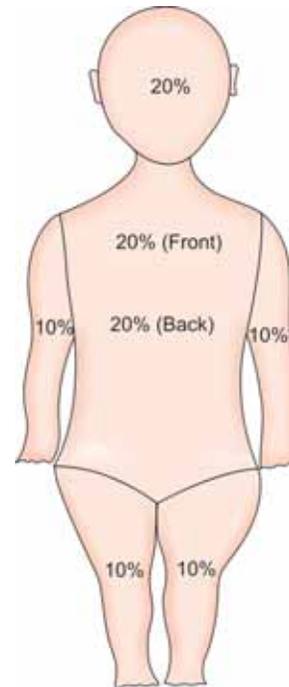
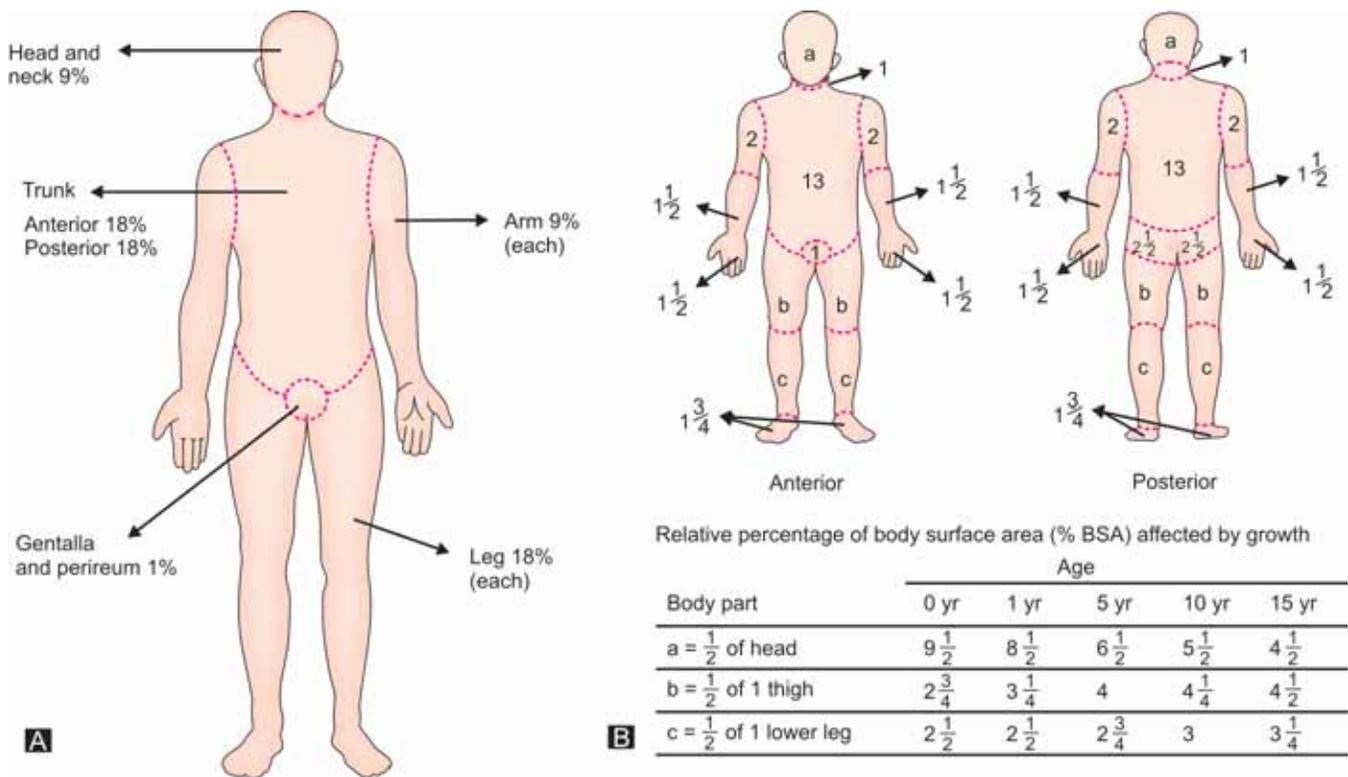


Fig. 42.4: Rule of five for estimating extent of burns in children

- iii. *Rule of palm*: For all age groups, palmar surface of the hand (from wrist to finger crease; excluding the fingers) represents 1 percent TBSA. This is useful for assessing scattered burnt areas.

### Estimating Burn Depth

Besides being a prognostic indicator, the depth of burn determines if the wound is going to heal from epithelial remnants or else require skin grafting for closure. Burn wounds are generally classified as: (i) Partial thickness, or (ii) Full thickness. In partial thickness burns, whole of epidermis and only a part of dermal thickness is burnt. These wounds heal by spontaneous epithelialization from the sweat and sebaceous glands and hair follicles which are deeply placed in dermis. On the contrary, the entire skin (epidermis and dermis) is burnt in a full thickness injury and this invariably requires skin grafting. Those cases where subcutaneous fat, deep fascia and even muscle are burnt also come under this



**Figs 42.5A and B:** Lund and Browder chart for estimation of extent of burns in different age groups

category. Although, scalds are generally considered more superficial as compared to flame burns, they can also be full thickness burn injuries due to thin skin of the child. Because the hair follicle does not extend deeper than dermis, it is an important marker for determining burn depth and potential for wound healing.

According to another classification, the burn wound can be graded into degrees depending on the depth of skin involved (Figs 42.5A and B). *First degree burns* (e.g. sunburns) have only epidermal involvement and are characterized by erythema, a mild pain and swelling. There is no blister formation and it heals in 3-5 days without scarring. Second degree burns have been further subdivided into superficial dermal and deep dermal. In *second degree burns*, dermis is also involved. The burnt area is mottled pink and white, moist and edematous in appearance. There is severe pain and hyperesthesia. Blisters may form if the overlying epidermis is intact. They are further divided into superficial (involvement up to papillary dermis) and deep partial thickness wounds (involvement of both papillary and reticular dermis). They appear very similar on examination, and their accurate evaluation is complicated by the fact that they are dynamic over

the first few days post-injury. However it is important to differentiate between these two sub-groups. This is because superficial partial burns heal spontaneously in about 10-20 days, however deeper wounds take longer and heal by contraction and scarring; hence must be treated with skin grafting. Also, there is the danger of getting converted into a full thickness wound by infection and drying. Laser Doppler imaging may be of value in estimating depth. In *third degree* or full thickness burns, the entire thickness of dermis is involved. The burnt skin which is tough, dry, inelastic, translucent and parchment like with thrombosed veins visible underneath is called an eschar. These wounds are insensitive to pain as nerve endings are destroyed. The eschar generally separates in 3-5 weeks leaving a granulating, raw area, which undergoes wound contraction unless splinted and skin grafted. It is common to find all 3 types in the same wound. Sometimes a deeper subgroup of full thickness burns is referred to as *fourth degree* burns which extend down to muscle or bone and are caused by prolonged heat. These usually require reconstruction or amputation but fortunately these are rare and mostly occur with electrical burns.

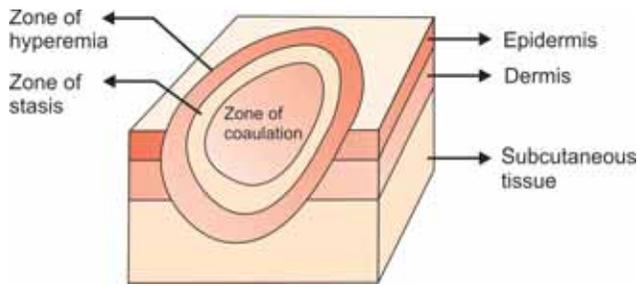


Fig. 42.6: Zones of burn injury

*Zones of injury:* Three zones of injury have been distinguished in burn-injured skin (Fig. 42.6). The outer *zone of coagulative necrosis* includes the tissue in most direct contact with the source and is irreversibly damaged, with no hope of recovery. The zone just below this is the *zone of stasis* which has some viable tissue. This zone is at risk for progression of the injury during resuscitation period unless adequate tissue perfusion is provided. The zone beneath this is the *zone of hyperemia* characterized by inflammation and increased blood flow.

*Inhalational injuries:* Inhalation injury may also sometimes occur in burns patients. It is usually due to inhalation of toxic products of combustion and not due to thermal injury as commonly thought. Clinical indicators of inhalation injury include face or neck burns, singeing of facial hair, carbon deposits and acute inflammatory changes in the oropharynx, hoarseness of voice or history of confinement in a burning environment. Inhalation of smoke and toxic gases leads to pulmonary complications including airway obstruction by bronchial casts, pulmonary edema, decreased pulmonary compliance and ventilation perfusion mismatch as well as systemic toxicity from CO poisoning and cyanide toxicity.<sup>8,9</sup>

CO poisoning may lead to headache, coma and death. Diagnosis is mostly made by a history of burns in enclosed areas. Carboxyhemoglobin levels may be checked and more than 10% is consistent with significant inhalation injury. High flow O<sub>2</sub> may be administered by a non rebreathing mask in these cases.

An assessment for associated injuries should also be made. In all major burns baseline determination of blood counts, serum glucose, serum electrolytes, and arterial blood gases should be done.

### Initial Management

It is convenient to categorize the burn patients as minor, moderate or critical for the purpose of establishing admission criteria.

### Critical Burns

1. Partial thickness burns >5 percent TBSA in infants and > 15 percent TBSA in older children.
2. Full thickness burns >3 percent TBSA.
3. Burns of special sites like hand, face and perineum.
4. Burns with associated injury, inhalation injury or any pre-existing illness.
5. Electrical burns need admission and observation because the full extent of deep damage may not be clear immediately.
6. Chemical burns.
7. Burns with concomitant trauma (such as fractures).

### Moderate Burns

1. Partial thickness burns 2-5 percent TBSA in infants and 10-15 percent TBSA in older children.
2. Full thickness burns 1-3 percent TBSA.

### Minor Burns

Partial thickness burns <2 percent TBSA in infants and <10 percent TBSA in older children.

Patients with minor burns are managed as out patients. All other patients are admitted and the critically burnt patients are preferably admitted to a specialized burn care facility. Burn injuries in cases of suspected child abuse and those requiring special social, emotional or long term rehabilitative intervention require admission in a specialized unit.

In the hospital, a quick estimate is made of the extent of burns. The respiratory status is assessed and associated injuries, if any, are evaluated. Intubation may be required if there is stridor or inhalation injury. If neck is burnt with swelling of tissues around the airway an early intubation may be considered. Also, if respiratory failure occurs with PaO<sub>2</sub> <60 mm Hg or PaCO<sub>2</sub> >50 mm Hg with optimal conservative management, intubation and ventilation is required. Adequacy of circulation and level of consciousness is assessed quickly. An intravenous line is established with an intravenous cannula. Central venous catheter is to be avoided, especially in the early phase, as it is associated with high risk of infection. Care must be taken to maintain temperature. Restoration of the blood volume is the single most important factor essential to the survival of a burnt patient in the initial period. Pain relief and sedation must be preceded by correction of hypovolemia and hypoxia as they are the cause of restlessness in a burnt patient. Morphine/pethidine/pentazocine and promethazine combination in appropriate doses are used intravenously (slowly) on 'as and when required' basis. After the initial shock

period is over, they may be given intramuscularly. For children with minor burns being treated on outpatient basis, paracetamol alone or its combination with nimesulide, etc., can be used.

Burns involving >5 percent TBSA in infants and >15 percent TBSA in older children are universally accompanied by paralytic ileus because of hypovolemia and neuroendocrine changes. Therefore, the child is given nothing by mouth, and if the stomach is already full, a nasogastric tube may be inserted for decompression, to prevent acute gastric dilatation. Oral intake is not restricted in children with less extensive burns. In fact, infants with <5 percent burns are encouraged to suckle their mother's breast. Many older children with less severe burns can also be completely resuscitated by using oral rehydration solutions and milk. Children admitted to the hospital should be given H<sub>2</sub> receptor antagonists (e.g. ranitidine) and antacids for prophylaxis against gastroduodenal erosions and ulcerations (Curling ulcers). In the absence of contraindications enteral feeds should be initiated within 24 hours.

Tetanus toxoid is given for prophylaxis against tetanus along standard recommended lines. In children not properly immunized, passive protection is also provided with 250 units of tetanus immunoglobulin.

In circumferential third degree burns of the chest and limbs it is necessary to perform escharotomies to prevent respiratory embarrassment and limb ischemia. This is generally done 'bedside' or in dressing room as the eschar is painless and does not require any anesthesia/analgesia.

Weight of the patient is recorded because it is an important factor in calculating the amount of intravenous fluid required. An indwelling catheter is placed for monitoring hourly urine output which is the single most important clinical parameter of adequacy of resuscitation. Average urine output must be maintained at 1 ml/kg body weight/hour to be considered adequate. Other variables to judge the state of hydration and appropriateness of fluid and electrolyte therapy are hematocrit, pulse rate, blood pressure (difficult to measure with extremity burns), body weight, levels of blood urea and electrolyte and urinary specific gravity.<sup>10,11</sup> In patients with hemoglobinuria or myoglobinuria the urine should be maintained at an alkaline pH by infusing sodium bicarbonate solution. Urinary catheter patency must be ensured before labelling a patient oliguric. Low urine output is treated by administering more fluids rather than by giving diuretics. However, a single dose of intravenous mannitol or furosemide may be required for persistent oliguria resistant to fluid therapy to rule out renal shutdown. Once a diuretic has been given, urinary

output cannot be relied upon to judge the adequacy of resuscitation. In contact electrical burns, where there may be a lot of muscle damage, myoglobinuria may occur in addition to hemoglobinuria. To clear these pigments and prevent renal tubular blockade, intravenous mannitol is administered every 6-8 hours till the urine is clear.

Blood transfusions are not required in the first 48 hours unless the child is severely anemic. It may be required later to maintain hematocrit between 30 and 35 percent and a hemoglobin level of more than 10 g/dl.

### Fluid and Electrolyte Therapy

Following a burn injury there occurs an increased capillary permeability which leads to leakage of protein rich plasma like fluid into the extracellular space. In extensive burns (involving >30 percent TBSA) this phenomenon is not limited to the burnt area but occurs throughout the body. Several vasoactive mediators have been implicated for this response including histamine, serotonin, kinins, arachidonic acid metabolites (thromboxane A<sub>2</sub> and leukotrienes), fibrin degradation products, etc. Capillary integrity gets restored within 24 hours of injury.<sup>12</sup>

Effective fluid therapy aims at restoring blood volume, maintaining acid-base and electrolyte balance, and preventing organ dysfunction. Several fluid regimens have been advocated but they all need to be modified in response to patient's vital parameters. Because capillaries are permeable to even larger molecules, like albumin, it is generally agreed that the initial resuscitation should be with colloid-free fluid formulae. If colloids are used, they leak into interstitial space due to increased capillary permeability caused by the burn injury. After the capillary permeability is restored, they help in increasing the tissue edema. However, albumin or plasma may be given to children with extensive burns after the first 24 hours or so. All formulae for resuscitation have been devised on adults and consequently they tend to underestimate requirements in children who have a larger surface area in relation to body weight. The most popular formula today is Parkland's formula.<sup>13,14</sup> According to this, in first 24 hours, Ringer's lactate solution is infused in a volume 4 ml/kg body weight/percent of TBSA burn. Half of the calculated requirement is transfused in first 8 hours, ¼ in the second eight hours and the remaining ¼ in the last 8 hours. The time periods are calculated from the time of burn and not the time of admission. In children below 40 kg in addition to this formula, maintenance intravenous fluids should also be administered (by Holiday Segar). In the second 24 hours the

fluid requirements are approximately halved and resuscitation is followed up with 5 percent dextrose in combination with N/4 or N/2 saline.

*Fluid creep phenomenon (Pruit):* Excessive volumes are being used for resuscitation with increasing frequency in many burn centers. The demand for more fluids may be increased due to administration of benzodiazepines and narcotics which cause vasodilation and discrepancy between intravascular volume/capacity of intravascular space. This phenomenon of administration of fluid volumes  $>4$  ml/kg% burn is known as 'fluid creep' and is associated with complications such as increased compartmental pressures, ARDS and multiorgan dysfunction. Despite success of various resuscitation approaches, 'optimal' fluid requirement still remains a matter of debate. Whatever the approach, it is important to dynamically titrate fluids to the individual patient to prevent problems of over/under resuscitation.<sup>15</sup>

Plasma or albumin have been traditionally used after 24 hours as it can minimize hypoproteinemia. This is significant when the burnt area exceeds 40% BSA. Albumin is given in a volume ranging from 0.3-0.5 ml/kg/percent of burn surface area. Demling and others demonstrated experimentally that the rate of edema formation was maximal at 8 to 12 hours after injury.<sup>16</sup> Except for a transient loss of capillary integrity, nonburn tissues soon regain the ability to sieve plasma proteins. The middle of the road approach of administering 5% albumin routinely in the second half of the first 24 hours is gaining popularity.

Although injured and burnt cells release potassium, hyperkalemia is noticed rarely. With adequate resuscitation, the excess potassium is effectively excreted. Additional potassium is only occasionally necessary during the diuretic phase. A close watch is maintained on serum electrolyte levels because rapid fluid and electrolyte shifts in burnt children can result in cerebral edema and convulsions.<sup>17</sup> From third day onwards the child is gradually started on liquid semisolid and solid diet over a period of 3-4 days with corresponding reduction in or omission of intravenous fluids. During this period, the patient should be watched for vomiting, paralytic ileus, abdominal distention, return of bowel sounds and activity and passage of stools. As the capillary permeability is restored, urinary volumes far exceed the total of oral and intravenous intake due to return of fluid from the extracellular compartment into the intravascular compartment.

### Systemic Antibiotics

A burn wound provides large, warm, moist and protein-rich medium for growth of microorganisms

from endogenous and exogenous sources. The patient is also more susceptible to infection due to a depressed immune system. Consequently, sepsis is the leading cause of death from burns.<sup>18</sup> Routine use of prophylactic systemic antibiotics, however, is not recommended as it leads to rapid emergence of resistant strains. For protection against beta hemolytic streptococcal infections especially in children, it was earlier recommended that crystalline penicillin should be used prophylactically for first 5 days following burns, but with changing wound flora and with emergence of new strains even this has been discontinued at many centers. However, the author's center still uses this antibiotic.

Routine bacteriological monitoring of the burn wound is carried out with surface swab cultures. Burn wound biopsies have been used to provide a quantitative estimation of the bacteria in the wound and infection is diagnosed when  $10^5$  bacteria are present per gram of tissue or there is invasion of subjacent healthy tissue. Local signs of burn wound sepsis include development of black or purple necrotic areas in the wound and hemorrhage in subeschar fat. Bacteria generally isolated in the burn wound are *Pseudomonas*, *Klebsiella*, *Staph. aureus*, *Strep. faecalis*, *Proteus* and *E.coli*. They are responsible for the septicemia which is the single, most important cause of death in burns all over the world. Fungi and viruses are also being increasingly isolated. Septicemia in burns can also result by invasion of bacteria from the respiratory tract, indwelling cannulae, catheters in urinary tract and sometimes from gastrointestinal tract. Whereas no clinical sign is diagnostic of septicemia, it is clinically suspected with a change in condition of the wound, presence of hyper or hypothermia, deterioration in level of consciousness, tachypnea, tachycardia, abdominal distention, diarrhea and oliguria. Although infection is accompanied by fever and leukocytosis, burn wound sepsis may manifest with hypothermia and leukopenia.

Systemic antibiotics are the mainstay of treatment. If the culture and sensitivity reports are available the appropriate antibiotic treatment is directed towards the identified bacteria. Otherwise, antibiotics are started in broad-spectrum combinations (e.g. cephalosporin and aminoglycoside) empirically, pending culture reports. Antibiotics are started at the first sign of sepsis, in maximal therapeutic doses and stopped only after seven days or so. The antibiotics useful in septicemia are penicillins (including carbenicillin, piperacillin and amoxicillin with clavulanic acid), third generation cephalosporins (e.g. ceftazidime, cefotaxime, ceftriaxone, cefoperazone), aminoglycosides (e.g. gentamicin, tobramycin, amikacin, netilmicin), quinolones (ciprofloxacin, ofloxacin, etc) and carbapenems (meropenem and imipenem).

## Nutrition

An extensive burn is characterized by hypermetabolism, increased heat loss, accelerated tissue breakdown and erosion of body mass proportional to the extent of burns. Children are at a special risk because of higher basal metabolic requirements, increased body surface area in relation to weight, decreased endogenous caloric reserves and increased requirements for growth and development. Malnutrition and hypoproteinemia lead to a lowered resistance and a delay in wound healing. Hypermetabolism can be minimized by keeping the child in a warm environment (32°C) and by use of occlusive dressings to limit evaporative losses. Excessive evaporative water loss results in an expenditure of 0.5 kcal/g of water lost. Preventing hyperpyrexia and treatment of sepsis also help in limiting metabolic requirements.

Enteral route is preferred for nutritional support and is generally available. It should be started as soon as initial burn resuscitation is complete; even within first 24 hours if no contraindication. Oral feeding is usually instituted by third post-burn day and by the fifth day it is increased to meet the predicted calorie requirements. If the child is unable to take orally, a nasogastric tube may be placed, through which freshly prepared feeds, at body temperature, can be given as a drip. The feeds should have 1 kcal/ml and a low osmolarity (300-700 mOsm/L) or else they lead to osmotic diarrhea. Fat intake of < 20% of overall caloric intake and Vitamin A supplementation reduce the incidence of diarrhea in burn victims. Parenteral alimentation or supplements are necessary if the child is having vomiting, diarrhea or malabsorption. Parenteral alimentation is done with 10-20 percent dextrose solution, with emulsified fats and amino acid solutions.

The daily caloric requirements in children can be estimated by the following formulae:

- i. *Curreri's formula*:<sup>18</sup> 60 kcal/kg body weight + 35 kcal/percent burn, and
- ii. *Carjaval's formula*:<sup>19</sup> 2200 kcal/m<sup>2</sup> of burnt area + 1800 kcal/m<sup>2</sup> of BSA.

Along with calories, an adequate amount of protein is given. Higher protein intake leads to better neutrophil function and improves resistance and survival. A calorie: nitrogen ratio of 100-150: 1 should be maintained. One gram of nitrogen is equivalent to 6.25 g of protein. These formulae overestimate requirements by 20 percent and should be used as target levels only. Diets calculated in the above manner can lead to positive nitrogen balance and prevent weight loss. Dietary supplements of vitamins and trace

elements including zinc, copper, chromium and molybdenum are also important for wound healing and given orally or in intravenous fluids.

## Management of the Burn Wound

A burn wound is an area of coagulative necrosis with ischemia of the surrounding tissue from thrombosis of underlying microcirculation. The aim of local treatment is to prevent microbial colonization and proliferation and allow a partial thickness burn to heal spontaneously or else prepare a full thickness burn for skin grafting. Bacterial growth can be prevented by a number of topical antibacterial agents. In extensive burns, it is essential that the topical agent used should not only be a broad spectrum agent but it should also effectively penetrate the eschar for control of infection at that level, which is actually responsible for sepsis. Because of impaired microcirculation the systemic antibiotics cannot reach this level in sufficient concentration to limit bacterial growth.<sup>20</sup>

### Topical Therapy<sup>21</sup>

Silver sulphadiazine, introduced by Charles Fox in 1968, is available as 1 percent cream and is the most commonly used topical agent all over the world. It is a broad spectrum chemotherapeutic agent, bactericidal to a wide range of bacteria known to colonize the burn wound, including *Pseudomonas*. It is applied as 0.5-1.0 cm thick layer and is painless. Transient leukopenia can occasionally result from its use. Cerium sulphadiazine has been developed for better control of Gram-positive infection. Similarly, it is claimed that zinc sulphadiazine can hasten epithelial proliferation.

The next most commonly used topical agent is nitrofurazone. It is also effective against a variety of Gram-positive and Gram-negative organisms but it penetrates the eschar less readily. Sensitivity reactions can also occur in about 5 percent of patients. In burn units, it is recommended, that this agent be periodically alternated with silver sulphadiazine to prevent development of bacterial resistance with either agent.

Mafenide (Sulfamylon) cream (11.1%) and silver nitrate solution (0.5%) are other topical agents used specifically in burns. Sulfamylon has a wide anti-bacterial spectrum and also penetrates the eschar readily. It is used as a substitute to silver sulphadiazine to control burn wound sepsis but unfortunately it is still not available in India. Its application is however, painful and being carbonic anhydrase inhibitor it can also lead to metabolic acidosis. Application of silver nitrate is tedious

and it penetrates the eschar rather poorly. It can also lead to methemoglobinemia, and electrolyte disturbances by leaching cations into the wound.

A combination of neomycin, polymyxin and bacitracin, or povidone-iodine or framycetin containing ointments and creams are recommended in cases of minor burns only. Although, povidone-iodine can sometimes be used in extensive burns to alternate with silver sulphadiazine, its routine use in these cases can lead to iodine toxicity.

#### *Dressing Technique*

The burn wound is gently cleaned with dilute cetavlon and saline solutions and mopped dry. A topical chemotherapeutic agent is applied and covered with a single layer of vaseline gauze (non-stick). Next, Gamgee pads (thick cotton sandwiched between layers of gauze) are applied and held in place with a gentle compressive dressing. The dressings are changed, atleast, daily. Soakage of dressing, foul smell and fever are indications for an earlier inspection of the wound.

Areas like face, perineum, and buttocks cannot be dressed and are kept exposed.<sup>22</sup> After cleaning, the wound is left to dry. The exudate along with the superficial layer of burned skin forms a protective cover under which a partial thickness wound can heal. This technique can also be used if only one surface of the body is burnt. However, it is not practical to manage extensive burns by this method.

#### *Burn Wound Excision*

By conventional dressing techniques, a deep dermal wound heals by hypertrophic scarring and a full thickness burn is ready for grafting after only 4-5 weeks time, leaving the patient with the attendant risk of septicemia and a prolonged period of negative nitrogen balance. Improvement in intensive care management has allowed surgeons to be positively aggressive towards the burn wound.<sup>23,24</sup> This involves excising the dead skin, layer by layer, till a healthy tissue is reached (tangential excision) which can then be immediately split skin grafted. If enough autograft skin is not available, then the excised wound is covered temporarily with a skin substitute to prevent plasma loss by exudation. Burn wound excision is done after the patient has been fully resuscitated but before significant bacterial proliferation has occurred. This is usually between 3rd to 7th day following the burn. This approach requires patient selection, an experienced team, sufficient operating time, and adequate blood, auto graft skin and skin substitutes. Even then, the technique is not generally practiced in

small children for the fear of causing physiological imbalance. Circumferential burns are associated with a unique problem of compromising blood flow to underlying viable tissues due to edema and lack of elasticity of the burn wound. Hence they require escharotomies (incision through eschar) to release subeschar pressure and relieve compartmental syndromes.

#### *Skin Grafting*

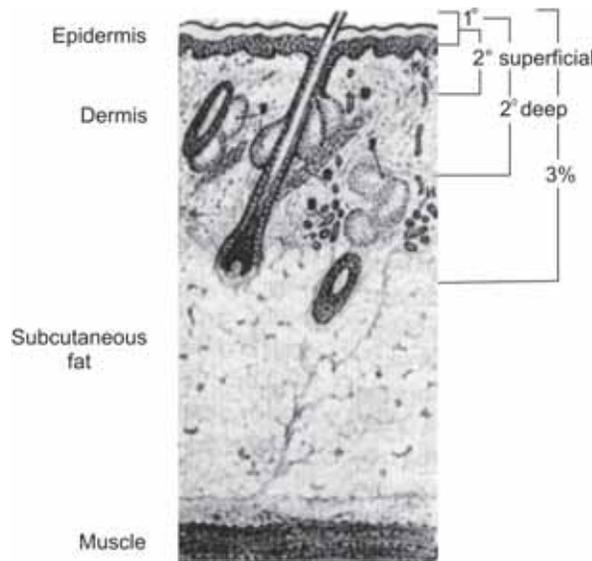
A full thickness burn will ultimately require autograft skin for permanent cover. Split skin graft can be harvested from any part of the body with a Humby's knife or a dermatome. The wound has to be adequately prepared to receive the graft. The donor area heals spontaneously from epithelial remnants in dermal appendages. Skin grafts can be applied as small stamps, strips or large sheets depending on the availability of the graft. Presence of beta hemolytic *Streptococci* is an absolute contraindication to skin grafting whereas *Pseudomonas* and *Staphylococcus* infections are relative contraindications.

#### *Care of Healed Burn Wound*

Once a burn wound has healed, either spontaneously or by skin grafting, it needs care. The patients usually complain a lot of itching, which is worse at night, in spontaneously healed areas and the donor sites of split skin grafts. Itching may be relieved by the use of oral antihistaminic drugs. There is also a tendency for hypertrophic scar formation in healed deep dermal burns. The healed burn wounds should be massaged with bland oils/cream (e.g. coconut oil) and pressure garments may have to be worn for a period of 9 months to one year to prevent/treat hypertrophy formation. Exposure to sunlight (ultraviolet rays) should be strictly avoided till the healed wounds regain their normal pigmentation/coloration, generally a period of 3-4 months, to avoid hyper pigmentation.

#### **Skin Substitutes**

A number of skin substitutes are available which can provide temporary wound coverage.<sup>25,26</sup> Because they adhere to the wound surface, they reduce pain and prevent exudative losses. They can also reduce bacterial proliferation and prepare a wound for autografting. If they are used to cover a partial thickness burn, they may aid the healing process. They are also valuable in providing temporary cover following excisional surgery when enough autograft is not available.



**Fig. 42.7:** A vertical section through skin to illustrate the basis of classification of depth of burns

*Biological skin substitutes* like homografts (allografts), heterografts (xenografts) and amnion have traditionally had much appeal. Skin transplant from live donors or cadavers is still awaiting legislative regulation in this country. Besides, their use involves a careful exclusion of hepatitis, syphilis and AIDS. *Synthetic skin substitutes*, like Epigard, Biobrane, Hydron, Opsite, etc., though expensive, are appealing because of 'off the shelf' availability. In laboratories, *Keratinocyte* culture techniques provide epidermal sheet of 1 m<sup>2</sup> in three weeks time, from a 1 cm<sup>2</sup> autograft. Although, it provides wound cover, it lacks skin texture because of the absence of a dermal layer. Burke and Yannas.<sup>27</sup> developed a bilaminar, *biosynthetic substitute* to simulate skin. This 'artificial skin' consists of an epidermal layer made from silastic and a dermal layer from bovine and shark collagen. It can be stored in 70 percent isopropyl alcohol. After removing the silastic sheet, autografts or cultured keratinocytes can be placed on the neodermis to complete the wound coverage.

### Factors Affecting Mortality in Burns

A number of factors affect the prognosis in a burn patient. The likelihood of death is inversely related to age in children. Higher the extent and deeper the burn injury, greater is the mortality (Fig. 42.7). Flame burns are generally associated with higher mortality as compared to scalds. The risk of death rises sharply with concomitant inhalation injury. Management of extensive burns is extremely expensive and often

prolonged. The poor socioeconomic status is certainly a contributing factor in increasing the mortality.

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Drowning is a major global public health problem. The global mortality rate from drowning is 6.8 per 1000,000 person – years.<sup>1</sup> In India the mortality rate from drowning is 8.5 per 1000,000. It is the second leading cause of accidental death in children. It is one of the most tragic conditions seen in pediatrics and the fact that most episodes are preventable by simple measures adds to the tragedy.

#### Definition 2000 World Congress on Drowning and WHO

Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid.<sup>2</sup>

Drowning affects all age groups throughout the world, but certain groups are particularly vulnerable. Infants 6 to 11 months of age largely drown in bathtubs. Older infants and toddlers may drown as a result of a fall into a shallow body of water such as wading pools, bathtub, buckets, etc. Large storage vessels and sumps are a common cause of drowning in our country. Events in the adolescent age group are related to recreational water activities—swimming, boating, etc. Certain medical conditions may predispose children to submersion—Seizure disorder, long QT syndrome or other channelopathies.

#### PATHOPHYSIOLOGY

Once submersion occurs, all organs and tissues are at risk for hypoxia. In minutes, hypoxia can lead to cardiac arrest, adding ischemia to the succession of events.

This global hypoxic ischemic injury is a common mechanism associated with drowning with the severity of injury primarily dependent on its duration. It is the magnitude of the hypoxic insult, as well as the body's ability to endure and recover from oxygen deprivation, that ultimately affects the patient's chances for survival and good neurological outcome.

The clinically described sequence of events after submersion comprises an initial period of panic, violent struggle, automatic swimming movements followed by

breath holding or laryngospasm. After a while, swallowing of large amounts of water occurs once the victim loses muscle tone. Subsequently, larger quantity of water is aspirated into the lungs. As a result of attempts to breathe as well as due to hypoxic termination of laryngospasm, water then passively enters the lungs.<sup>3</sup>

Much has been said about the type of water that is aspirated. The respiratory disturbance depends less on water composition and more on the amount of water aspirated.<sup>4</sup>

Fresh water is hypotonic in comparison with plasma and hence is rapidly absorbed across the alveoli into the circulation. This causes hypervolemia and hemodilution resulting in hyponatremia and hemolysis. Salt water (sea water) is hypertonic and hence water is drawn into the lung from the circulation resulting in pulmonary edema, hypovolemia, hypernatremia and hemoconcentration.<sup>5</sup>

Most victims are intravascularly hypovolemic because of excessive capillary permeability secondary to endothelial damage from hypoxia and the loss of protein rich fluid into the third space.

#### Pulmonary Effects

Functional residual capacity (FRC), is the only source of gas exchange at the pulmonary capillary level in the submerged state. Increased metabolic demands because of struggling, breath holding, a depletion of FRC from breathing, efforts results in seriously compromised O<sub>2</sub> uptake and CO<sub>2</sub> elimination, with consequent hypoxia and hypercarbia. A combined respiratory and metabolic acidosis caused by hypercapnia and anaerobic metabolism subsequently develops.<sup>6</sup>

If the victim is rescued prior to fluid aspiration, this hypoxia and acidosis tend to resolve rapidly as lung damage and pathophysiologic changes are minimal.

Aspiration of fluid into the airway triggers a cascade of pathophysiologic events resulting in persistently abnormal gas exchange. There is a significant

ventilation/perfusion mismatch and diffusion defect leading to intrapulmonary shunting.<sup>7</sup>

The surfactant system of the lung is affected differently in fresh water and sea water aspiration. Fresh water causes surfactant to denature and become non-functional. Sea water either dilutes surfactant concentrations or washes the surfactant out of the alveoli entirely. This results in alveolar instability, atelectasis and decreased lung compliance.<sup>8</sup>

Large and small airway dysfunction may occur, exacerbating gas exchange problems by trapping gas. In combination, these processes create the clinical syndromes of acute lung injury and later acute respiratory distress syndrome (ARDS). Aspiration of gastric contents may add caustic injury to airway and alveoli, worsening gas trapping and hypoxemia. Neurogenic pulmonary edema may contribute to deficits in gas exchange and lung function.<sup>9</sup>

### Cardiovascular Effects

The two integral components of oxygen delivery, namely the arterial O<sub>2</sub> content and cardiac output can be affected by the immersion episode. A decrease in PaO<sub>2</sub>, if sufficiently severe, decreases O<sub>2</sub> saturation and therefore arterial O<sub>2</sub> content. Cardiac output can be affected by decreased stroke volume. Cardiogenic shock can result from hypoxic damage to the myocardium. Metabolic acidosis can further impair myocardial performance.<sup>9</sup> Life-threatening dysrhythmias such as ventricular fibrillation or tachycardia and asystole may result from hypoxemia.<sup>10</sup>

The hallmark of cardiovascular dysfunction with submersion injury is shock. Systemic and pulmonary vascular resistances are raised with hypothermia and sympathetic activity associated with the diving reflex. With these processes, ventricular end diastolic pressures are raised, as are arterial pressures, with resultant congestion of central and pulmonary veins. Myocardial contractility is diminished with hypoxemia. Poor myocardial contractility, in combination with raised systemic vascular resistance (afterload on the heart), results in lower cardiac output. The clinical examination is one of “cold shock” with poor perfusion and end organ dysfunction.

### Renal, Hepatic and Gastrointestinal Effects

Multisystem failure can result from the hypoxic ischemic insult.<sup>11</sup> Renal dysfunction is secondary to anoxic injury to kidney and can result in acute tubular

necrosis. Albuminuria, hemoglobinuria, hematuria, oliguria and anuria can occur.<sup>12</sup>

Liver dysfunction is manifested by elevation of bilirubin levels, elevated transaminase levels and impaired production of procoagulant factors. It can also lead to disseminated intravascular coagulation.

Gastrointestinal injury is manifested as mucosal sloughing due to ischemia resulting in foul smelling bloody mucus filled stools. This can result in bacterial translocation and perforation of the GI tract.

### CNS Effects

CNS injury is the most important determinant of outcome. The severity of brain injury depends on the magnitude and duration of hypoxia. The most important sequelae of submersion injuries is global hypoxic ischemic brain injury.

Progressive oxygen depletion and impaired neuronal metabolism result in loss of consciousness. General pathogenic mechanism have been described for the CNS injury. These include increased intracranial pressure, cytotoxic cerebral edema, excessive accumulation of cytosolic calcium and oxygen derived free radical damage.<sup>13</sup> At the biochemical level the primary insult is due to ATP depletion which is a likely trigger for a number of pathogenic cascades as ATP is necessary to maintain neuronal metabolic functions and ionic gradients.<sup>14</sup>

The combination of hypoxemia and low flow states results in a host of pathologic processes, including energy failure, lipid peroxidation, production of free radicals, inflammatory responses and release of excitotoxic neurotransmitters. Disruption of neuronal and glial functions and architecture occurs.

### Hypothermia and Diving Reflex

The most important effect of severe hypothermia is a decrease in energy utilization. Cerebral metabolism is depressed and oxygen consumption reduced.<sup>15</sup> Hypothermia also increases the blood viscosity from hemoconcentration. The oxyhemoglobin dissociation curve shifts to the left. Hypothermia decreases white blood corpuscle (WBC) function and so there is increased risk of infection.<sup>16</sup> Hypothermia also decreases insulin production and impairs tissue glucose utilization resulting in hyperglycemia.<sup>17</sup> Diving reflex acts as an oxygen conserving adaptation in response to submersion. It appears to be triggered by breath holding and cold stimulation.<sup>18</sup> Cerebral blood flow is maintained while blood flow to gastrointestinal tract, skin, muscle, etc. is markedly reduced.

### Rescue and Resuscitation

The most important step in the rescue of a drowning victim is the immediate institution of resuscitative measures.<sup>19</sup> For the apneic victim, pulmonary resuscitation should be commenced as soon as the rescuer reaches the victim and quickly makes an assessment. For a victim who is far from shore or away from the side of a pool, pulmonary resuscitation must be instituted where the victim is retrieved, instead of rushing the victim to shore for assessment and pulmonary resuscitation.

The goal is to improve tissue oxygen delivery as rapidly as possible in order to minimize cerebral hypoxic-ischemic damage. Improving oxygen delivery optimally begins at the scene and continues during transport to a medical facility.

The full extent of CNS injury cannot be determined immediately after rescue and therefore all victim should receive aggressive basic and advanced life support at the site of the accident and in the emergency room. Prompt and effective management of hypoxia and acidosis is the key-determining factor of survival and maximal neurosalvage.

The success or failure of CPR (cardiopulmonary resuscitation) at the site of the accident often determines the outcome.<sup>20</sup>

### Management at the Scene

After the initial rescue, assessment of ABC's should be done to ensure the adequacy of airway, breathing, and circulation, which is the goal of BLS (basic life support). CPR should be initiated after removal of any debris from the oropharynx. Mouth-to-mouth breathing may have to be performed. No attempt to drain the water from the lungs should be made before pulmonary resuscitation as this fluid will get absorbed anyway. Heimlich maneuver should not be performed as it may increase the risk of aspiration of regurgitated stomach contents.<sup>21</sup>

The hemodynamic status should be evaluated soon after the victim is removed from the water. If the patient is pulseless, closed-chest compression should be started. CPR should be continued for as long as needed during transport to an emergency care facility.

### Emergency Department Evaluation and Stabilization

As with any form of accidental injury, other forms of associated trauma must be considered. Occult injury to the head, cervical spine and other areas should be assessed. Maintaining adequate airway, respiration and

peripheral perfusion with continued attention to oxygenation, ventilation and cardiac performance should take priority. Oxygen saturation and ECG are to be monitored. If the patient has adequate respiratory effort, then supplemental oxygen is all that is indicated. The indications for endotracheal intubation include:

1. Loss of airway protective reflexes due to depressed level of consciousness.
2. A deteriorating neurological status.
3. Severe respiratory distress or severe hypoxia despite administration of supplemental oxygen.
4. Cardiorespiratory arrest.
5. Severe hypothermia (core temp < 30°C).

Early use of PEEP is effective in reversing hypoxemia.<sup>22</sup> PEEP improves oxygenation and ventilation by alveolar recruitment and increasing FRC of the lungs thus decreasing ventilation perfusion mismatch.

Hypovolemia is commonly encountered. Isotonic crystalloids (20 ml/kg) or colloids (10 ml/kg) should be given for intravascular volume expansion. Repeated assessments are important. CVP monitoring is extremely helpful for ongoing assessment and management of intravascular volume. If poor perfusion continues even after adequate expansion of the intravascular volume, inotropic support may be needed.

Mild to moderate metabolic acidosis will often resolve with improvement of oxygenation and tissue perfusion. In more severe cases, sodium bicarbonate administration intravenously may be required.<sup>23</sup> Arrhythmias can occur in the drowning patient. Common rhythms include bradycardia and asystole, atrial and ventricular fibrillation. The goal of cardiovascular stabilization is return of end organ perfusion. Continuous ECG monitoring should be performed.

The initial support of CNS is best accomplished by ensuring adequate oxygenation combined with circulatory stability. After establishing respiratory and circulatory stability, a brief but thorough neurologic examination should be performed. The Glasgow Coma score on arrival should be noted and will provide prognostic information.<sup>24</sup>

Cerebral edema and increased intracranial pressure often develop and should be managed conservatively with techniques aimed at reducing the ICP. The routine use of ICP monitoring is not indicated.

### Management

Hypothermia from cold water drowning presents a unique clinical challenge. Efforts at rewarming should be instituted as soon as possible. Wet clothing should be removed to prevent continued conductive heat loss. Active external rewarming should be instituted in

patients with core temperature greater than 30°C by using electric warming devices, hot water bottles, warm bedding and radiant heat sources.

If core temperature is less than 30°C, active internal rewarming is needed by using warmed intravenous fluids, warmed humidified oxygen, gastric or rectal lavage with warmed fluids and peritoneal lavage.<sup>25</sup> Hypothermic heart is resistant to the effects of defibrillation and cardiotoxic agents. Hence the patient should be aggressively rewarmed and repeat defibrillation attempted. Hypothermia slows renal and hepatic excretion of drugs and hence cardiotoxic drugs should be used with caution.

Most patients swallow a large amount of water and may vomit. Hence an orogastric tube should be inserted and the stomach aspirated. Children who do not regain full consciousness in the emergency department should be transferred to a pediatric intensive care facility where ongoing efforts should be to aggressively treat any cardiopulmonary dysfunction.

### Management in PICU

The drowning event is a global hypoxic-ischemic insult that results in multiorgan dysfunction. ICU management attempts to minimize secondary neurologic damage, from hypoxia, ischemia, acidosis, seizures activity, fluid electrolyte abnormalities (Table 43.1). A PaO<sub>2</sub> less than 60 mm Hg while on 50 percent O<sub>2</sub>, O<sub>2</sub> saturation less than 90 percent or worsening hypercapnea may indicate the need for ventilatory support. Most often a high PEEP is required. High frequency ventilation may be needed if respiratory failure is unresponsive to conventional mechanical ventilation.<sup>26</sup> Extracorporeal membrane oxygenation (ECMO) and administration of exogenous surfactant may be used in the treatment of severe lung injury and ARDS. Continuous vasoactive infusions may be required to treat myocardial dysfunction and correct abnormal peripheral vascular resistance. Treatment should concentrate on normalizing blood pressure, organ perfusion and gas exchange as quickly as possible. Frequent repeated examinations are necessary to detect deterioration in cardiopulmonary function. The routine use of prophylactic antibiotics has not been shown to be effective in preventing pneumonia. However, fulminant *S. pneumoniae* sepsis and pneumonia can occur and therefore empiric antibiotics may be administered to those patients with severe cardiopulmonary deterioration especially after a period of stability.<sup>27</sup> There is no role for the use of steroids in the management of aspiration pneumonia.<sup>28</sup>

### Prognostic Evaluation

Common sequelae leading to death from drowning include

- Brain death attributable to severe hypoxic ischemic brain injury
- ARD
- MODS
- Sepsis syndrome attributable to aspiration pneumonia or nosocomial infections.

The outcome of drowning victims depends largely on the success of resuscitative measures at the scene of injury. A number of studies have attempted to predict what variables affect a drowning victim's outcome. However, no prognostic scoring system to date has been found to be entirely accurate. Most victims who resume spontaneous respirations in the field, become responsive, have a sinus rhythm and have been submerged < 5 minutes in water warmer than 5°C, survive without neurological sequel. Those victims submerged in warm water who present in cardiac arrest may still have return of spontaneous circulation within 10 minutes and intact survival if aggressive prehospital care is given.<sup>29</sup> For victims submerged in non-icy water (75°F) the most reliable predictors of death or severe neurological sequel include:<sup>30</sup> (i) Unresponsiveness on arrival at the hospital; (ii) Elevated blood glucose level; (iii) Fixed pupils in the emergency room; (iv) Cardiac arrest requiring > 25 minutes of advanced life support; (v) Initial GCS less than 5; and (vi) Seizures, flaccidity. Orłowski constructed a prognostic scoring system using five criteria:<sup>31</sup> (i) Age younger than 3 years, (ii) Immersion time longer than 5 minutes, (iii) No resuscitation for 10 minutes, (iv) Coma at initial presentation, and (v) Arterial pH less than 7.1. A point was given for each item present. Patients with 2 or less poor prognostic factors had a 90 percent likelihood of good recovery with standard therapy, whereas patients with 3 or more poor prognostic factors had only 5 percent likelihood of good recovery.

### Predictors of Outcome<sup>32</sup>

Much of the clinical literature on drowning has focused on predictors of outcome.

*Victim related factors:* Associated with increased risk of death or poor outcome.

- Male
- Seizure disorder
- Alcohol use

**Table 43.1: Principles of management of children with submersion injury**

<i>At the scene</i>	
Initial rescue	Assess ABC Begin CPR <ul style="list-style-type: none"> <li>— Remove debris from oropharynx</li> <li>— Mouth-to-mouth breathing</li> <li>— No Heimlich maneuver</li> <li>— Chest compressions</li> </ul>
Continue CPR till reaching ER	
<i>In the ER</i>	
Establish adequate oxygenation and ventilation	Intubate airway of unconscious or hypoventilating children Provide supplemental oxygen
Establish normal circulation	Bolus IV fluids (NS) Vasopressor infusions for continued hypotension
Neurologic examination	Determine GCS Control seizures - (Lorazepam, Phenobarbital, Fosphenytoin)
Rewarming for hypothermia	Use warmed fluids and ventilation with heated gas Consider bladder wash with warmed fluids Consider cardiopulmonary bypass
<i>In the PICU</i>	
Employ ventilator strategies for ALI/ARDS	Limit ventilator peak pressures to < 25 torr Limit tidal volume to 6-8 ml/kg Limit fraction of inspired O <sub>2</sub> to < 0.6 Liberal use of PEEP Consider the use of exogenous surfactant or ECMO for continued hypoxemia
Treat myocardial dysfunction	Titrate vasoactive infusions to obtain normal cardiac output adequate end organ perfusion
Employ brain protective strategies	Avoid hyperthermia Use mild systemic cooling (35-36°C) for 24-48 hrs. Treat clinical and subclinical seizures Frequent neurologic reassessments and adjunct studies of function as indicated

- Incident related factors
- Prolonged duration of submersion
- Failure to receive bystander CPR
- Acute resuscitation efforts lasting > 25 min

*Factors identifiable at hospital admission*

1. Level of consciousness – especially if unconsciousness is prolonged
2. Elevated serum glucose
3. Hypothermia
4. Signs of brain dysfunction – absent pupillary reflex
5. Absent spontaneous respiration
6. PRISM scores.

### Prevention

No discussion of drowning would be complete without mentioning the importance of 'prevention'. Drowning episodes produce global hypoxia, with the CNS being

particularly sensitive to the effects of decreased tissue oxygenation. Until more effective neuronal salvage techniques are available, prevention of the submersion event itself is the most powerful tool available. Increased awareness and attention to drowning prevention measures are important.

Children should never be left unattended near any waterbodies. Floatation devices are never a substitute for supervision. Swimming pools should be fenced and life saving equipments should be readily available. CPR instructions should be posted near the pool area.

Effective prevention measures of drowning requires programs and policies that address known risk factors.

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Fever is elevation of core body temperature above 38°C (100.4°F).<sup>1</sup> The importance of fever relates to the underlying disorder that it represents, and not on fever as a harmful entity itself. Nevertheless, fever increases the demand for oxygen and can aggravate pre-existing cardiac or pulmonary insufficiency. It is estimated that there is a 13 percent increase in O<sub>2</sub> consumption for every increase of 1°C temperature over 37°C.<sup>2</sup> Therefore, treatment of fever in some patient groups who are at risk of cardiopulmonary decompensation because of increased metabolic demand is recommended. In addition, elevated temperature can induce mental changes in patients with organic brain disease. Children with a previous febrile seizure may also require antipyretic therapy aggressively; however, the clear benefit of such therapy on reducing the recurrence of febrile seizure has not been found.

An extraordinarily high fever (above 41.5-41.7°C) is called hyperpyrexia. Hyperpyrexia is a medical emergency and is associated with multi-system tissue damage and organ dysfunction. Hyperpyrexia can be observed in patients with severe infections, but it is most commonly a result of hyperthermia which occurs due to environmental heat exposure and certain pharmacological agents.<sup>2</sup> In contrast to fever, hyperthermia is relatively uncommon in children and is most commonly seen in athletes, laborers, and military recruits in hot and humid climates. However, infants and children are more vulnerable to deleterious effects of hyperpyrexia because of a higher surface area to weight ratio, inability to control environmental stresses and compromised sweating mechanisms especially in preterm newborns.

For a better understanding of pathophysiology of heat illnesses, a pertinent reference to thermoregulatory mechanisms would be useful at this juncture.

### Thermoregulation

Humans produce enormous amount of heat during metabolism and may easily be considered as biochemical furnaces. In the absence of cooling mechanisms, this heat production is likely to raise body temperature by

approximately 1.1°C per hour.<sup>3</sup> This heat production increases manifold during strenuous exertion and in condition of high environmental temperature. This heat is lost from body by means of conduction, convection, radiation and evaporation. Conduction is the transfer of heat from warmer to cooler object by means of direct contact between the two. Thermal conductivity of water is 32 times that of air, therefore temperature loss during cold water immersion is rapid making it the main modality of treatment of heatstroke.<sup>4</sup> Convection is the heat lost to air and water vapor molecules circulating around the body. Loose clothes and rapid wind movement maximizes convective heat loss. Radiation is heat transfer by electromagnetic waves. Radiation is a major mode of heat loss in cool environments; however, in hot climates it is also a major source of heat gain thus making it important in pathogenesis of heatstroke. Evaporation of sweat from skin is the most important mechanism of cooling in hot conditions. The net effect of all these could be summarized in a formula for heat transfer:

$$S = M \pm R \pm C - E$$

S = Rate of heat storage or loss

M = Heat production as the sum of all heat resulting from basal metabolism

R = Radiant heat exchange

C = Convective heat exchange

E = Evaporative heat loss

The human body temperature is regulated by means of complex anatomic and physiologic mechanisms. Thermosensors are located centrally in preoptic area of anterior hypothalamus and peripherally in skin. The central integrative area in the hypothalamus receives information from thermosensors and instructs thermoregulators. Peripheral vasodilatation and evaporation (sweating) are the major mechanisms to dissipate heat. Heat stress causes cutaneous vasodilatation thus allowing dissipation of heat effectively through convection and radiation. Evaporation of sweat is the most important mechanism of heat dissipation in warm environment. Human exocrine sweat glands have

enormous capacity to produce sweat. One gram of glands can produce about 250 grams of sweat daily.<sup>5</sup> Cooling effect is achieved by evaporation of this sweat from body surface. This cooling effect is minimized as humidity increases and at 100 percent humidity, evaporation is almost zero. Wind velocity increases evaporative loss from skin with maximum effect at wind velocity of 0.5 to 5 m/sec.<sup>6</sup>

### Predisposing Factors for Heat Illness

Human body's heat dissipation mechanisms can be easily compared with cooling mechanisms of an automobile (Fig. 44.1). Hypothalamus acts as a thermostat and acts by altering coolant (blood) flow by a system of pipes, valves and reservoirs (vasculature). The coolant is circulated by a pump (heart) from the hot inner core to a radiator (skin surface cooled by evaporation of sweat). Failure of any of these components may result in overheating. Overheating from prolonged operation (vigorous exercise) or working under extreme conditions (environmental factors) may overwhelm even a normally functioning cooling system. Figure 44.1 also depicts the analogy between the human and automobile cooling system and the disorders related to it.<sup>3</sup>

Infants and children are more vulnerable to deleterious effects of hyperpyrexia because of a higher surface area to weight ratio, inability to control environmental stresses and compromised sweating mechanisms,

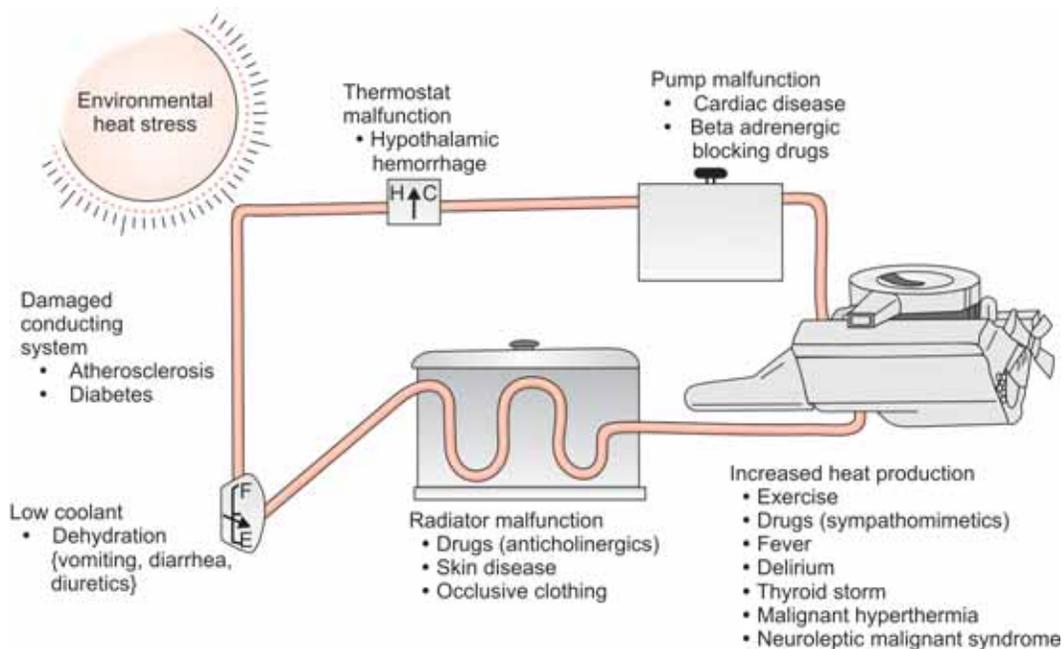
**Table 44.1: Thermoregulation in children in comparison to adults**

<i>Characteristic</i>	<i>Response of children compared to adults</i>
Ability to acclimatize	Adequate
Speed of acclimatization	Slower
Set point (change in rectal temperature at which sweating starts)	Higher
Sweating rate	Lower
Conditioning induced increase in sweating rate	Lower
Thermoregulatory impairment by dehydration	Greater

especially in preterm newborns.<sup>7</sup> Other characteristics of children which make them less efficient thermoregulators than adults are summarized in Table 44.1.

### Thermometry

Measurement of core temperature is important as it is the temperature which determines the body's response to heat stress. Glass mercury thermometers are traditionally the most common types used. Digital thermometer measurements also correlate well with glass mercury thermometer measurements and take less



**Fig. 44.1:** Analogy between human and automobile cooling system (adapted from reference 3)

time. Axillary temperature measurement correlates poorly with core temperature in heat illness. Oral measurement is affected by mouth breathing and thus is a poor approximation of core temperature. Lack of co-operation on part of child also affects the reading. Rectal thermometry is better but alters slowly to changes in core temperature because a large muscle mass insulates rectal area. Tympanic membrane measurements are faster and safe but lack reliability in detecting core temperature. Although esophageal thermistor catheter and pulmonary arterial (Swan Ganz) catheter temperature measurements are most accurate and reliable, these are too invasive to be taken routinely in practice. Thus rectal temperature measurements suffice for routine clinical use in cases of heat illness.

### Fever versus Hyperthermia

Fever is elevation of body temperature above the normal circadian variation as the result of a change in the thermoregulatory center located in the anterior hypothalamus. Fever is often a result of pyrogens—either exogenous or endogenous in response to infection or inflammation. This temperature elevation in most cases is not of any significance and the cause of fever is more important to be treated. However, if metabolic demand of fever is too high for the patient to tolerate, it should be controlled effectively. Antipyretics alone are effective in most cases. These drugs act by reducing the thermostat setting in hypothalamus. Paracetamol in doses of 15 mg/kg/dose used 4-6 hourly is an effective antipyretic. Ibuprofen in a dose of 10 mg/kg/dose and Nimesulide in a dose of 2.5 mg/kg/dose are equally effective but probably less safe. External cooling by means of tepid sponging and water immersion should

never be used alone for control of fever, as these modalities tend to oppose the reset thermostat of body. Body responds to this by vigorous shivering thus generating more heat, which further increases the metabolic demand and renders the cooling mechanisms ineffective. External cooling thus must be used in combination with antipyretics (which lowers the hypothalamic thermostat) to be effective in cases of high fever.

On the other hand, hyperthermia is elevated body temperature that occurs in presence of an unchanged hypothalamic set point. Exogenous heat exposure and endogenous heat production (vigorous exercise, certain pharmacological agents) are two mechanisms by which hyperthermia can result in dangerously high internal temperatures. Hyperthermia must be distinguished from fever as hyperthermia can be rapidly fatal and its treatment differs from that of fever. Hyperthermia characteristically does not respond to antipyretics. External cooling mechanisms are crucial in treatment of hyperthermia. Table 44.2 highlights the important differences between fever and hyperthermia.

### Minor Heat Illnesses

These illnesses include *heat cramps*, *heat edema*, *heat syncope*, *prickly heat* (Miliaria) and *heat exhaustion*. *Heat cramps* occur in over-worked muscles usually after exertion. These seem to be related to copious exertional sweating and subsequent ingestion of hypotonic fluids like water. This can be prevented and relieved by consumption of salt containing fluids. In severe cases, infusion of normal saline solution may be required. *Heat edema* characterized by swelling of feet and ankles are seen in elderly after long periods of sitting or standing. Underlying cardiac and hepatic disease must be

**Table 44.2: Differentiating features between fever and hyperthermia**

	<i>Fever</i>	<i>Hyperthermia</i>
Setting	Of infection	Of environmental exposure to heat
Temperature	Hyperpyrexia (> 41.5°C) rare	Hyperpyrexia (>41.5°C) common
Sweating	Profuse	Usually absent or minimal but may be present continuously
Skin	Moist	Dry, flushed
Shivering	Present	Absent
CNS dysfunction	Not because of fever itself Febrile seizures may occur	Common
Multiorgan dysfunction	Not because of fever itself	Present
Response to antipyretics	Marked	Absent

excluded by careful clinical examination. Simple leg elevation helps in most cases and edema resolves after several days of acclimatization. *Heat syncope* is characterized by pooling of blood in periphery and dilatation of cutaneous vessels resulting in decreased cardiac output while standing for protracted periods in hot and humid environments. There is cerebral hypoperfusion resulting in transient loss of consciousness and falling. This setting is commonly observed in students attending school prayer assemblies. It is a self-limiting condition as horizontal position assumed by fall cures the pathology. Maintaining the horizontal position and leg elevation should be done transiently. *Prickly heat* or *miliaria* is common in children as a result of blockage of sweat pores by macerated stratum corneum. Neonates are predisposed because of immaturity of sweat ducts. These rashes undergo four stages. *Miliaria crystallina* is formation of very small pruritic vesicles on an erythematous base. The involved area is anhydrotic. Over a few days, keratin plug fills the vesicles causing deeper obstruction of sweat duct (*Miliaria rubra*). This obstructed duct ruptures again producing a deeper vesicle in dermis (*Miliaria profunda*). This can get complicated by secondary staphylococcal infection (*Miliaria pustulosa*). Application of chlorhexidine and salicylic acid (1%) to the affected area assists in desquamation. Oral antibiotics may be used in secondarily infected cases. Miliaria is prevented by wearing loose, light and clean clothes, meticulous body hygiene and avoiding situations causing prolonged and profuse sweating. *Heat exhaustion* is characterized by volume (water) or salt depletion during conditions of heat stress. The symptoms are fatigue, headache, malaise, nausea, vomiting and vertigo. Tachycardia, orthostatic hypotension and clinical dehydration may occur. The core temperature is usually normal or mildly raised. CNS signs are characteristically absent in heat exhaustion; if present, the patient should be managed as heatstroke and other major illnesses are to be ruled out. Heat exhaustion is treated by rest in a cool environment and oral replacement of fluids by water and electrolyte solution (0.1 percent salt solution). Patients with clinical dehydration, dyselectrolytemia and orthostatic hypotension should receive slow infusion of saline containing solutions.

### Heat Hyperpyrexia (Heatstroke)

Heat hyperpyrexia or heatstroke is a medical emergency and unless appropriate therapeutic measures are usually taken urgently, it may be fatal in a significant percentage of cases. In contrast to the minor heat illnesses discussed above, there is a failure of homeo-

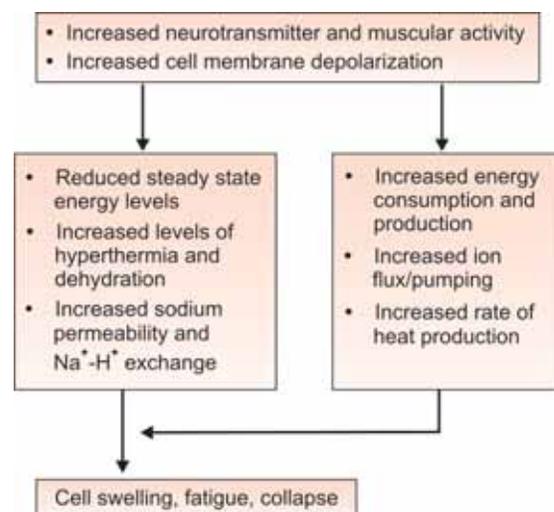
static thermoregulatory mechanisms in heatstroke raising the temperature to extreme levels ( $> 40^{\circ}\text{C}$ ) reaching the hyperpyrexia range ( $> 41.5^{\circ}\text{C}$ ). As discussed earlier, hyperpyrexia is less frequently observed in relation to serious systemic infections. Such an extreme elevation of temperature results in a multisystem tissue damage and organ dysfunction.

### Pathophysiology

The exact mechanisms causing the failure of thermoregulatory mechanisms in heatstroke remains unclear. Failure of sweating mechanisms which are the predominant body defenses against hyperthermia seem to be the primary culprit as supported by frequent clinical observation of dry skin in patients of heatstroke.<sup>8,9</sup> The energy depletion model (Flow chart 44.1) offers a possible explanation for this failure of thermoregulation.<sup>10,11</sup> This model suggests that increased heat production combined with increased ATP use and flux of sodium into the cell depletes the organism of energy for thermoregulation. The integrity of cardiovascular system and acclimatization to heat to augment evaporative heat losses are important to prevent this thermoregulatory failure. Thus, heat related cellular damage is a function not only of temperature but also of exposure time, workload, tissue perfusion and individual factors, which vary markedly.

Heatstroke is a multisystem disorder affecting almost all the organ systems. Neurological dysfunction is a hallmark of heatstroke and cerebral edema is common. Marked cerebellar Purkinje cell damage is also seen.<sup>12</sup> Petechial hemorrhages are seen in the walls of the

Flow chart 44.1: Energy depletion model  
(adapted from reference 10)



ventricles. Myocardial damage has been reported in cases of heatstroke and may be a key factor in individuals presenting as circulatory failure.<sup>13-15</sup> Heat stress causes tremendous burden on cardiovascular system. Cutaneous blood flow increases in response to heat stress to dissipate heat effectively. Splanchnic and renal vasoconstriction occurs as compensatory mechanisms to prevent functional hypovolemia. Nausea, vomiting and diarrhea may occur as a result of this compensatory mechanism. Ultimately, these compensatory vasoconstrictive mechanisms fail, thus reducing the mean arterial pressure. This reduction in mean arterial pressure combined with a raised intracranial pressure produce cerebral hypoperfusion resulting in the CNS dysfunction characteristic of heatstroke.

Hepatic damage associated with heatstroke is quite frequent. This is manifested as a rise in transaminases but clinical jaundice is less common. Pathologically, there is centrilobular necrosis and cholestasis. Acute tubular necrosis and acute renal failure may complicate 10-35 percent of patients of heatstroke.<sup>16</sup> Diminished renal blood flow because of compensatory splanchnic vasoconstriction, myoglobinuria and hyperuricemia due to rhabdomyolysis, hypotension, disseminated intravascular coagulation and direct thermal injury all contribute to glomerular and tubular damage resulting in acute oliguric renal failure. Coagulation abnormalities seen in severe heatstroke occur as a result of complex mechanisms which activate fibrinolysis, cause depletion of clotting factors and endothelial and platelet dysfunction.<sup>3</sup> Respiratory alkalosis and lactic acidosis are common metabolic derangements. Pancreatitis and elevated serum amylase levels have also been described.

### Clinical Features

Heat hyperpyrexia characteristically occurs in the hot and humid months of April to July in northern part of India.<sup>17</sup> There is usually a history of exposure to heat stress which is both endogenous and exogenous like playing outside in hot and humid weather. The onset of symptoms is usually sudden but a preceding fever of 1-2 days duration is also not unusual as febrile illness predisposes to heatstroke. Cases of heatstroke have occurred in young infants who were overclothed in a febrile illness.<sup>18</sup> Prodromal symptoms like headache, nausea, vomiting, diarrhea and dizziness may be observed in few cases. Core temperature is usually more than 41°C but sometimes may be lesser especially in newborns and young children where symptoms of heatstroke come at a lower threshold.<sup>17,19</sup> The classically described feature of heatstroke is presence of dry flushed

skin with absent sweating. However, sweating may persist in infants and children and presence of sweating does not preclude the diagnosis of heatstroke.<sup>20</sup> Young children sometimes present with shock with no cutaneous features of classical heatstroke. It is only when a rectal temperature is taken that the exact cause of shock is understood. Thus, it is imperative that a rectal temperature is taken in all cases of shock (with or without dehydration), especially in summer months.

CNS dysfunction is a hallmark of heatstroke and all children with heatstroke have signs of profound CNS dysfunction like confusion, tremors, delirium, coma or seizures. Profound muscular rigidity with tonic contractions, opisthotonus, decerebrate rigidity, oculogyric crisis and dystonic movements have also been observed. Pupils may be fixed and dilated. These changes are potentially reversible, although permanent damage can occur in severe cases.<sup>3</sup> The diagnosis of heatstroke should be considered in all such cases of profound CNS dysfunction whenever these occur in adverse environmental settings.

Cardiovascular manifestations include a hyperdynamic circulation, tachycardia and shock. Elevated CVP and right-sided cardiac failure may occur as a result of myocardial injury. Jaundice may occur but is usually obvious only 1-3 days after onset of heatstroke syndrome. Elevation of transaminases occur universally and early in the course of the disease.<sup>21</sup> Coagulation abnormalities are manifested as purpura, conjunctival hemorrhage, orificial bleeds and malena and their presence is associated with poor prognosis. Acute oliguric renal failure may occur. Urine is scanty, brownish and examination reveals proteinuria, abundant granular casts and red blood cells. Respiratory alkalosis, lactic acidosis, hypoglycemia, hypokalemia, hypernatremia and hypocalcemia are important metabolic derangements and require judicious management.

### Investigations

The diagnosis of heatstroke is mainly clinical and investigations are required only to exclude alternative diagnosis or to manage the complications. Blood glucose should be checked immediately with dextrostix and the blood should be drawn for complete blood count, electrolytes, blood urea, glucose, transaminases, calcium and arterial blood gas. The patient should be catheterized and urine output is to be measured.

### Differential Diagnosis

Initiation of cooling measures is the foremost in management of hyperpyrexia under conditions of heat stress. Rapid improvement in mental status and blood

pressure by cooling measures alone reaffirms the diagnosis of heatstroke. However, if there is no response in temperature or sensorium, alternative diagnoses like meningitis, encephalitis, cerebral malaria and Reye's syndrome should be considered. A careful history and thorough physical examination would help to exclude these diagnoses. Presence of shaking chills suggests a diagnosis of fever due to an altered hypothalamic set point rather than heat hyperpyrexia. Lumbar puncture should be performed in cases of doubt. The CSF in heatstroke is crystal clear with occasional lymphocytic pleocytosis and mildly elevated protein.

Certain drug overdoses like anticholinergic (Atropine), amphetamines and haloperidol produce illness resembling heatstroke. Anticholinergic (*Datura*) poisoning closely resembles heatstroke syndrome. Presence of dilated pupils is seen in all cases of anticholinergic poisoning while pupils are constricted in most patients with heat illnesses. Other serious systemic infections, typhoid fever and CNS hemorrhage sometimes resemble heatstroke. Measurement of hepatic transaminases might help as these are invariably elevated in heatstroke while remaining normal in most of above mentioned illnesses.

### Treatment

Heat hyperpyrexia is a medical emergency and must be managed aggressively to reduce the complications and mortality associated with it.

#### General Measures

1. **Airway** should be secured. Secretions should be drained and proper positioning should be done. Placement of Guedel's airway or endotracheal intubation may be required.
2. **Oxygen** administration at 5-10 liters/min. is provided, as the metabolic demands are very high in hyperpyrexia.
3. Secure intravenous line and give Ringer's lactate or N/2 saline through it.
4. Blood glucose should be checked by dextrostix and provide 25-50 percent dextrose in case of hypoglycemia.
5. Circulatory support should be provided initially by fluid pushes and later as guided by CVP.

#### Cooling Modalities

External cooling methods are the mainstay of treatment in heat hyperpyrexia and must be initiated as soon as possible. The patient is immediately removed from the

hot environment and all clothing should be removed. Rectal temperature is monitored every 5 minutes initially. Cooling efforts take precedence over any time consuming search for the cause of hyperpyrexia.

1. **Immersion in ice-water** keeping the head above is the preferred cooling modality and brings down the temperature rapidly ( $<39^{\circ}\text{C}$  in 10-40 min).<sup>22</sup> Although technically difficult, it has proven efficacy and extensive clinical experience to support its use. Ventricular fibrillation as a result of cold water immersion is very rare in heatstroke. Tap water immersion has been found to be effective in animals and may be used if iced-water is not available.<sup>23</sup>
2. **Evaporative cooling** by means of large circulating fans and skin wetting is also very effective but requires complex set-up (body cooling units) for it. The combination of atomized spray of tepid water ( $40^{\circ}\text{C}$ ) and standing fans have been shown to achieve comparable cooling.<sup>24</sup> However, ice-water immersion remains the preferred modality and must be employed if evaporative methods fail to achieve cooling below  $39^{\circ}\text{C}$  within 30 minutes.
3. **Adjunctive measures** like application of ice packs, vigorous skin massage to prevent vasoconstriction, cooling blankets, rectal, gastric or peritoneal lavage with cold water are mainly experimental modalities, which may be used in conjunction with the immersion or evaporative methods. However, if used alone they are not much effective and waste precious time before a more vigorous cooling method like immersion is employed.
4. **Cooling measures** should be discontinued once core temperature reaches  $39^{\circ}\text{C}$  to avoid hypothermic overshoot. However, continued monitoring of temperature is still necessary to maintain core temperature at  $37-38^{\circ}\text{C}$ .
5. **Antipyretics** like paracetamol and salicylates are not indicated in heat related illnesses and may be harmful as these worsen hepatic and hematological damage. However if the cause of hyperpyrexia is fever, antipyretics must be used in addition to external cooling modalities.

#### Management of Complications

1. **Circulatory support** must be provided initially with intravenous fluids like Ringer lactate, normal saline or N/2 saline. Hypotension in most patients is because of peripheral vasodilatation and responds well to external cooling methods. If this does not occur, fluid push is given rapidly while monitoring the blood pressure. Further fluid replacements should be guided by CVP as pulmonary edema also

occurs in heatstroke. Aggressive fluid replacement is continued in case of low CVP while low-dose isoproterenol infusion may be used if CVP is high. Alpha-adrenergic drugs are not recommended because they promote vasoconstriction thus decreasing cutaneous heat exchange.<sup>3</sup>

2. **Vigorous shivering** produced by cooling methods can be controlled by chlorpromazine. As this drug itself can cause hypotension and convulsions, it should be used only if cooling mechanisms fail because of vigorous shivering.
3. **Convulsions** should be controlled by intravenous diazepam. Phenobarbitone and phenytoin are also used if they tend to recur. Diazepam can also be used cautiously to sedate an agitated child while immersing in iced-water tub. Mannitol can also be used to reduce cerebral edema.
4. **Coagulopathy** should be treated by replacement therapy with fresh frozen plasma and platelets. The role of heparin therapy in DIC remains controversial.
5. **Renal failure** should be anticipated and the patient is to be catheterized to monitor urinary flow. Use of mannitol has been suggested to increase renal blood flow and minimize damage from myoglobinuria. Urinary alkalinization is also indicated in presence of myoglobinuria. Dialysis should be done whenever indicated.
6. **Metabolic derangements** like hypokalemia, metabolic acidosis (pH < 7.2) and hypoglycemia require correction appropriately. Hypocalcemia does not require any treatment unless cardiac manifestations occur.
7. **Monitoring** is required continuously for these sick patients. In addition to the core temperature, pulse and blood pressure should be monitored frequently. Urine output and renal functions are also monitored carefully. ECG monitoring should be done, as cardiac arrhythmias are common. Biochemical monitoring of liver and renal functions, electrolytes and acid-base status is required as often as warranted. All children with heatstroke must be closely monitored for at least 24 hours after normalization of temperature for late complications like hepatic and renal dysfunction.

### Epilogue

Pediatricians caring for children in hot and humid areas must be aware of the possibility of heatstroke. A high index of suspicion is required as appropriate management of this condition markedly reduces the mortality. Liberal fluid and salt intake, avoidance of prolonged exposure to high ambient temperatures, avoidance of strenuous play in hot and humid

conditions and early recognition and management of heat illnesses is important for preventing heatstroke and the damage associated with it.

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Electric current passing through the human body causes electric shock injuries. Lightning can produce similar type of damage. Death occurring as a consequence of electric shock is termed electrocution. Electric injuries in children usually occur at home and are accidental in most instances.<sup>1</sup> The incidence of electric injury has witnessed an upsurge in the recent years because of increasing use of electrical appliances for daily chores in an urban environment as well as increased electrification of even far-flung rural areas.

### Pathophysiology of Electric Injury

It would be useful to understand the basics of electricity flow. For a current to flow, there has to be a circuit (closed path), and difference in electric potential between the two point in this circuit (voltage). The real measure of intensity of the electric shock lies in the amount of current (amperes) forced through the body and not voltage. Although it takes voltage to make current flow, the amount of shock current will also vary depending on body resistance between points of contact. As per ohm's law, the flow of current is directly related to the voltage difference and inversely proportional to the electrical resistance between two points in a circuit:

$$I = V/R$$

Where I is the current that flows through body (measured in amperes), V is the voltage difference between two points (in volts), and R is the resistance between the same two points in the closed circuit (in ohms). A decrease in the resistance therefore, causes an increase in the current, while the voltage remains constant.<sup>2</sup>

The severity and extent of electrical injury thus depends upon: (i) Voltage and frequency of current, (ii) Body resistance which is influenced by the skin condition and path of current, and (iii) The duration of contact.

#### *Voltage and Frequency*

Electric shock can occur due to low voltage (<500 volts) or high-tension voltage (>500 volts). Most of electric

injuries are low voltage injuries and are caused by domestic accidents. Low voltage contact usually does not result in magnitude of tissue necrosis seen with high voltage injury. However, sudden death can follow low voltage shock due to direct myocardial injury resulting in ventricular fibrillation. Current is high when the voltage is high, unless the resistance is increased to a great extent. High voltage injury damages the medullary center in brain, causing cardiac asystole and respiratory arrest. The child is stuck to the wire by low voltage currents while he is thrown off by contact with high-tension wires. Grounding can minimize the voltage difference between two points in the electric current and reduce the intensity of current flowing through the body.<sup>3</sup>

Alternating current (AC) is more dangerous than the direct current (DC) at a low voltage because of dissociation of electrical impulses from brain, tetanic spasms and inability to release the person. At a high voltage, the consequences of shock due to AC and DC remain the same.

#### *Current Amount*

The real measure of shock's intensity lies in the amount of current (in amperes) forced through the body, and not the voltage. People have been electrocuted by a current of as little as 42 volts DC. Any amount of current over 0.01 amperes is capable of producing cardiorespiratory aberrations and severe shock. Currents between 0.1 to 0.2 amperes can be lethal. Above 0.2 amp, the muscular contractions are so severe that the heart is forcibly clamped during the shock. Clamping protects the heart from fibrillation and the victims chances of survival are thus better in a high voltage shock due to similar mechanism. The differential effects of increasing current (amperes) on human body are shown in Table 45.1.<sup>4</sup>

#### *Resistance of the Body*

The property of a conductor due to which it opposes the flow of current through it is called resistance. The

**Table 45.1: Effects of increasing current (in amperes) on human body**

Current (amperes)	Effects
0.001	Threshold of sensation
0.01	Mild sensation
0.01 to 0.1	Painful cannot let go, muscular paralysis, shock, upset or labored breathing, extreme breathing difficulties, ventricular fibrillation
0.1 to 0.2	Immediate death can result from ventricular fibrillation, central respiratory arrest or asphyxia due to spasm of respiratory muscles, may be associated with burns
0.2 to 1.0	Severe burns, cardiac clamping, breathing stops, severe muscular contraction

resistance of a conductor depends on length, thickness, nature of material, and temperature. The effects of electric shock on human body are more devastating because the body resistance tends to decrease when the current flows through it. Resistance of the body circuit depends on points of contact, area of contact, path of contact and condition of the skin (moist/dry).

Tissue resistance is important in determining outcome-if resistance is high, there will be considerable local tissue destruction and if its low, systemic effects like those on heart and brain predominate. Maximum resistance to the electric current is offered by bone. Thick skin, as in the palm, offers good resistance. Vascular areas, such as cheek are better conductors. Nerves and blood offer least resistance and are the best conductors. Body tissues can be arranged in the following sequence in order of their increasing magnitude of resistance: blood vessels, muscles, skin, tendon, fat and bone.

The path of current is also crucial. If the heart lies between the point of entry and exit, immediate cardiac manifestations such as asystole and fibrillation may occur. Wet skin has less resistance as compared to the dry skin. Sweating also reduces skin resistance. Brain is a good conductor and offers a path of least resistance when the current passes between the two ears.<sup>3</sup> The resistance of different body areas is as shown in Table 45.2.

Duration of contact, if more, results in a severe injury. Contact of a dry battery with chest for long period can cause cardiac dysfunction.

### Types of Electric Burns

A contact with electric current may result in different types of burns. *True electric burns* occur because of heat

**Table 45.2: Resistance to current by different body areas**

Area	Resistance (ohms)
Dry skin	1,00,000 to 600,000
Wet skin	1,000
Internal body (hand to foot)	400-600
Ear to ear	100

generated by passage of current in the tissues. *Arc (flash) burns* are caused by current passing externally to body, i.e. from the area of contact to ground favoring a path of least resistance. *Flame burns* are the indirect result of flash burns, resulting in ignition of clothing or nearby objects, by electric sparks. They are like any other thermal burns, but depth is more.<sup>3</sup>

### Clinical Features<sup>5</sup>

#### Local Effects

Hands, heels and head are the common point of contact. There is an electric mark at the point of entry (Joule burn), the size varies depending upon the area of contact. The entry wound is usually dry and depressed and the wound of exit is irregular and raised, as if exploded. The flexor surfaces of wrist, elbow and axillae are mostly involved and the hand is most common body part involved. Electric burns are leathery or charred with areas of full thickness skin loss. Children may present with a mouth or lip burn from biting on an electric cord.

Pathologically there is coagulation necrosis. There is also presence of randomly interspersed patchy myonecrosis. Paraosseous groups of muscles are typically more severely damaged than superficial ones, because of heat generated by increased bony resistance.

#### Cardiorespiratory Effect

These occur immediately and mostly include anoxia and ventricular fibrillation, which may cause death due to cardiorespiratory arrest. Other cardiac manifestation include a bundle branch or nodal block. Electric shock may cause apnea, pleural injury, hydrothorax and lobar pneumonia. Traversing current can also result in deep venous thrombosis and pulmonary embolism. Smaller vessels may be badly damaged because of thrombosis and this may contribute to amputation. Delayed hemorrhage because of mural necrosis of large blood vessels may occur.

#### Neurological Changes

Immediately following a shock, the child may become comatose and develop apnea. Nervous system is most

susceptible to injury because of decreased resistance. The children remain disoriented, and may develop seizures. The child may complain of brilliant flashes or a dark spot in the field of vision. Histopathological changes include perivascular hemorrhage, demyelination with vacuolization, reactive gliosis and neuronal death.

Lesion of CNS may cause varying levels of consciousness and respiratory and motor paralysis, which are usually transient and recovery is rule. If the effects are permanent, it can be similar to cortical encephalopathy or hemiplegia with or without aphasia.

The neurologic deficit can be seen initially or up to 3 years later. Neurological aberrations are the most frequent non-fatal sequelae of electric injury. Spinal cord damage is most common permanent sequelae of electrical injury. Many deficits resolve spontaneously, some may develop after 6 to 9 months and be permanent like gait abnormalities. Neuropathies can develop in unburned limbs. Autonomic nervous system dysfunction may also be present like reflux sympathetic dystrophy or causalgia. Late onset burning pain associated with vasomotor, trophic and dermal changes is characteristic.<sup>6</sup>

#### *Other Systemic Effects*

Acute renal failure may occur due to anoxia and increased tissue damage. Myorenal syndrome and pigmenturia may also be observed due to massive muscle necrosis.<sup>7</sup> Gastrointestinal manifestations include adynamic ileus, gastric atony and focal pancreatic necrosis with autolysis and focal necrosis of gallbladder. A syndrome of hyperamylasemia, hyperglycemia and ketosis has also been observed. Cataract may occur especially following high voltage injuries, particularly when entry wound is on the head.<sup>3,5</sup>

#### **Cause of Death**

Electrocution is caused by ventricular fibrillation or asystole, hypovolemic shock because of rapid loss of fluid into areas of tissue damage and from body surface burns, spinal cord injury caused by muscular spasms, or respiratory muscle spasm. Late death is attributable to burn infection, hemorrhage and renal failure.<sup>7-9</sup>

#### **Laboratory Investigations**

The hematocrit is elevated and the plasma volume is reduced. Serial determination of central venous pressure (CVP), packed cell volume, electrolytes and urine output may provide a good estimate of adequacy of fluid replacement therapy. Urine should be exami-

ned for myoglobinuria and hemoglobinuria. Arterial blood gas analysis should be done to document metabolic acidosis. ECG should be obtained in all cases for evidence of heart block or dysrhythmia. Obtain baseline liver and kidney function tests. Chest X-ray, and skull and neck radiographs should be obtained, if indicated. A lumbar puncture should be done to rule out raised intracranial tension or a CNS bleed. CT scan may be done to document a brain injury.<sup>9</sup>

#### **Management**

The principles of management include the following:<sup>3,5,8-10</sup>

1. Immediately removing the source of current.
2. Cardiopulmonary resuscitation and hemodynamic stabilization.
3. Care of burns and fluid replacement.
4. Monitoring and treating associated complications including infection.

#### *Rescue Therapy*

The patient must be separated immediately from electric current, but rescuers must not touch or approach the patient until main power has been shut off. Flames must also be extinguished. If this cannot be done and the current is still flowing through victim; it is advisable to stand on a dry, non-conducting surface like folded newspaper, flattened cardboard carton, or a rubber mat and use non-conductive object such as wooden broomstick, etc. to push the victim away from the source of current. Never use a damp or metallic object to approach the victim. The victim and source of current must not be touched while the current is still flowing.<sup>3</sup>

#### *Resuscitation*

Check for heartbeat and breathing. If the victim is not breathing, attempt mouth to mouth breathing. Provide chest compression if there is no heartbeat. Victims with low voltage shock may require defibrillation. Take care of bony fractures and spinal cord injury, if any during resuscitation. Immobilize broken limbs before transportation.

Once in the hospital, assess the general condition, cardiorespiratory and renal status, spinal injuries and the burns. Institute fluid therapy and take care of electrolytes and blood gases. Monitor CVP, urine output, and hematocrit.

#### *Care of Burns and Replacement Therapy*

Assess the depth and severity of burns. The wounds are cleaned and debrided. Burn areas are daily irrigated

with an antiseptic solution, and topical antimicrobials are applied. Minor burns may be treated with topical ointment and dressings. In case of high voltage injury there may be devitalized skin, fat, muscle and they are mainly surgical problems. Amputation, fasciotomy and other surgical procedures may be required. The ultimate treatment goals are stabilization of patient, salvation of limbs, debridement of devitalized tissue, and wound coverage.

Fluid replacement is essential. Hypovolemia results because of rapid loss of fluid into damaged tissue. Intravenous ringer lactate is the fluid of choice, but plasma or plasma substitutes may also be given. The standard burns formulae based on extent of body surface are not applicable as burns are deep; these are instead managed according to guidelines for crush injuries. Presence of urinary hemoglobin or myoglobin, and require administration of mannitol and frusemide. Maintain a good urinary output  $>1$  ml/kg/h.

The urine should be made alkaline to prevent precipitation of these pigments in kidney. Persistence of myoglobinuria for  $>6$  hours following institution of adequate volume replacement is a sign of major muscle loss, and may require debridement and amputation.<sup>7</sup>

Empty the stomach contents and instill antacids to prevent stress ulcers. Red cell transfusion may be needed to replace the blood loss during 2-5 days after burns.

#### *Monitoring and Managing Complications*

Regular monitoring of cardiovascular, pulmonary and renal function is required for deciding ongoing care, detecting and managing complications. Since neurological condition fluctuates rapidly, close observation is required. Look for other complications, i.e. hyperthermia or hypothermia, acute gastric dilatation, stress ulcers, renal failure, etc. and manage accordingly.

**Prevent infections:** Burn wound sepsis may occur earlier (2-4 days) and at lower colony counts ( $>10^3$  per gram eschar) than in adults. Tetanus immunization should be given. Antibiotics are used prophylactically to prevent both Gram-positive and Gram-negative infections. Anticlostridial prophylaxis consisting of penicillin or metronidazole should be given in all severe burns. *Candida* is another opportunistic organism that may cause oral thrush or disseminated septicemia. *Candida* cultured simultaneously from 2 organ systems indicates need for systemic therapy.

### Prognosis

Electric shock causes death in 3-15 percent of cases. Otherwise, the prognosis is good and complete recovery takes place. Injuries from household appliances and other low voltage sources are less likely to produce extreme damage.

### Prevention

Parents and other adults need to be alerted to possible electric dangers. Children should be kept away from electric appliances and should be taught about danger of electricity when they are old enough. Parents should not allow children to play with electrical cord. Adolescents should be refrained from climbing any electrical system such as a transformer. Never switch on or off the electrical appliances with wet hands or while standing in water.<sup>10</sup>

Damaged electric appliances, wiring, cord and plugs in the house should be repaired or replaced. All electric sockets should be covered with plastic or rubber safety caps, so children cannot stick their finger or metal objects in the sockets. Limit the use of extension cords. The location of fuse boxes and circuit breakers in the home and place of work should be clearly identified. Replace old ungrounded electrical outlets to a 3 pin grounded system.<sup>11</sup>

If a high voltage line has fallen on the ground, there may be a circle of current spreading out from the tip of the line. Keep away and inform the electrical company.

### Lightning Injury

Lightning is a brief atmospheric discharge of electricity of enormous energy. Injury is caused by direct strike, side flash or ground (step) current.

**Direct strike:** The majority of lightning energy flows around, rather than through the body, often vaporizing sweat droplets and blasting clothes apart. Fortunately, this flashover phenomenon minimizes corporal current flow so electrical injury to tissues is usually less severe and mutilating than injuries seen with high voltage electricity accidents.

**Side flash:** Injury occurs when lightning jumps from an object of high resistance to a path of lesser resistance.

**Step current** is established from potential difference generated between two grounded but spatially separated body parts such as feet. The phenomenon is a result of the lightning striking and dissipating along earth.

### Manifestations

Lightning may result in immediate death, electrical burns, disruption of electrical integrity in nerve and muscle cells, and blast injury from accompanying shock wave. Immediate manifestation include coma, convulsions, fractures, and visual confusion. Cardiac ischemia, paralysis, hypertension, and vasoconstriction are the other important outcomes. Late consequences include hysteria, psychosis, hemiplegia, scar, infection, or cataract.

### Treatment

Cardiorespiratory resuscitation (CPR) should be initiated promptly and aggressively, as soon as possible. Lightning strike inhibits the cellular metabolism by some unknown mechanism and may delay onset of degeneration process. In this setting the normal criteria for death-fixed, dilated pupils and lack of spontaneous movements are not necessarily applicable. Prolonged efforts of CPR should, therefore, be instituted in all lightning struck victims who are apneic and pulseless even if an appreciable interval has already elapsed.<sup>12</sup> Subsequently, the treatment is same as for electrical injury.

### Prevention During Lightning

During thunderstorms, immediately pull the children indoors. If moving indoors is not feasible, move away from metallic objects and lie down. Do not stand or lie under or next to metallic structure. You can take shelter in a car, as long as the radio is off. Switch off cellular phone. Do not use telephone, computer, hair dryer during a thunderstorm; these can act as conduits for lightning.<sup>10,13</sup>

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The major families of snakes in the Indian subcontinent are *Elapidae* which includes common cobra, king cobra and krait; *Viperidae* which includes Russell's viper, pit viper and saw-scaled viper and *Hydrophidae* (the sea snakes).<sup>1</sup> Of the 52 poisonous species in India, only 5 are responsible for most of the morbidity and mortality. They are *Ophiophagus hannah* (King cobra), *Naja naja* (common cobra), *Daboia russellii* (Russell's viper), *Bungarus caeruleus* (Krait) and *Echis carinatae* (saw-scaled viper). There are 14 venomous species in Nepal including pit vipers (5 species), Russell's viper, kraits (3 species), coral snake and 3 species of cobra.

The cobra (*nag*) is described as having a hood bearing a single or double spectacle shaped mark on its dorsal aspect. A white band in the region where the body touches the hood is another identifying feature. The common krait (*karayat*) is steel blue, often shining and has a single or double white band across the back. The head is covered with large shields. In general, Elapidae have relatively short, fixed front fangs; as do the Hydrophiidae. Russell's viper (*daboia, kander*) is identified by its flat, triangular head with a white 'V' shaped mark and three rows of diamond-shaped black or brown spots along the back. The saw-scaled viper (*afai*) is distinguished from the other species by a white mark on the head resembling a bird's footprint or an arrow. The fangs of vipers are long, curved, hinged, front fangs, which have a closed venom channel, giving them a structure akin to a hypodermic needle. Besides these, there are several other differentiating characteristics, which are of more interest to an expert than medical personnel. It has been claimed that most venomous species produce characteristic sounds, which may help in identification. These include hissing (Russell's viper), rasping (saw-scaled viper) and 'growling' (king cobras).

Although the precise epidemiological profile of snake bites is not known, Swaroop reported about 200,000 bites and 15,000 deaths in India as far back as 1954.<sup>2</sup> Based on an epidemiological survey of 26 villages in West Bengal, an annual incidence of 0.16 percent and

mortality rate of 0.016 percent per year was worked out.<sup>3</sup> A large number of snake bite cases occur in West Bengal, Tamil Nadu, Maharashtra, Uttar Pradesh and Kerala.

In India, almost two-thirds of bites are by saw-scaled viper (as high as 95 percent in some areas like Jammu), about one-fourth by Russell's viper and smaller proportions by cobra and kraits. In Sri Lanka, *Daboia russellii* accounts for 40 percent of bites and *Naja naja* for another 35 percent. *Daboia russellii* alone accounts for 70 percent bites in Myanmar. The estimated "fatal dose" of venom varies with species. The average yield per bite in terms of dry weight of lyophilized venom is around 60 mg for cobras, 63 mg for Russell's viper, 20 mg for krait and 13 mg for saw-scaled viper. The respective "fatal doses" are much smaller, viz, 12 mg, 15 mg, 6 mg and 8 mg.<sup>4</sup> However, clinical features and outcomes are not as simple to predict because every bite does not result in complete envenomation. The symptomatology of snake bite is termed as 'ophitoxemia'.

### Pathophysiology of Ophitoxemia

Snake venom is a mixture of enzymatic and non-enzymatic compounds as well as other non-toxic components. There are over 20 different enzymes including phospholipases A<sub>2</sub>, B, C, D, hydrolases, phosphatases (acid and alkaline), proteases, esterases, acetylcholinesterase, transaminase, hyaluronidase, phosphodiesterase, nucleotidase and ATPase and nucleosidases (DNA and RNA). The non-enzymatic components are loosely categorized as neurotoxins and hemorrhagens.<sup>5</sup> Different species have differing proportions of most if not all of these—this is why poisonous species were formerly classified exclusively as neurotoxic, hemotoxic or myotoxic. The pathophysiological basis for morbidity and mortality is the disruption of normal cellular functions by these enzymes and toxins. Envenomation results in increase of capillary permeability and loss of blood and plasma into the extravascular space, causing edema. The

decreased intravascular volume may be severe enough to compromise circulation and lead to shock. Snake venom also has direct cytolytic action causing local necrosis and secondary infection which is a common cause of death. Venom may also have direct neurotoxic effects causing paralysis and respiratory arrest, cardiotoxic effect causing cardiac arrest as well as myotoxic and nephrotoxic effect. Venom also causes coagulation disturbances and bleeding.

### Clinical Manifestations

The clinical manifestations ranges from no symptoms at all to severe systemic manifestations and death.

### Snake Bites with no Manifestations

Snake bite does not always lead to clinical manifestations. In a study of 432 snake bites in North India, Banerjee noted that 80 percent of victims showed no evidence of envenomation.<sup>1</sup> This figure correlates almost exactly with a more recent observation from Brazil.<sup>6</sup> Saini's study of 200 cases in Jammu region reported that only 117 showed symptom/sign of envenomation.<sup>7</sup> The reason for the relatively low frequency of poisoning may be that snakes on the defensive do not inject much venom. Other explanations could be a dry bite (bite without release of venom). In some cases, venom is spewed onto the victim's body as the snake attempts to bite, thereby reducing the overall quantity of venom in the bloodstream. Other protective factors include clothing and footwear.

### Local Manifestations

Local changes are the earliest manifestations of snake bite.<sup>8,19</sup> They occur within 6-8 minutes though may be delayed up to 30 minutes. Local pain with radiation and tenderness and the development of a small red-dish wheal are the first to occur. This is followed by edema and appearance of bullae—these can progress quite rapidly and extensively. Tingling and numbness over the tongue, mouth, scalp and paresthesias around the wound occur mostly in viper bites. Local bleeding including petechial and/or purpuric rash is also seen most commonly with this family. Regional lymphadenopathy has been reported as an early and reliable sign of systemic poisoning. The local area of bite may become devascularized with necrosis and gangrenous changes. Generally Elapid bites result in early gangrene—usually wet type whereas vipers cause dry gangrene of slower onset. Secondary infection including tetanus and gas gangrene can also occur.

### Systemic Manifestations

The most common symptom following snake bite (poisonous or non-poisonous) is fright, particularly of rapid and unpleasant death. Owing to fright, the victim attempts 'flight' which unfortunately results in enhanced systemic absorption of venom. These emotional manifestations are almost instantaneous and can produce psychological shock and even death. Fear may cause transient pallor, sweating and vomiting.

Other systemic manifestations depend upon the pathophysiological changes induced by the venom. Though, snakes were formerly classified as neurotoxic (cobras and kraits), hemorrhagic (vipers)<sup>10</sup> and myotoxic (sea snakes), it is now well recognized that every species can produce a mixture of manifestations. Neurotoxic features are a result of selective d-tubocurarine like neuromuscular blockade which results in flaccid paralysis of muscles. Cobra venom is 15-40 times more potent than tubocurarine. Ptosis is the earliest neuromuscular manifestation followed closely by ophthalmoplegia. Paralysis then progresses to involve muscles of palate, jaw, tongue, larynx, neck' and muscles of deglutition—but not strictly in that order.<sup>5</sup> Generally muscles innervated by cranial nerves are involved earlier. However, pupils are reactive to light till terminal stages. Muscles of chest are involved relatively late with diaphragm being the most resistant. Thus, respiratory paralysis is often terminal. Reflex activity is generally not affected and deep tendon jerks are preserved till late stages.<sup>1</sup> Symptoms that portend paralysis include repeated vomiting, blurred vision, paresthesiae around the mouth, hyperacusis, headache, dizziness, vertigo and signs of autonomic hyperactivity.

Hemostatic defects are caused by a number of different mechanisms. For instance, *Daboia russellii* has procoagulant activating factors V and X which activate intravascular coagulation resulting in consumption coagulopathy. Certain other venoms cause defibrinogenation by activating endogenous fibrinolytic system.<sup>11</sup> Besides direct effects on the coagulation cascade, venoms can also cause qualitative and quantitative defects in platelet function.<sup>12</sup> Bleeding may occur from multiple sites including gums, gastrointestinal track (hematemesis and malena), urinary tract, injection sites and even as multiple petechiae and purpurae.<sup>8</sup> In addition subarachnoid hemorrhage,<sup>7</sup> cerebral hemorrhage<sup>12</sup> and extradural hematoma have also been reported.

Cardiotoxic features include tachycardia, hypotension and ECG changes. In addition, sudden cardiac standstill may also occur owing to hyperkalemic arrest. Non-dyselectrolytemic acute myocardial infarction<sup>13</sup> and tetanic contraction of heart following a large dose

of cobra venom have also been reported. Myalgic features are the most common presentation of bites by sea snakes. Muscle necrosis may also result in myoglobinuria.

Almost every species of snake can cause renal failure. It is fairly common following Russell's viper bite and is a major cause of death.<sup>14</sup> The extent of renal abnormality often correlates with the degree of coagulation defect; however, in the majority, renal defects persist for several days after the coagulation abnormalities normalize: suggesting that multiple factors are involved in venom induced acute renal failure.

Rare systemic manifestations that have been reported include hypopituitarism<sup>15,16</sup> bilateral thalamic hematoma<sup>17</sup> and hysterical paralysis.<sup>18</sup>

### Long-term Effects of Snake Bite

In most cases, swelling and edema resolve within 2 to 3 weeks. However, they may occasionally persist up to 3 months. In exceptional circumstances, they may be permanent. Rarely coagulation disturbances and neurotoxicity may persist beyond 3 weeks. Necrosis of the local tissue, resultant gangrene and consequent cosmetic defects are obvious long-term complications of ophitoxemia.<sup>8</sup>

### Factors Affecting Severity and Outcome in Ophitoxemia

#### Host Factors

Children overall fare worse than adults owing to greater amount of toxin injected per unit body mass.<sup>5</sup> Individuals in a better state of health have a better outcome than more debilitated counterparts. Patients bitten on the trunk, face and directly into bloodstream have a worse prognosis. Exercise and exertion following bite results in enhanced systemic absorption of venom. This is why individuals who panic and flee from the scene of bite generally have a worse outcome.<sup>9</sup> There is significantly higher mortality among victims who develop neurotoxicity.<sup>20,21</sup> Clothing or shoes sometimes mitigate the effects of envenomation to a considerable extent. Individual sensitivity to venom also modifies the clinical picture. Victims of ophitoxemia who develop secondary infection at the site of bite do worse than those not infected.

#### Agent Factors

The 'lethal dose' of venom varies with species.<sup>4</sup> The number and depth of the bites is a relative index of the amount of venom injected. Indirect evidence for this is

also available by studying the volume of venom remaining in the glands and fangs. The condition of fangs—intact or broken, also indicates the amount of venom injected. The length of time a snake clings to its victim and the presence or absence of pathogenic organisms in its mouth are two other important factors affecting outcome.

#### Environment Factors

The nature of first aid and the time elapsed before administration are the most important factors affecting outcome.<sup>22</sup> The circumstances that provoked the snake to bite may also have a bearing on clinical presentation and survival of victims.

### Laboratory Aids

The laboratory serves rather poorly in the diagnosis of snake bite, with the exception of ELISA studies based on antigens in venom which can identify the species that has bitten.<sup>23</sup> These tests are expensive and not freely available hence of limited value; except for epidemiological study. Recently emphasis is being laid on the value of immuno-enzymatic tests to identify the offending species accurately.<sup>24</sup>

Laboratory tests are useful for monitoring prognosticating and determining stages of intervention. Blood changes include anemia, leukocytosis and thrombocytopenia. Peripheral smear may show hemolysis, particularly in viperine bite.<sup>7</sup> Deranged coagulant activity manifested by prolonged clotting time and prothrombin time may also be evident.<sup>8</sup> The quality of clot formed may be a better indicator of coagulation capability than the actual time required for formation, since clot lysis has been observed in several patients who had normal clotting time.<sup>7</sup> Hypofibrinogenemia may also be present.<sup>5</sup>

Serum cholesterol at admission has been found to correlate negatively with severity of envenomation. Hyperkalemia and hypoxemia with respiratory acidosis, especially with neuroparalysis may be present. Urine examination may show hematuria, proteinuria, hemoglobinuria or myoglobinuria. In cases of ARF, all features of azotemia are also present. CSF hemorrhage has been documented in a minority of victims.<sup>5,7</sup>

ECG changes are generally non-specific and include alterations in rhythm (predominantly bradycardia) and atrioventricular block with ST segment elevation or depression. T wave inversion and QT prolongation<sup>1</sup> have also been noted. Tall T waves in lead V2 and patterns suggestive of acute anterior wall infarction have been reported as well.

EEG changes have been described starting within hours of bite, though patients may not show any

clinical features of encephalopathy. Grade I changes are defined as decrease in activity or/and increase in activity or presence of sharp waves, Grade II changes include sharp waves or spikes and slow waves; classified as moderate to severe abnormality. Severe abnormality involves diffuse activity (Grade III).

### MANAGEMENT OF OPHTHOXEMIA

The management of snake bite resolves around three pillars, namely, (a) First aid, (b) Specific therapy, and (c) Supportive therapy.

#### First Aid

Reassurance and immobilization of the affected part with prompt transfer to a medical facility are the cornerstones of first aid care. Most experts also advocate the application of a wide tourniquet or crepe bandage over the limb to retard the absorption and spread of venom.<sup>5,8</sup> The tourniquet should be tight enough to occlude the lymphatics, but not venous drainage.<sup>1</sup> Enough space to allow one finger between the limb and bandage is most appropriate. If the limb becomes edematous, the tourniquet should be advanced proximally. Tourniquets should never be left in place too long due to the risk of distal avascular necrosis.

It was formerly believed that incision over the bite drains out venom. However, animal experiments have shown that systemic venom absorption starts almost instantly; hence incision is of no benefit. Most experts also reject suction of the local area, though there are others who advise this method on the grounds of rapidly removing a large amount of venom. Ideally the wound site should be minimally handled. It may be cleaned with saline with the option of applying a sterile dressing.<sup>8</sup> There is disagreement over the use of drugs in first aid care. NSAIDs particularly aspirin may be beneficial to relieve local pain. However, it is dissuaded for fear of precipitating bleeding. Similarly there are proponents as well as opponents for use of sedatives.<sup>22</sup>

Despite disagreements and controversies over the specifics of first aid, there is consensus among experts that the measures used should be prompt and efficient, avoiding undue delay in transferring the patient to a center for specific treatment.

#### Specific Therapy—Antivenom

Antivenoms are prepared by injecting horses with venom, extracting the serum and purifying it. Antivenoms or antivenins may be species specific (monovalent) or effective against several species

(polyvalent). Monovalent antivenom is ideal,<sup>1</sup> but the cost and non-availability, besides the difficulty of accurately identifying the offending species, makes its use less common.

#### Indications for Use

There are specific indications for use of antivenom.<sup>25,26</sup> Every bite if by a poisonous species does not merit its use. This caution against the empirical use of antivenom is due to the risk of hypersensitivity reactions. Therefore, antivenom is indicated only if serious manifestations of envenomation are evident, *viz*, coma, neurotoxicity, hypotension, shock, bleeding, disseminated intravascular coagulation (DIC) acute renal failure, rhabdomyolysis and ECG changes.<sup>5</sup> In the absence of these systemic manifestations, swelling involving more than half the affected limb, extensive bruising or blistering and progression of the local lesions within 30-60 minutes<sup>1</sup> are other indications, where use of antivenom is recommended.

#### Dose

There are virtually no clinical trials to determine the ideal dose of antivenom. Conventionally, a starting dose of 50 ml (5 vials) of reconstituted antivenom is infused for mild manifestations like local swelling with or without lymphadenopathy, purpura or ecchymosis. Moderate envenomation defined by presence of coagulation defects or bradycardia or mild systemic manifestations, merits the use of 100 ml (10 vials). A total of 150 ml (15 vials) is infused in severe cases, which includes rapid progression of systemic features, DIC, encephalopathy and paralysis.<sup>5</sup> Thomas and Jacob attempted to study the effect of a lower dose in a randomized controlled trial and found that with half the conventional dose, there was no significant difference in the time taken for clotting time to normalize.<sup>27</sup> Theoretically, there does not seem to be an upper dose limit and even 45 vials (4500 units) have been used successfully in a patient.<sup>28</sup>

#### Administration

The freeze dried powder is reconstituted with 10 ml of injection water or saline or dextrose. A test dose is administered on one forearm with 0.02 ml of 1:10 solution intradermally. Similar volume of saline in the other forearm serves as control. Appearance of erythema or wheal greater than 10 mm within 30 min is taken as a positive test. In this event, desensitization is advised starting with 0.01 ml of 1:100 solution and

increasing concentration gradually at intervals of 15 minutes till 1.0 ml subcutaneously can be given by 2 hours.

Antivenom is administered intravenously and never into fingers or toes.<sup>22</sup> Infusion is started at 20 ml/kg per hour initially and slowed down later. Some authors recommend that 1/3 to 1/2 the dose can be given at the local site to neutralize venom there. However, this is not necessary as systemic administration of antivenom is effective at the local site as well. Intramuscular administration has also been found to be effective, though it has not been fully evaluated. This route is likely to have value in a field setting prior to transfer to better facilities.

### Timing

There is no consensus as to the outer limit of time of administration of antivenom. Best effects are observed within four hours of bite. It has been noted to be effective in symptomatic patients even when administered up to 48 hours after bite. Antivenom may be efficacious even 6-7 days after the bite.<sup>29</sup> It is obvious that when indicated, antivenom must be administered as early as possible and data showing efficacy with delayed administration is based on use in settings where patients present late.

### Response

Response to infusion of antivenom is often dramatic with comatose patients sitting up and talking coherently within minutes of administration. Normalization of blood pressure is another early response. Within 15 to 30 minutes, bleeding stops though coagulation disturbances may take up to 6 hours to normalize. Neurotoxicity improves from the first 30 minutes but may require 24 to 48 hours for full recovery. If response to antivenom is not satisfactory, use of additional doses is advocated. Infusion may be discontinued when satisfactory clinical improvement occurs even if recommended dose has not been completed.<sup>4</sup> In experimental settings, normalization of clotting time has been taken an end-point for therapy.

### Reactions

Hypersensitivity reactions including the full range of anaphylactic reactions may occur in 3-4 percent of cases, usually within 10 to 180 minutes after starting infusion. These usually respond to conventional management including adrenaline, antihistamines and corticosteroids.<sup>26</sup>

### Availability

Several antivenom preparations are available internationally. In India, the Serum Institute prepares SiiASVS (Bivalent) effective against the viperine venoms and SiiASVS (Polyvalent) effective against the cobra, common krait, russell's viper and saw-scaled viper. Antivenom produced at the Haffkine Corporation, is also efficacious against the four common poisonous species.

### Supportive Therapy

In cases of bleeding, replacement with fresh whole blood is ideal. Fresh frozen plasma and fibrinogen are not recommended. Volume expanders including plasma and blood are recommended in shock, but not crystalloids. Persistent shock may require inotrope support under CVP monitoring. Early mechanical ventilation is advocated in respiratory failure though dramatic responses have also been observed with edrophonium followed by neostigmine.<sup>30</sup> Cases of acute renal failure generally respond to conservative management. Occasionally peritoneal dialysis may be necessary. In cases of DIC, use of heparin should be weighed against risk of bleeding and hence caution is advocated.<sup>1</sup> Routine antibiotic therapy is not a must<sup>8</sup> though most Indian authors recommend use of broad spectrum antibiotics. Chloramphenicol has been claimed to be useful as a post bite antibiotic even when used orally since it is active against most of the aerobic and anaerobic bacteria present in the mouths of snakes. Alternatives include cotrimoxazole, fluoroquinolones with or without metronidazole or clindamycin for anaerobic cover.<sup>31</sup>

Recent studies have reported the beneficial effects of intravenous immunoglobulin (IVIg) in ophitoxemia. There are suggestions that its administration may improve coagulopathy, though its effect on neurotoxicity is questionable. A pilot study indicates that IVIg with antivenom eliminates the need to repeat antivenom for envenomations associated with coagulopathy.<sup>32</sup> There is no role for steroid therapy in acute snake bite.<sup>22</sup> Although it delays the appearance of necrosis, it does not lessen the severity of outcome.

A compound extracted from the Indian medicinal plant *Hemidesmus indicus* R 2-hydroxy-4 methoxy benzoic acid<sup>33</sup> has been noted to have potent anti-inflammatory, antipyretic and antioxidant properties, particularly against Russell's viper venom. These experiments suggest that chemical antagonists from herbs hold promise in the management of ophitoxemia; particularly when used in the presence of antivenom. Four cases of tetanus have been documented following snake bite<sup>22</sup> hence administration of tetanus toxoid is a must. Early

surgical debridement is generally beneficial though fasciotomy is usually more harmful than useful.

### Conclusion

Snakes do not generally attack human beings unprovoked. They are reputed to be more afraid of man than *vice versa*. Nevertheless once bitten, a wide spectrum of clinical manifestations may result. The emphasis for treatment should be placed on early and adequate medical management, including prompt first aid followed by appropriate specific and supportive therapy.

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**CASE VIGNETTES**

1. A ten year old girl was stung by a black scorpion while opening her suitcase after an overnight journey by bus. She developed pain vomiting, shivering within 15 minutes. Her extremities were cold, blood pressure 130/100 mm Hg and heart rate 148/minute. She required three doses of oral prazosin and was discharged 24 hours later.
2. A 2-year-old male child was sleeping beside his mother in a thatched house. At midnight he was stung by a red scorpion. He developed vomiting and excessive sweating 30 minutes later. At the emergency services, the child was restless, tachypneic with cold extremities and priapism. His HR was 180/minute; systolic BP was 50 mm Hg, with S3 gallop rhythm on cardiac auscultation. He was managed for myocardial dysfunction and pulmonary edema and was discharged 96 hours later.

**THE PROBLEM**

The above cases highlight the intriguingly varied presentation of scorpion envenomation, which is a common medical emergency in the tropical and subtropical regions all over the world. Worldwide scorpion envenomation is common in Latin America, Africa, the Middle East and India.<sup>1,2</sup> In India it is commonly found in the states of Maharashtra, Karnataka, Tamilnadu, West Bengal and the union territory Pondicherry.<sup>3</sup> The true incidence of scorpion envenomation in India is not known as numerous envenomations are unreported. The case fatality rates reported among children hospitalized for scorpion stings in various studies conducted in India, Saudi Arabia and South Africa is of the order of 3-22%.<sup>2,4</sup>

Of the 86 species of scorpions found in India, the red scorpion (*Mesobuthus tamulus*) and the less poisonous black scorpion (*Palamneus swammerdami*) are implicated in most stings.<sup>1,5</sup> The severity of scorpion envenomation varies with the scorpion's species, age, and size, and is much greater in children owing to their lesser

body surface area. Clinical effects vary from species to species. For example in Indian species cardiac manifestations dominate the clinical picture whereas in South Africa and USA neurological features are common.<sup>1,5,6</sup> Acute pancreatitis and tissue necrosis are common in Trinidad and Iran respectively.<sup>7,8</sup>

By elucidating the natural history of this condition, observant physicians like Bawaskar and Bawaskar set the stage for research on scorpionism in our country. Their landmark study in rural Maharashtra first reported the beneficial effects of Prazosin in victims of scorpion sting.<sup>9</sup>

**DISTRIBUTION**

Scorpions live in warm, dry regions. They inhabit commonly the crevices of dwellings, underground burrows, under logs or debris, paddy husk, sugarcane fields, coconut and banana plantations. Scorpions retreat in the crevices of dwellings during the day only to emerge at night; thus most stings are reported at night. Also stings are more common during summer months as compared to winter. The scorpion stings only when roughly handled or trodded upon and even then, it does not always inject venom since it can control its ejaculation; thus the sting may be total, partial or non-existent.<sup>1</sup>

**PATHOPHYSIOLOGY**

Various animal studies, reports on clinical profile and effect of therapeutic interventions on scorpion envenomation have led to our understanding of its pathophysiology, though a lot more research needs to be done in this regard before a consensus can be made.

**VENOM**

The scorpion venom is a complex mixture of short neurotoxic proteins, amino acids, serotonin, hyaluronidase and enzymes which on entering the bloodstream has a tissue distribution half life of 5-6 minutes and

reaches peak tissue concentration in 36 minutes. Excretion half life is 30 minutes.<sup>10</sup>

The toxin affects all major systems of the body either directly or by release of mediators like the autonomic nervous system, cardiovascular system, central nervous system, hematopoietic system, the lungs, skin, kidney, liver and pancreas. It also induces systemic inflammatory response syndrome which causes widespread inflammation.

### EFFECT OF THE VENOM ON VARIOUS TISSUES/ORGANS

#### Ion Channels

The side chains of scorpion venom are positively charged which facilitates their binding to specific **voltage dependent ion** channels.

The toxin acts by opening sodium channel at presynaptic nerve terminals and inhibiting calcium dependant potassium channels (direct effect on the gating mechanisms of excitable membranes) leading to continuous, prolonged, repetitive firing of the somatic, parasympathetic and sympathetic, neurons. This repetitive firing results in autonomic and neuromuscular overexcitation symptoms due to release of neurotransmitters such as epinephrine, norepinephrine, acetylcholine, glutamate, and aspartate. Release of acetylcholine produces cholinergic symptoms which is subsequently followed by adrenergic hyperexcitation due to release of epinephrine and norepinephrine.<sup>11,12</sup>

#### Autonomic Nervous System

Stimulation of  $\alpha$  adrenergic receptors and angiotensin I levels facilitate sympathetic outflow resulting in hypertension, tachycardia, pulmonary edema, myocardial dysfunction and peripheral circulatory failure.<sup>13</sup> The unopposed  $\alpha$ -receptor stimulation also leads to suppression of insulin secretion, hyperkalemia, free radical accumulation and myocardial injury. In addition, release of catecholamines results in a variety of metabolic changes including glycogenolysis (leading to depletion of tissue glycogen content of atria, ventricles, and liver) and lipolysis.<sup>14</sup>

#### Cardiovascular System

The hemodynamic effects of scorpion envenomation can be broadly divided into two patterns—a predominantly vascular effect (*vasoconstriction*) and a predominantly myocardial effect (*left ventricular failure*). Clinical and experimental data suggest that the pathogenesis of hemodynamic effects is often multifactorial.<sup>15</sup> The mechanisms commonly implicated are:<sup>13</sup>

- Circulating catecholamines and angiotensin resulting in intense vasoconstriction.
- Increased myocardial oxygen demand with changes in systolic and diastolic functions due to catecholamine induced cardiac stimulation.
- Alteration in myocardial perfusion and metabolism due to: (1) increased left ventricular diastolic pressure due to diastolic dysfunction (2) reduced effective cardiac output or (3) as a result of increased circulating levels of renin angiotensin on the coronary circulation and myocardium.
- A possible **direct effect** on the myocardium (myocarditis and focal necrosis has been observed at autopsy).

#### Hemopoietic System

The venom can lead to clotting alterations and disseminated intravascular coagulation (DIC). The microthrombi produced could result in acute lung injury.<sup>16,17</sup>

#### Central Nervous System (CNS)

The CNS manifestations such as seizures, hemiplegia, and encephalopathy might develop secondary to the effects of venom or following DIC. Systemic hypertension (during adrenergic storm) could lead to intracranial bleed/infarct.<sup>18,19</sup>

#### Other Organs

- *Skin*: Local inflammation is unusual in Indian red scorpion envenomation.<sup>5</sup> Varied skin reaction, namely, erythema, edema, lymphangitis and severe necrosis is seen with yellow scorpion found in Iran (*Buthus cosmobuthus* and *Hemiscorpus*).<sup>7</sup>
- *Kidneys*: Severe hemolysis may cause secondary renal failure.<sup>7</sup>
- *Liver*: Rise in liver enzymes and necrosis of liver were seen at autopsy in some cases.<sup>20</sup>

#### Scorpion Venom and Systemic Inflammatory Response

Increased levels of interleukin-6, IL-1 $\alpha$  and IFN- $\gamma$ , nitric oxide (NO), alpha-1-antitrypsin were seen in patients stung by the scorpion species *Tityus serrulatus*. These cytokines stimulate production of inducible nitric oxide (iNOS) which may lead to direct tissue injury. Studies on interleukin and other cytokines involved in scorpion envenomation might provide a rationale for anti-cytokine treatment in this potentially dangerous condition.<sup>21</sup>

## Clinical Features

Species differences, venom dose/weight relationship and changes in body temperature may determine the toxicity and clinical picture.<sup>22</sup> Clinical picture may evolve within 30 minutes to six hours and subside within a day or two. The symptomatology can be broadly classified into local, systemic and complications/unusual manifestations.<sup>23</sup> The evolution of clinical features seen in our context is depicted in Figure 47.1.

**Local manifestations** include severe pain and paresthesias. There is usually little or no reaction at sting site. Children may be screaming within seconds to minutes due to pain after the sting, may appear irritable and at times excitable. Severe shock-like pain by tapping over the sting site (Tap Test) is usually not reported in Indian patients. Whenever local pain was severe, there was often no further progression of symptoms. Older children report paresthesia near the sting site. Some children complain of pain at the site during recovery which may be due to improvement in the peripheral circulation.<sup>23</sup> Serotonin found in scorpion venom is thought to contribute to pain associated with scorpion sting.<sup>24</sup>

**Systemic manifestations** are a result of the autonomic storm that follows envenomation. Features of cholinergic stimulation merge imperceptibly into those of adrenergic stimulation. Vomiting, salivation, sweating, priapism and bradycardia are early diagnostic signs. Sweating and salivation persist for 6-13 hours. Increased oral secretions and bronchorrhea in the early

cholinergic phase may lead to respiratory compromise.<sup>1,2,5,12</sup>

Adrenergic stimulation is seen within 4 hours and may persist for 24-72 hours. This phase may be characterized by tachycardia, hypertension (15-43% patients), myocardial dysfunction, arrhythmias, peripheral circulatory failure and/or pulmonary edema (non cardiogenic).<sup>25</sup> Myocardial injury is preceded by vomiting and palmoplantar sweating. Marked tachycardia, S3 gallop and ice-cold extremities may be seen in these children.<sup>25</sup> The clinical picture may be dominated by one of the following phases (*vide Infra*). Though described separately for convenience, these phases are not distinct entities in that an individual patient can have features of more than one phase; also one phase could progress to another in the same patient.<sup>15,26-28</sup>

- Tachycardia with PCF:** Children may present with tachycardia (HR 110-215/min), apical systolic murmur and cool peripheries. Pulmonary edema eventually develops in 10% of these patients. Death may result from cardiac arrest due to refractory pulmonary edema.
- Hypertension with or without bradycardia** may last for 4-8 hours in many due to outpouring of catecholamines from adrenal stimulation; it is prolonged in some due to direct stimulation of sympathetic centers in medulla. Hypertensive stress on myocardium, may cause myocyte toxicity and catecholamine induced injury may contribute to rhythm disturbances and LV failure in a significant

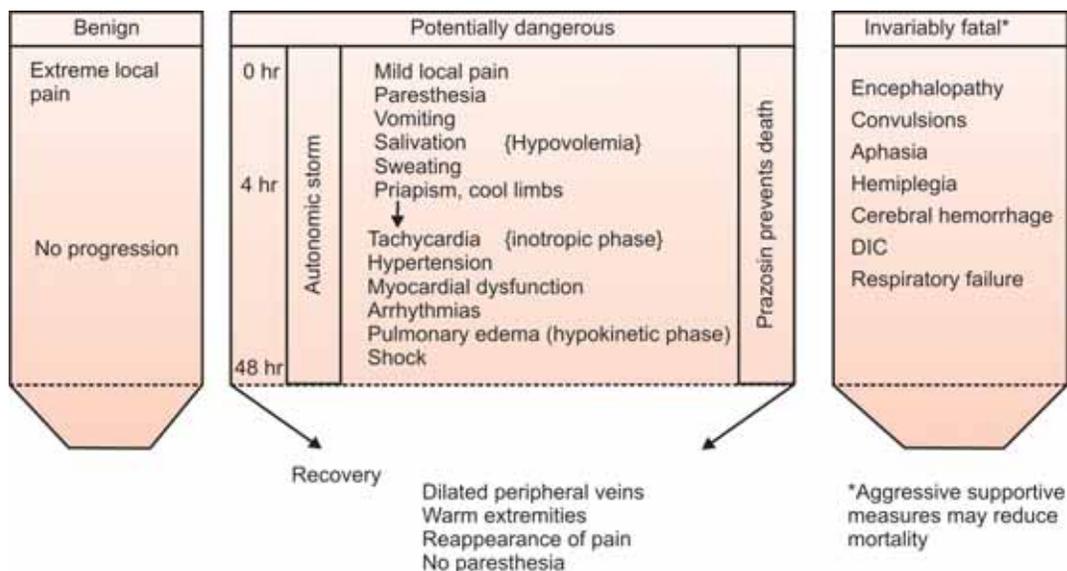


Fig. 47.1: Clinical features of scorpion (*M. tamulus*) sting in Indian children

proportion of children. These children may also present with priapism, facial swelling, proptosis, sweating, salivation and vomiting.

c. **Pulmonary edema with hypotension and PCF** may develop within 30 minutes to three hours after a sting due to myocardial dysfunction secondary to intense vasoconstriction or probable direct injury as described in the pathophysiology. Development of symptoms associated with pulmonary edema is variable but may be rapid. Tachypnea or intractable cough at admission could mean pulmonary edema in evolution. Close monitoring is indeed vital to detect and treat pulmonary edema. Children appear pale (ashen pallor of skin) with clammy skin and have tachycardia with elevated blood pressure, retractions, nasal flaring and grunting. Pink frothy sputum as classically described in adults is not always present in children. Some children develop acute pulmonary edema while showing apparent signs of recovery. Death within 30 minutes in some of these children is due to ventricular arrhythmias. Non-cardiac pulmonary edema due to ARDS is commonly reported from Brazil (*Tityus serrulatus* scorpion).

d. **Hypotension and bradycardia** may be encountered within 1-2 hours of sting due to cholinergic stimulation; hypotension and tachycardia later (4-48 h) indicate severe LV dysfunction. During recovery stage (48-72 h) hypotension can be seen; but the extremities are warm with good volume pulse and child is otherwise well. This state, due to an exhausted catecholamine stores awaiting replenishment, requires no intervention with dopamine agonists.

**Shock syndrome** may be observed in few patients due to hypovolemia from fluid loss due to vomiting, excessive salivation and perspiration.<sup>13, 25</sup> It may also be precipitated by administration of atropine for bradycardia during the cholinergic phase which abolishes the parasympathetic effect and causes hypertension and pulmonary edema with shock.<sup>25</sup> Despite the above theories the precise mechanism is not clearly understood and shock may follow hypertension and may be associated with bradycardia.

**Central nervous system** manifestations are infrequently encountered in our country. They are however a common finding in South Africa and Latin America. Neurological manifestations usually indicate severe envenomation and are associated with poor prognosis. Encephalopathy, convulsions within 1-2 hours of sting, miosis, mydriasis, squint and agitation are some of the manifestations observed in these patients. Three

mechanisms have been proposed to explain the neurotoxicity which include:<sup>18,19</sup>

1. Hypertensive encephalopathy leading to hemorrhage, infarct
2. Hypoxic ischemia from a defect in oxygen transport secondary to the pulmonary edema and cardiogenic shock observed in severe scorpion envenomation
3. A probable direct action of the scorpion venom on the CNS.

**Complications/unusual manifestations** are a result of progression of symptoms and include dehydration, hypovolemia, encephalopathy, convulsions, cerebral infarcts, aphasia, hemiplegia, cerebral hemorrhage, DIC, respiratory failure and pancreatitis.

A grading system has been proposed to grade the severity of envenomation which is given below (Table 47.1).<sup>29</sup>

**Table 47.1: Grading of severity**

Grade I	Isolated pain
Grade II	Hypertension, sweating, vomiting, priapism, fever, shivering
Grade III	Cardiogenic shock, pulmonary edema, altered consciousness

## Management

Treatment is mainly supportive and directed towards providing symptomatic relief as specific therapy (antivenom) is not available, nor recommended for routine use. The goals of management include:

- Identifying early manifestations
- Initiating first-aid and appropriate supportive care
- Closely monitoring the child especially in the initial few hours
- To recognize peripheral circulatory failure early in the course and intervene appropriately
- Instituting appropriate medications and fluid therapy based on the initial presentation and further course and
- Monitoring for complications and managing them appropriately.

## Investigations

Investigations are mainly directed towards identification of myocardial dysfunction and pulmonary edema and commonly include X-ray chest, ECG and echocardiography. Myocardial perfusion abnormalities may be identified by nuclear scans. Neurological abnormalities/complications require imaging modalities like CT and MRI brain.

1. **ECG:** It is a sensitive indicator of myocardial injury. The changes commonly seen are peaked T waves in V2-6, ST segment elevation in leads I, aVL, increased QR duration (ventricular activation time) and LVH by voltage criteria. The most common abnormality found in one series was prolonged QTc and inverted T-waves. Low voltage complexes throughout the record and left anterior hemiblock indicate poor prognosis.<sup>5,25</sup>
  2. **Chest X-ray:** In majority of children, changes in chest X-ray suggestive of pulmonary edema are seen even within 3 hours of sting. The features include normal cardiac silhouette with pulmonary vascular congestion, straight non-branching lines in upper lung field that run diagonally towards hilum, and horizontal non-branching lines in periphery of lower lung indicating interlobular septal edema. Surprisingly, most of the children with these features are usually not tachypneic at least in the first few hours; some of them become symptomatic in the next 6 hours.<sup>23</sup>
  3. **Echocardiography:** It reveals left ventricular systolic dysfunction in these children. Left ventricular dilatation with regional wall motion abnormalities are also seen infrequently. Right ventricle is less severely affected.<sup>30</sup>
  4. **Laboratory investigations:** These include serum electrolytes (for hyperkalemia), lipid profile (low serum cholesterol and triglycerides with rise in free fatty acids), serum amylase, LDH, SGOT, and SGPT (all elevated).<sup>3</sup>
    - Fluid balance chart including total fluid intake, rate of administration, and total output; urine output should be measured accurately. Weight should be recorded 12 hourly
    - Serum electrolytes and blood gases every 12 hourly and as required
    - DIC profile and liver function tests as and when indicated
- Sedation: In some cases to restrain an agitated child. Diazepam is recommended (in concert with GABA opens ion channels and antagonizes toxin's ability to stimulate specific ion channel). Long-acting sedatives should be avoided.<sup>23</sup>

**Drug therapy:** Various pharmacological agents have been used in experimental animals as well as humans to treat the systemic manifestations of scorpion envenomation. The rationale behind the use of these agents has been to counter the effects of the mediators released during envenomation. Prazosin has clearly emerged as the first line agent in our country because of the predominant cardiovascular manifestations seen in these patients. The various agents tried in scorpion envenomation with their current recommendation are described below.

#### *Prazosin*

Prazosin should be the first line of management, since alpha receptors stimulation plays a major role in the evolution of clinical spectrum.<sup>9,26,27</sup>

**Rationale:** A competitive post-synaptic alpha 1, adreno-receptor antagonist, prazosin suppresses sympathetic outflow and activates venom-inhibited potassium channels. It decreases the preload, after load and blood pressure without increasing the heart rate. The metabolic and hormonal effects of alpha receptors stimulation are reversed by prazosin. It also counters vasoconstriction induced by endothelins through accumulation of cyclic GMP (cGMP). cGMP, a second messenger of nitric oxide in vascular endothelium (eNOS) and myocardium prevents further myocardial injury. Thus prazosin has been appropriately called as the cellular and pharmacologic antidote in scorpion envenomation.<sup>9,26,27,32</sup>

**Dose, indication, precautions:** The dose recommended is 30 microgram/kg/dose in children with evidence of autonomic storm. It should not be given as prophylaxis in children when pain is the only symptom. It is advisable not to lift the child immediately after administration due to 'first dose phenomenon'. Oral hydration and milk feeds must be encouraged.

## Treatment

It comprises of local measures, general measures, and drug therapy to counter the effects of envenomation.

**Local measures:** The sting site should be cleaned. Pain relief is useful since it allays anxiety and avoids myocardial stress. However, many children have only mild and tolerable pain. When pain is severe, NSAIDs can be used for pain relief. Local ice packs, xylocaine infiltration, dehydroemetine (counter irritant), and streptomycin (neuromuscular blockade) have been reported to be useful.<sup>31</sup>

**General measures:** These include

- Oxygen administration via face mask/nasal cannula in case of respiratory distress, shock/impending shock.
- Frequent monitoring of
  - Vital signs—every 15-30 minutes until the patient is stable and every 1-2 hours thereafter

If needed, intravenous maintenance fluids should be given to correct dehydration due to excessive sweating and vomiting. Prazosin can be given irrespective of blood pressure provided there is no hypovolemia.

*Monitoring:* The child's blood pressure, heart rate and respiration needs to be monitored every 30 minutes for 3 hours, every hour for next 6 hours and later every 4 hours till improvement. Repeat dose may be administered at the end of 3 hours according to clinical response and later every 6 hours till extremities are warm, dry and peripheral veins are visible easily. The time lapse between the sting and administration of prazosin for symptoms of autonomic storm determines the outcome.<sup>3,5,32</sup>

#### *Dobutamine*

*Rationale:* Scorpion envenomation causes a transient hyperkinetic phase followed by hypokinetic phase in which hypotension, shock and pulmonary edema predominate. Heart failure was the main finding in clinical studies dealing with cardiocirculatory disturbances. Dobutamine corrects hemodynamic parameters relevant to LV and RV functions.

Dobutamine increased contractility, cardiac index and SAP without increasing the SVR hence it is preferred in hypokinetic phase with pulmonary edema. It also reduced the PAOP, thus decreasing the ventricular preload.<sup>33</sup>

*Precautions* should be used only in normotensive or hypertensive patients with optimal preload.

#### *Vasodilators (Nitroprusside, Nitroglycerine)*

*Rationale:* Vasodilators reduce afterload and relieve pulmonary congestion. Nitroprusside is a predominant arteriolar dilator while nitroglycerine acts mainly on veins and pulmonary vessels.<sup>27</sup>

*Precautions, contraindications* should be used only in normotensive or hypertensive patients. Preload should be optimal. Methemoglobin levels should be monitored. Nitroprusside is contraindicated in renal failure.

#### *Specific Therapy—Antivenom*

Antivenom against the toxins of Indian scorpions is **not available** for clinical use. Also its efficacy is questionable in patients reaching the hospital late as the venom reaches its target too rapidly ( $t_{1/2}$  is 5 minutes). Once bound to the receptors, neutralization is impossible. If antivenom is administered within 30 minutes of sting effect may be reversed. Studies have shown controversial results. Therefore till further evidence is available routine

administration of antivenom is not recommended, irrespective of clinical severity.<sup>29</sup>

#### *Other Treatment Strategies*

Standard therapy was not clearly defined in earlier days; many therapies were in vogue without experimental justification. Most of these have been later proved to be of **no benefit** in the management of scorpion envenomation.<sup>23</sup>

- i. **Lytic cocktail** (pethidine + promethazine + chlorpromazine): The drug mixture produces a state of suspended animation ('artificial hibernation') thereby reducing the cerebral metabolism and further complications of scorpionism. Chlorpromazine produces diabenamine-like effect in mitigating the course of shock, potentiating antihistaminic effect, and lowering cerebral metabolism; the alpha blocking effect of chlorpromazine might also be beneficial.<sup>3,31</sup>

However, lytic cocktail could potentially result in serious adverse effects including orthostatic hypotension, respiratory depression, and convulsions. Studies have also shown that pethidine may convert sublethal dose of scorpion venom into a lethal one; it also interferes with protective respiratory reflexes. Therefore, lytic cocktail is no longer preferred in most centers.
- ii. **Insulin dextrose:** Release of catecholamines inhibits insulin secretion thereby leading to release of free fatty acids (free radical injury) and myocarditis. Administration of insulin reverses these effects and thus is cardioprotective. However, a recent study found no reduction in either mortality or cardiovascular morbidity after treatment with insulin-glucose-potassium drip.<sup>27</sup>
- iii. **Morphine:** It has been found to worsen dysrhythmias.<sup>3</sup>
- iv. **Steroids:** In 600 consecutive patients of scorpion sting randomly assigned to receive hydrocortisone and placebo, no significant difference was found in steroids and placebo groups.<sup>34</sup> Moreover steroids might enhance the necrotizing effects of excessive catecholamines on myocardium.
- v. **Atropine:** Complete abolition of parasympathetic effects may cause sympathetic overstimulation thus potentiating the actions of the venom.<sup>35</sup>
- vi. **Nifedipine:** Reflex tachycardia and negative inotropic effect argues against its use; despite its antihypertensive and vasodilator effect, 35% of scorpion victims developed myocardial failure and 14% acute pulmonary edema.<sup>32,36</sup>

vii. **ACE inhibitors:** They aggravate hyperkalemia and inhibit breakdown of bradykinin, which is implicated in experimental pulmonary edema due to scorpion sting. Captopril failed to correct hemodynamics in two cases and did not prevent cardiac arrhythmias.<sup>15</sup>

As the symptomatology might differ depending on the severity and the clinical phase (see *clinical features*), a uniform protocol cannot be employed for *all* patients with scorpion envenomation. Instead, an algorithm based approach is being proposed (Fig. 47.2).

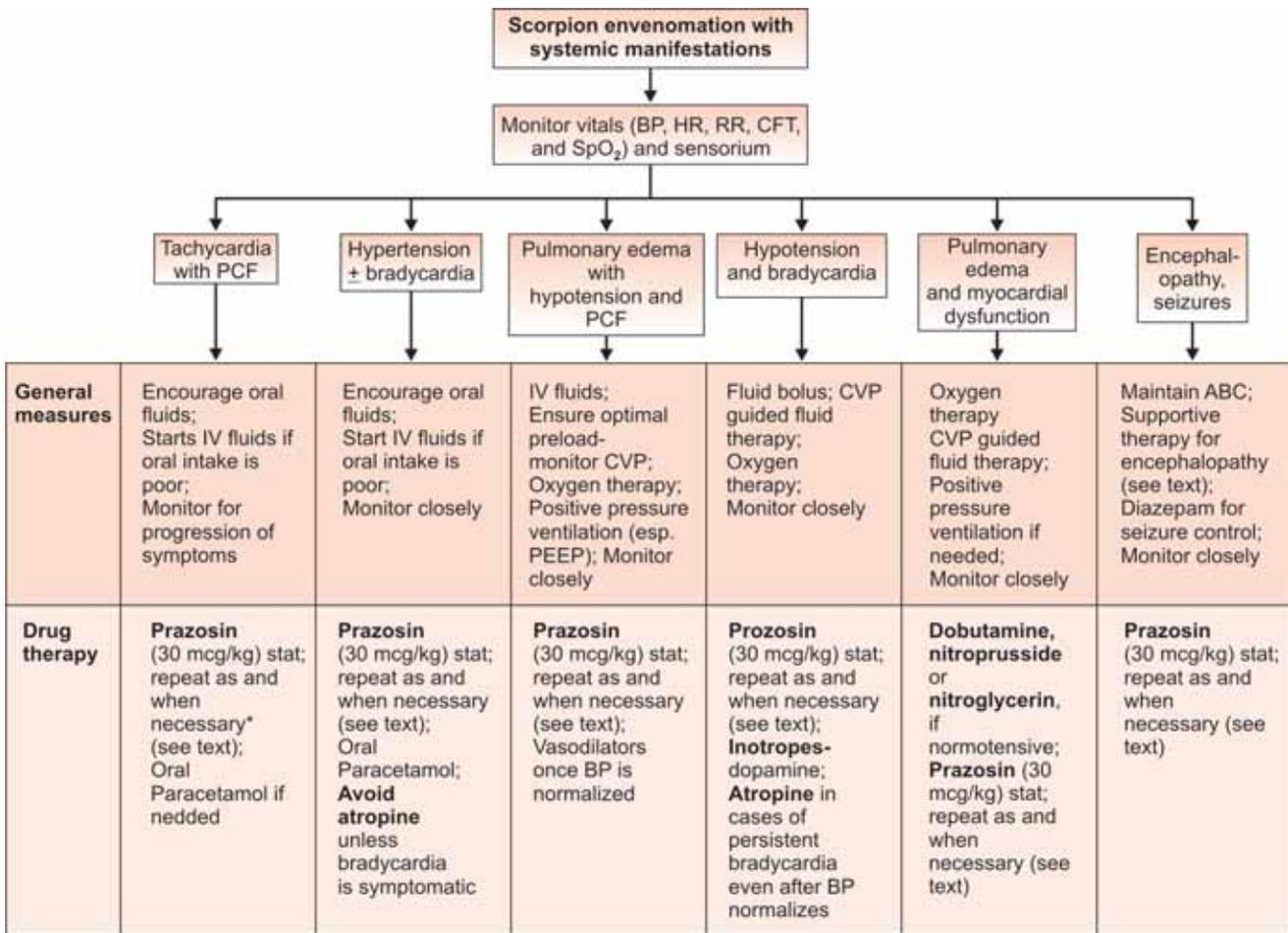
**Critical Care Issues**

Children with severe systemic envenomation and/or complications require ICU admission and care. The common indications for ICU admission are pulmonary edema, myocardial dysfunction, hypovolemic

shock, respiratory failure, encephalopathy, pancreatitis, bleeding manifestations and renal failure (Table 47.2).

**Mortality**

In the pre-prazosin era (1961-1983), 25-30% fatality was reported in scorpion victims from Western India due to pulmonary edema. Since the use of prazosin (1984 onwards) the mortality in these victims is reduced to less than 1%.<sup>3,5</sup> Case fatality rate in children due to scorpion sting has declined from 13 to 3% after prazosin was introduced as the first line of management.<sup>3</sup> Therefore there should be no delay in administration of prazosin in these children at the primary health care level and cases with severe envenomation should be immediately referred to higher centers.<sup>23</sup>



(PCF-peripheral circulatory failure; CVP-central venous pressure; PEEP-positive end expiratory pressure; ABC-airway breathing circulation)

Fig. 47.2: Algorithm for management of scorpion envenomation

**Table 47.2: Critical care issues and management**

Issues	Management
<b>Pulmonary edema</b>	<ul style="list-style-type: none"> <li>Management should be directed towards relieving afterload without compromising preload by using drugs like nitroprusside, nitroglycerin, prazosin, etc.</li> <li>Use of diuretics to minimize or reduce fluid overload seems a reasonable measure but only when renal water excretion is impaired</li> <li>Positive pressure ventilation may be required in those with hypoxia secondary to pulmonary edema</li> </ul>
<b>Myocardial dysfunction</b>	<ul style="list-style-type: none"> <li>Treatment of myocardial dysfunction is primarily supportive</li> <li>Cardiac output should be maintained at an optimum using agents like dobutamine (at 5-15 mcg/kg/min) with/without vasodilators</li> <li>Morphine should be avoided since narcotics could worsen dysrhythmias</li> </ul>
<b>Fluid management</b>	<ul style="list-style-type: none"> <li>Loss of fluid due to profuse sweating and vomiting should not be overlooked</li> <li>Oral fluids must be encouraged, whenever feasible</li> <li>When children present with tachypnea and altered sensorium, parenteral fluids (N/5 saline) are required</li> </ul>
<b>Respiratory failure/ARDS</b>	<ul style="list-style-type: none"> <li>In children with pulmonary edema, CVP monitoring is essential</li> <li>Children with ARDS should be managed with positive pressure ventilation as and when required</li> </ul>
<b>Encephalopathy</b>	<ul style="list-style-type: none"> <li>Supportive care (maintaining normothermia, oxygenation, ventilation, fluid and electrolyte balance, blood sugar, head end elevation, head midline, seizure control, etc.) should be instituted to prevent secondary brain injury</li> </ul>
<b>Bleeding manifestations</b>	<ul style="list-style-type: none"> <li>Blood components should be transfused as required.</li> </ul>

### Criteria for Discharge

Before discharge, the following criteria should be fulfilled:

- The child should be hemodynamically stable
- Sensorium should be normal
- Respiratory distress should have settled
- Extremities should be warm and
- Should be free of complications.

### Prognosis

Younger age (< 6 years), delay in initiating prazosin therapy, encephalopathy, pulmonary edema and arrhythmia have been found to be associated with poor prognosis.<sup>3</sup> Long term complications reported from a study include dilated cardiomyopathy. The risk factors identified were catecholamine excess (uncoupling of beta receptors) calcium channel alterations, myocyte loss and hypertrophy.<sup>37</sup>

### Preventive Measures

The following preventive measures can be considered:

1. Clear debris and trash from areas one inhabits.
2. Inspect boots, clothing and bedding for scorpion.
3. Never explore into places one cannot see.
4. Spraying 10% DDT + 0.2% prethrin + 2% chlorine in oil base or Fuel oil + Kerosene + Creosote as spray in roof complexes and building foundations.

### CONCLUSION

Management of scorpion sting in India is no longer a problem with the use of prazosin which is effective, cheap and easily available in our country even at the village level. The time lapse between the sting and administration of prazosin for autonomic storm determines the outcome therefore therapy should not be delayed. Unhelpful treatment, often practiced, should be avoided.

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S e c t i o n

5



# General Management of a Poisoned Child

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Poisoning represents one of the most common medical emergencies encountered by young children and adolescents. The pediatrics emergency toxicology is unique because of its natural division into two distinct components. Young children aged 1 to 5 years who innocently ingest a small amount of a single substance constitute the first group. Those at higher risk include male gender, hyperactivity and increased finger mouth activity or pica. Environmental factors like new baby in house, marital disharmony among parents, illness and economic crisis add further risk. Pediatricians can play an important role to prevent poisoning in these children by providing anticipatory guidance. The second group of children, which is more prone to poisoning, includes adolescents who purposefully ingest larger amounts of one or more substances because of emotional or psychiatric distress. Children between these groups are less commonly poisoned. The exact incidence and prevalence of acute poisoning are not known in India but it is a quite common and unreported problem in children.

The field of toxicology (the science of poisons) is broad and multidisciplinary. Emergency toxicology is the application of toxicological knowledge with a limited data to formulate the most effective management plan. The range of possible substances that can cause poisoning is vast. To provide the details of all possible poisons is therefore impossible for practical purposes. So this chapter aims at formulating a general approach to a poisoned child. A poisoned child should be approached like a polytrauma case where a primary survey aims at supporting vital functions and secondary survey (called detoxification phase) is aimed at evaluation, decontamination, and neutralization with continued supportive care. The basic elements of the medical management of poisoning are:

1. Support vital functions.
2. Identify agent (when possible).
3. Remove, neutralize or reverse toxic effects of poison
4. Hasten recovery.

5. Treat damaged or poisoned organs or systems and prevent further damage whenever possible.

## Initial Management

When a patient has been poisoned, the immediate priority must be to maintain life. The general approach to evaluation and support of airways and cardiorespiratory function remains same as taught in pediatric advanced life support course (PALS). In a poisoned child some points deserve special attention. Special care should be given to any impaired airway protective reflexes. Children with poisoning tend to vomit more or undergo gastric lavage, which puts them at increased risk of aspiration. So these children may require early endotracheal intubation, if neurologically depressed. Comatose poisoned patients can suddenly develop respiratory failure and arrest. Respiratory support should be provided at the earliest evidence of respiratory insufficiency as evident on arterial blood gas study. An intravenous access should be obtained at the beginning.

During the initial evaluation and support of vital functions, a member of the emergency team should make every effort to identify the poison. A constellation of signs and symptoms consistent with ingestion or exposure to a toxin is called toxidrome. It is important to recognize toxidrome when an acutely ill patient does not have any obvious history of poisoning. For some of these toxidromes,<sup>1</sup> life saving therapies are available (Table 48.1).

At the completion of initial management, the patient should have been assessed for airway, breathing, circulation, and neurological status. Appropriate resuscitative measures should have been instituted by this time. The critical evaluation of respiratory status is essential in any comatose child. A therapeutic trial of oxygen, glucose and naloxone<sup>2</sup> may be tried in an unconscious child if required. The anticonvulsant or antiarrhythmic drugs should have been used wherever indicated. A thought process for the decontamination options should have begun by now.

**Table 48.1: Toxidromes for which life saving therapies are available**

Toxidromes	Therapy
1. <i>Opioid</i> : Miosis, central nervous system, depression, respiratory depression	Intravenous naloxone
2. <i>Cholinergic</i> : (caused by organophosphates and carbamates) SLUDGE syndrome (salivation, lacrimation, urination, defecation, garlic odor, emesis with pin-point pupils)	Atropine and pralidoxime
3. <i>Cyclical antidepressant toxidrome</i> : Altered sensorium, seizure, wide QRS complexes, arrhythmias	Sodium bicarbonate
4. <i>Hypoglycemia</i> : It should be suspected in any child with altered sensorium or seizures, (occurs due to oral hypoglycemics, beta-blockers, salicylates and ethanol)	Intravenous 25% glucose

## Evaluation

The evaluation of a poisoned patient involves an interpretation of history, physical examination and investigations. Following is the outline of the questions that must be kept in mind.

### History

What is the type of toxic exposure? What form was the toxin in (liquid, gas, or pill)? Was it regular release or sustained release pill? What is the route (inhalation, oral, intravenous, etc.) of exposure? When did it occur? How much (number of pills) and how long the exposure occurred? Was there any exposure to other substances? Were other people also exposed? Is there any underlying medical condition or medications? Did the patient receive any prior therapy or home management?

### Symptoms

Are there any symptoms present (Obtain a specific list of symptoms.)? When did these symptoms start and in which order did they present? Are the symptoms and their progression same in all involved patients?

### Physical Examination

Certain toxins are associated with characteristic alteration in vital signs.<sup>1,2</sup> Recognition of these trends may prove useful in improving the diagnostic skills. Tables 48.2 and 48.3 present some of the more common associations but these are not designed to be all inclusive.<sup>1,2</sup> Multiple ingestion, underlying medical problems, and maintenance medications may significantly alter these findings, and must be included in the history.

## Vital Signs and Initial Patient Assessment

Although the history of drug ingestion or toxin exposure is important, many clinical decisions are based on the patient's physical examination. A thorough

evaluation can confirm the suspected diagnosis and detect the unexpected, as well as follow the response to therapeutic interventions.<sup>3</sup> All physical assessment must begin with an analysis of the vital signs. The abbreviation WNL (**w**ithin **n**ormal **l**imit) is not acceptable information as normal means different things to different people. Frequently WNL means, "We Never Looked".

## Laboratory Evaluation

The laboratory investigations may be helpful in confirming diagnostic impressions or in demonstrating toxin induced metabolic derangement. Specific investigations may be required for various poisonings. Metabolic acidosis with increased anion gap occurs in cases of methanol poisoning, uremia, diabetic ketoacidosis, paraldehyde, phenformin, isoniazid, iron, lactic acidosis, ethanol, ethylene glycol and salicylates poisoning (remember mudpiles). Chest radiography is often done for hydrocarbon ingestion. Children with caustic ingestion may require esophagoscopy. Abdominal X-ray is useful in iron poisoning and radio-paque foreign body ingestion. Recently ultrasound has been investigated as a means of identifying the presence of pharmaceutical material in the gastrointestinal tract.

Emergency toxicological screen rarely has been found useful in patient management.<sup>4,5</sup> On the other hand, specific quantitative analysis can be helpful for some of the drugs like acetaminophen, salicylates, methanol, ethylene glycol, iron, theophylline, and lithium. There are specific interventions based on these results. But the facilities for their estimation are usually not available at most of the centers.

## Remove, Neutralize or Reverse Effects

While the patient is being stabilized, the decision process for removal of toxin from body should be taken. This may involve gastrointestinal decontamination, hastening the excretion of toxin, and use of appropriate antidote.

**Table 48.2: Clinical manifestations of poisoning**

<i>Pulse</i>	
Bradycardia	Digoxin, narcotics, organophosphates, cyanide, carbon monoxide, clonidine, beta-blockers, calcium channel blockers
Tachycardia	Alcohol, amphetamines, sympathomimetics, atropinics, tricyclic antidepressants, theophylline, salicylates, phencyclidine, cocaine
<i>Respiration</i>	
Slow depressed	Alcohol, barbiturates (late), narcotics, sedative—Hypnotics
Tachypnea	Amphetamines, barbiturates (early), methanol, salicylates, carbon monoxide
<i>Blood pressure</i>	
Hypotension	Methemoglobinemia (Nitrates, nitrites, phenacetin), cyanide, carbon monoxide, phenothiazines, tricyclic antidepressants, barbiturates, iron theophylline, clonidine, narcotics, beta-blockers, calcium channel blockers
Hypertension	Amphetamines, sympathomimetics (especially phenylpropanolamine in over-the-counter (OTC) cold remedies), tricyclic antidepressants, phencyclidine, MAO inhibitors, antihistamines, atropinics, clonidine, cocaine
<i>Temperature</i>	
Hypothermia	Ethanol, barbiturates, sedative—Hypnotics, narcotics, phenothiazines, antidepressants, clonidine, carbamazepine
Hyperpyrexia	Atropinics, quinine, salicylates, amphetamines, phenothiazines, tricyclic antidepressants, MAO inhibitors, theophylline, cocaine
<i>Neuromuscular</i>	
Coma	Narcotics, sedative—Hypnotics, anticholinergics (Antihistamines, antidepressants, phenothiazines, atropinics), alcohol, anticonvulsants, carbon monoxide, salicylates, organophosphate insecticides, clonidine
Delirium/Psychosis	Alcohol, phenothiazines, drugs of abuse (phencyclidine, LSD, mescaline, marijuana, cocaine, heroin, methaqualone), sympathomimetics and anticholinergics (including prescription and OTC cold remedies), steroids, heavy metals
Convulsions	Alcohol, amphetamines, cocaine, phenothiazines, antidepressants, antihistamines, camphor, boric acid, organophosphates, isoniazid, salicylates, lindane, lidocaine, phencyclidine
Ataxia	Alcohol, barbiturates, carbon monoxide, diphenylhydantoin, heavy metals, organic solvents, sedative/hypnotics, hydrocarbons
Paralysis	Botulism, heavy metals, tick paralysis, shellfish poisoning
<i>Eyes</i>	
Miosis	Narcotics, organophosphates, plants (Mushrooms of muscarinic type), ethanol, barbiturates, phenothiazines, phencyclidine, clonidine
Mydriasis	Amphetamines, atropinics, barbiturates (if comatose), cocaine methanol, glutethimide, LSD, marijuana, phencyclidine, antihistamines, antidepressants
Nystagmus	Diphenylhydantoin, sedative—Hypnotics, carbamazepine, glutethimide, phencyclidine, barbiturates, ethanol
<i>Skin</i>	
Jaundice	Carbon tetrachloride, acetaminophen, naphthalene, phenothiazines, plants (Mushrooms, fava beans), heavy metals (iron, phosphorous, arsenic)
Cyanosis	Methemoglobinemia due to aniline dyes, nitrites, benzocaine, phenacetin, nitrobenzene, phenazopyridine
Pinkness to redness	Atropinics, antihistamines, alcohol, carbon monoxide, cyanide, boric acid
<i>Smell</i>	
Acetone	Acetone, isopropyl alcohol, phenol and salicylates
Alcohol	Ethanol (Alcoholic beverages)
Bitter almond	Cyanide
Garlic	Heavy metal (Arsenic, phosphorous and thallium), organophosphates
Hydrocarbons	Hydrocarbons (gasoline, turpentine, etc.)

**Table 48.3: Toxidrome (constellation of signs/symptoms due to poisonings)**

Poison syndrome	Symptoms and signs	Possible toxins
<i>Cholinergic syndrome</i>	Bradycardia or tachycardia, tachypnea Confusion to drowsiness to coma, convulsions, muscle fasciculations, weakness to paralysis, miosis, blurry vision, lacrimation, sweating, garlic odor, salivation, bronchorrhea, bronchospasm, pulmonary edema, urinary frequency, diarrhea	Organophosphates Drugs for Myasthenia
<i>Anticholinergic activity</i>	Fever, tachycardia, hypertension, cardiac arrhythmia, delirium, psychosis convulsion, coma, mydriasis, flushed dry skin	Atropine, antihistamines Antidepressants (TCA) Antispasmodics, Antiparkinson drugs, Mushroom poisoning
<i>Increased sympathetic activity</i>	Fever, tachycardia, hypertension, mydriasis, sweating, hyperactive to delirious, tremor, myoclonus, psychosis, convulsions Bradycardia, bradypnea, hypotension, hypothermia, euphoria to coma, hyporeflexia, pin-point pupils Hypothermia, hypotension, bradypnea, confusion to coma, ataxia, nystagmus, miosis or mydriasis, vesicles, bullae Fever, hyperpnea, lethargy to coma, vomiting Postural hypotension, hypothermia, tachycardia, tachypnea, lethargy, coma, tremors, convulsion, extrapyramidal syndrome (ataxia, torticollis, back arching, oculogyric crisis, trismus, tongue protrusion or heaviness), miosis (majority of cases) Tachycardia, hypotension, cardiac arrhythmias, tachypnea, agitation, convulsions, vomiting	Amphetamines, cocaine Decongestant preparations Ecstasy, Theophylline Narcotics, Clonidine Barbiturates  Salicylates Phenothiazines  Theophylline
<i>Methemoglobinemia</i>	Cyanosis resistant to oxygen therapy	Alanine dyes, nitrates, Nitrobenzene, chlorates sulphonamides
<i>Renal failure</i>	Oliguria or anuria, hematuria myoglobinuria	Carbon tetrachloride Methanol, ethanol mushrooms, oxalates

### Gastrointestinal Decontamination (GID)

This area of patient management has evolved considerably over the last decade, and now we can take decisions about GID based on the scientific data. Gastrointestinal decontamination can be divided into four distinct categories: Syrup of ipecac (SOI), gastric lavage (GL), activated charcoal (AC), and whole bowel irrigation (WBI). Which of these is most likely to be beneficial depends on the poison ingested, the clinical presentation, and the time since ingestion occurred. At times, some of these modalities can be combined in a single patient. Trends in the use various modalities of GID have changed dramatically in last several years.<sup>6</sup> There is now less emphasis on SOI and GL and increased emphasis is placed on AC. An addition to the armamentarium of GID is WBI. Not all children with poisoning require gastrointestinal decontamination. It depends on whether the child has really

ingested the toxic dose or just a trivial dose, time passed since ingestion, likely efficacy of the particular method to remove poison and risks of that method of GID.

### Syrup of Ipecac (SOI)

Syrup of ipecac induces emesis by both central and peripheral mechanisms. The studies that evaluated the success of SOI in inducing emesis have shown it to be efficacious in 90 to 100 percent. The mean time to vomiting is between 14 to 29 minutes after administration. About one in five patients may require a repeat dose to induce emesis. SOI may remove an average of approximately 30-40 percent of the ingested toxin when administered soon after the ingestion.

Syrup of ipecac may have a role in the early home treatment of some poisoning that occur at a location, distant from the medical care. However, its benefits are limited.<sup>7,8</sup> It may be useful in ingestion of small foreign

**Table 48.4: Recommended dose of syrup of ipecac**

Age	Dose
Below 6 months	Not indicated
6 months-1 year	10 ml
1-12 years	15 ml
Adolescents	30 ml

It is preferable to give 50 to 150 ml of water after the dose of SOI.

bodies or portion of mushrooms that are not accessible to GL and believed to place the patients at risk. Recommended dose of SOI depends on the age of the child (Table 48.4).

Syrup of ipecac is contraindicated in children less than 6 months because the gag reflex is poorly developed in this age. Induced emesis should not be done after the ingestion of corrosives, hydrocarbons or any foreign body sharp enough to cause perforation or laceration. It is also contraindicated in patients with depressed mental status or those patients who have ingested substances, which can lead to seizure or depressed gag reflex.

The most common adverse effects from SOI are persistent vomiting, diarrhea, and central nervous system depression. It also delays the administration of AC. Other rare reported side effects include intracranial bleed, pneumomediastinum and Mallory-Weiss tear.

### Gastric Lavage (GL)

Gastric lavage is an alternative technique for stomach emptying that theoretically allows direct irrigation and removal of unabsorbed toxin from the stomach. Before gastric lavage the gag reflex of the child should be evaluated. If it is absent, endotracheal intubation should be done before passing the lavage tube to protect the airway. The patient should be placed in left lateral position. The size of the lavage tube should be as large as possible, which can be accommodated in the patient safely. A 28 French tube (the size of pediatric endoscope) may be safely passed in the newborn. A fully grown child may easily accommodate a 36 F tube. Continuous pulse oximetry is advisable. Gastric lavage may be done with 0.9 percent saline or tap water in 15 ml/kg cycles until the lavage fluid is clear. The lavage return should approximate the amount of fluid given to avoid fluid or electrolyte abnormalities. If the ingested substance is in liquid form, aspiration from the stomach with or without lavage by using a smaller nasogastric tube is appropriate.

Gastric lavage is indicated in those patients who ingest highly toxic substances and are brought to the emergency department soon after ingestion. The use of GL in an asymptomatic patient is controversial. The clinical benefits of GL in patients who have ingested mild to moderately toxic substances are not as clear.<sup>9</sup> Except for the subgroup presenting with altered mental status and who may be lavaged within one hour, GL does not appear to alter clinical outcome and may increase the risk of complications. In addition, GL is labor intensive procedure that may delay the definitive treatment with AC. AC alone may be the sole preferred method of GID in this group.

Contraindications to GL include corrosive poisoning (acid as well as alkali) and hydrocarbon ingestion. GL in corrosive poisoning may lead to esophageal perforation from a misplaced tube whereas GL in hydrocarbon ingestion increases the risk of pulmonary aspiration of oropharyngeal/gastric contents.

### Activated Charcoal (AC)

Activated charcoal is considered to be the main method for preventing absorption of most drugs and toxins. Charcoal is produced from wood, coconut, petroleum or other organic material, which is heated to approximately 900°C with steam and carbon dioxide in the "activation process". This increases the surface area of charcoal, removes previously absorbed materials, and reduces the particle size. The net result is a marked increase in total adsorptive surface area as high as 1600-1800 m<sup>2</sup>/g. Since the vast majority of toxins can be adsorbed to AC, it is indicated in the treatment of most poisoning.<sup>10</sup> The current recommended dose is 1-2 g/kg and under certain circumstances in multiple doses also. The tablet form of AC is not recommended. Activated charcoal should be given as premixed slurry with or without a cathartic. Multiple dose AC provides an adsorption surface for removal of toxins during enteroenteric or enterohepatic recirculation in addition to increased mass for direct adsorption of unabsorbed toxin onto the charcoal. Drugs for which multiple dose charcoal has been shown to be effective are carbamazepine, barbiturates, phenytoin, digitoxin, phenylbutazone, dapsone, methotrexate, nadolol, quinine, theophylline, salicylates, nortriptyline and amitriptyline (though controversial), propoxyphene and many others.

AC is an ineffective adsorbent for caustics, hydrocarbons, some heavy metals (although not sufficiently studied), iron, methanol, ethanol, ethylene glycol and lithium. Multidose activated charcoal should be used

cautiously in the patient with depressed bowel sounds, and is contraindicated in patients with ileus or mechanical obstruction. The complications are rare but include aspiration into the lungs, constipation and intestinal obstruction.

### Whole Bowel Irrigation (WBI)

There is considerable clinical experience with flushing the gastrointestinal tract with an electrolyte balanced non-absorbable solution to cleanse the bowel in preparation for elective surgery or colonoscopy. The use of these solutions to remove ingested toxins has been suggested. The solution used most often is a polyethylene glycol; a non-absorbable vehicle mixed in a balanced electrolyte solution that has been specifically formulated not to cause electrolyte abnormalities.

The full potential of WBI is still not clear. There are certain situations that make this type of therapy attractive.<sup>11</sup> This therapy has been found to be effective in the overdose of iron and sustained release theophylline. It is also effective in cocaine or heroin body stuffers and packers. Another attractive use of WBI is for ingestion of drugs or toxins that are not well adsorbed to AC, such as lithium and possibly lead.

The recommended dosage is 25-40 ml/kg/h, either orally or by way of nasogastric tube for 4-6 hours or until the rectal effluent becomes clear contraindication to the use of WBI includes bowel obstruction, perforation, or ileus. Vomiting is a complication that can be decreased by having the patient in a semi-Fowler's position or using an anti-emetic. WBI should be considered only for those substances, which are not bound to activated charcoal. WBI should not replace AC as the sole method of GID.

### Conclusion

Regarding GID, the tide is turning in favor of AC alone in most overdose patients.<sup>12</sup> Activated charcoal slurry is not available in India. The author has used activated charcoal tablets after crushing and mixing in saline. Gastric lavage is indicated in the potentially serious overdose, and in those patients who present obtunded and require endotracheal intubation, particularly if they arrive early after ingestion. Whole bowel irrigation is the newest addition to the armamentarium available for GID in pediatric ingestion. The current mainstay of poisoning treatment in the vast majority of pediatric ingestions should be the use of AC, possibly combined with gastric lavage in serious or potentially serious ingestion.

### Hastening Elimination of Toxin

Various methods have been tried to remove the already absorbed toxin from the body. Commonly used methods are discussed below:

**Diuresis and alkalinization:** Forced diuresis is an overused and probably ineffective treatment for most poisonings.<sup>13</sup> There is virtually no role for diuresis in the management of acutely poisoned patient. However urinary pH manipulation may increase the excretion of weak acids or bases by maintaining the drug/toxin in its ionic state within the renal tubules, thereby preventing its reabsorption into the circulation. Maintaining an adequate output of alkaline urine is useful to enhance the excretion of salicylates and phenobarbitone. The urinary pH should be maintained between 7 and 8. Attempts should be made to avoid systemic alkalosis. The serum pH should not go beyond 7.5.

**Hemodialysis:** It is not a widely used tool in toxicology, but it can be effective in certain selected poisonings. For dialysis to be effective, a toxin must be of low molecular weight (< 500 relative molecular mass (RMM)) and highly water soluble. It must have a small volume of distribution (< 2l/kg) and bind poorly to protein. Examples include salicylates, ethylene glycol, methanol, lithium, theophylline, vancomycin and isopropranolol poisonings. Dialysis is of particular value when concomitant electrolyte or acid base disturbance exists.<sup>14</sup> Peritoneal dialysis is rarely useful.

**Hemoperfusion:** Hemoperfusion over a charcoal or resin column may be an effective treatment in certain poisonings. It is better suited to toxins with low water solubility. Such substances must have a high affinity for the adsorbant, a fast rate of equilibrium from peripheral tissues to the blood and low affinity for plasma proteins. Examples include carbamazepine, barbiturates and theophylline poisonings. The risks however are numerous including the destruction of blood components especially platelets.

**Hemofiltration:** Hemofiltration can remove compounds with high molecular weight (> 500-40,000 RMM). It is of particular use in aminoglycoside, theophylline, iron and lithium overdose.<sup>15</sup>

### Specific Antidote Therapy

Unfortunately, there are very few poisoning in which a specific antidote is useful to reverse the toxicity. For this reason, meticulous attention must be given to the

techniques for gastrointestinal decontamination or enhanced elimination. A timely supportive care alone may result in a good outcome. Table 48.5 list the common antidotes that may need to be used for patients presenting with acute toxic ingestion or dermal or inhalation exposure.

### Supportive Care

An important rule in toxicology is to “treat the patient, not the poison”. There are few agents for which a specific antidote dramatically reduces the patient’s symptoms. More often, supportive care with meticulous

**Table 48.5: Antidote therapy for poisonings<sup>16</sup>**

Toxins	Antidotes	Pediatric doses
Acetaminophen	N-acetylcysteine	Loading dose: 140 mg orally; Maintenance doses: 70 mg/kg/every, 4 hours for 17 doses orally
Anticholinergics	Physostigmine salicylate	0.02 mg/kg slow IV infusion over 3-5 minutes titrated to effect
Arsenic	Succimer (DMSA) British anti-Lewisite (BAL) (dimercaprol) only if unable to tolerate oral succimer	10 mg/kg/orally 3 times a day 3-5 mg/kg intramuscular every 4-6 hours
Benzodiazepines β-blockers	Flumazenil Glucagon	0.01 mg/kg IV bolus titrated to effect or total dose of 1-3 mg 0.15 mg/kg IV bolus, then 0.1 mg/kg/h IV infusion titrated to effect
Calcium channel blockers	Calcium chloride 10% Glucagon	0.1-0.2 ml/kg IV bolus, repeat doses and IV infusions are commonly required 0.15 mg/kg IV bolus followed by 0.1 mg/kg/h IV infusion titrated to effect
Carbamates Cyanide	Atropine Cyanide antidote kit: Sodium nitrite 3% Sodium thiosulfate	0.1 mg/kg IV bolus, repeat doses titrated to effect 0.15-0.33 ml/kg to maximum of 300 mg slow IV infusion 400 mg/kg up to 12.5 g IV infusion
Digoxin	Digoxin immune Antibody fragment	Empiric dosing: 10-20 vials IV bolus for life-threatening toxicity (see package insert for other dosing regimens)
Ethylene glycol, Methanol	Ethanol 10% Fomepizole	Loading dose 10 ml/kg IV or orally followed by maintenance dose 1-2 ml/kg/h IV infusion or orally 15 mg/kg IV bolus, repeat doses may be necessary
Iron Isoniazid	Desferoxamine Pyridoxine	5-15 mg/kg/h IV infusion 1 g per gram ingested or empiric dosing 75 mg/kg IV bolus up to 5 g
Lead	Succimer (DMSA) if Patient is able to tolerate oral medication BAL (dimercaprol) (only for lead encephalopathy) Calcium disodium EDTA	10 mg/kg orally 3 times a day, repeat doses are common 3-5 mg/kg IM or 50-75 mg/m <sup>2</sup> 20-30 mg/kg diluted in 250 ml IV infusion over 12-24 hours (start 4 hours after BAL administration)
Methemoglobinemia	Methylene blue	1-2 mg/kg slow IV infusion, repeat doses as needed
Opioids	Naloxone hydrochloride	0.4-2 mg IV titrated to effect
Organophosphates	Atropine Pralidoxime	0.1 mg/kg IV bolus, repeat dose titrated to effect 20-40 mg/kg slow IV infusion followed by 5-10 mg/kg/h continuous infusion or 20 mg/kg every 4 hours
Salicylates	Sodium bicarbonate	150 mEq + 40 mEq KCl in one liter of D5 w infused to maintain urine output at 1-2 mL/kg/h and a urine pH approximately 7.5
Tricyclic antidepressants	Sodium bicarbonate	1-2 mEq (kg IV bolus, titrate repeat boluses, do not exceed arterial pH 7.55)
Warfarin, Superwarfarins	Fresh frozen plasma Vitamin K <sub>1</sub>	fresh frozen plasma for life-threatening hemorrhage 0.6 mg/kg/slow IV infusion, subcutaneously or orally

**Table 48.6: Non-toxic substances**

*Pharmaceuticals:* Antacids, antibiotics, contraceptives, corticosteroids, laxatives, mineral oil, vitamins (without iron), zinc oxide

*Cosmetics:* Baby products, cologne, deodorants, eye makeup, hand lotion, hair products, hydrogen peroxide (household, 3%), lipstick, perfumes

*Soaps and detergents:* Suntan lotion, soap, bath foam, bubble bath, fabric softener, hand and dish washing soap, laundry detergent, shampoo

*Household products:* Artificial sweeteners, lubricating oil, ballpoint pen ink, bath oil, matches, candles, crayons, dehumidifying packets, deodorizers, silica gel, household bleach, shaving cream, shoe polish, thermometers (mercury), water colors

*Miscellaneous:* Chalk, cigarettes, clay, glues and paste, greases, pencil lead, paint (without lead)

attention to vital functions, is all that is needed to ensure a good outcome. The ABCs should always take to priority with adequate support for a clear airway, breathing and circulation throughout the management. The supportive measures needed depend on the clinical status of the child. For hypotension, the use of Trendelenberg's position, intravenous fluid or pressors agent (e.g. dopamine or norepinephrine) may be indicated. For hypertension, administration of agents appropriate for the severity of the hypertension may be necessary. Appropriate antiarrhythmic therapy may be needed for the treatment of drug induced cardiac arrhythmias. Seizures deserve special attention because toxin induced seizures may be difficult to control. Certainly if a specific antidote is available to counteract a toxin induced seizure, it should be given. For example—isoniazid induced seizures are difficult to control without the administration of pyridoxine. For most of toxin induced seizures there is no specific antidote and diazepam should be given intravenous to control the seizures. Phenytoin, phenobarbitone or both in appropriate doses should follow.

### The Stable Accidental Poisoned Patients

The approach to the stable accidental poisoning patient includes all the components as for any other poisoned patient like history, physical examination, clinical investigation (as needed) and management. The point that needs to be stressed is that many of the accidental poisonings are trivial. These children do not require

any gastrointestinal decontamination, investigation or treatment. A few hours observation may be all that is needed. Many of the household products are non-toxic, which do not necessitate any kind of treatment (Table 48.6). These children can be safely sent home after providing anticipatory poison prevention guidance.

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# Management of Specific Toxicological Emergencies

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## 49.1 Hydrocarbon (Kerosene) Poisoning

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Hydrocarbon constitute a large group of compounds, organic as well as inorganic, composed of varying amounts of carbon and hydrogen. Most of the hydrocarbons are derivatives of petroleum distillates, some are of plant origin also, e.g. turpentine oil and pine oil. So all petroleum products are hydrocarbons but not all hydrocarbons are petroleum products. Among the hydrocarbons associated with poisoning, kerosene is the most common as it is widely used as fuel due to easy availability and low cost.

### Classification of Hydrocarbons

Authors have classified hydrocarbons differently. However, the most common classification used is according to structural similarities (Table 49.1.1).<sup>1</sup> Another classification, which has been used widely, is according to the toxic potential of hydrocarbons (Table 49.1.2).<sup>2</sup> This second classification has been very helpful in deciding the management strategies.

The incidence of hydrocarbon poisoning particularly kerosene in children is largely unknown in the Indian settings due to under reporting. In general the incidence varies from 3.1 percent of all exposures in children less than 6 years of age to 20-25 percent of all childhood poisonings less than 5 years of age. Hydrocarbons account for 12-25 percent of all poisoning deaths in children less than 5 years of age.<sup>1</sup>

### Routes of Exposure

Exposure to hydrocarbon can occur via ingestion, inhalation or through skin contamination. Each route of exposure can be hazardous depending upon the amount of the hydrocarbon exposed to. Most of the effects of hydrocarbon poisoning are due to aspiration, which may occur at the time of ingestion, from vomiting after ingestion or during gastric lavage if

**Table 49.1.1: Classification according to structure similarities**

1. *Aliphatic hydrocarbons* (Straight chain hydrocarbons-Acetone, propane, butane, isopropane)  
Household products, furniture polish, lamp oils, lighter fluids
2. *Aromatic hydrocarbons* (Cyclic structures incorporating one or more benzene rings and include toluene, xylene and benzene)  
Solvents, glues, nail polish, paint and paint removers
3. *Toxic hydrocarbons*
  - a. Halogenated hydrocarbons include carbon tetrachloride, trichloroethylene, trichloroethane and fluorinated-chlorinated hydrocarbons, e.g. refrigerants, propellants, adhesives and correction fluids.
  - b. Hydrocarbons that serve as vehicles for toxic substances, e.g. Pesticides
4. *Petroleum distillates* Kerosene, gasoline, mineral seal oil (lamp fuel, furniture polish)

**Table 49.1.2: Classification according to toxic potential**

1. *Non-toxic hydrocarbons* (Unless complicated by gross aspiration)
2. *Systemic toxicity*: Halogenated hydrocarbons, aromatic hydrocarbons and hydrocarbons with additives, e.g. Camphor, heavy metals, organophosphates
3. *Aspiration hazard* (without systemic toxicity unless ingested in very large amounts) turpentine, gasoline, kerosene, ether, petrol, naphtha, furniture polish, lighter fluids, mineral spirits

attempted. Aromatic hydrocarbons especially toluene and benzene are very well absorbed from the gastrointestinal tract and can cause substantial systemic toxicity, so ingestion of these substances should be

considered an emergency. Hydrocarbons existing as gas, e.g. methane and butane have toxic potential as simple asphyxiants. Most hydrocarbons are highly irritant and cause severe skin burns, if exposed to in large quantities.

### Pathophysiology

Toxicity of the hydrocarbons is directly related to volatility, viscosity and the type of substance. Some agents are toxic if ingested, whereas others pose high aspiration risk. Viscosity or “resistance to flow” determines the aspiration potential of a hydrocarbon (measured in Saybolt Universal Seconds). Aspiration is inversely related to viscosity, i.e. lower the viscosity, higher the aspiration potential (Table 49.1.3).<sup>1,3</sup> Although highly viscous hydrocarbons have less aspiration potential, they cause systemic toxicity because of good gastrointestinal absorption.

The high volatility of these substances is responsible for the alteration in the mental status including narcosis and even frank coma. Most hydrocarbons have anesthetic properties and can cause transient CNS depression. Other CNS effects include confusion, weakness, ataxia, cognitive impairment and decreased ventilatory drive. Chlorinated hydrocarbons especially carbon tetrachloride causes hepatic and renal toxicity.<sup>4,5</sup> Long-term exposure to benzene has been associated with malignancy particularly acute myeloid leukemia. Nitrobenzene aniline and related compounds cause methemoglobinemia. Other toxicity reported with hydrocarbons include bone marrow suppression and cardiac toxicity (dysrhythmias and cardiomyopathy).

Kerosene is the most common hydrocarbon associated with poisoning and is being considered the prototype for further discussion. On aspiration the pathophysiologic changes result from foreign body reactions in the airways. Kerosene is highly irritant. On initial aspiration, irritation of the oral mucosa and the tracheobronchial tree occurs. This may be seen within minutes of the exposure. Cyanosis may occur due to displacement of the alveolar gas by the volatilized kerosene. Bronchospasm may occur which can further aggravate ventilation/perfusion mismatch. Areas of

atelectasis develop due to decrease in the surface tension, decrease in surfactant and destruction of the airway epithelium. Once set in, this progresses on to cause chemical pneumonitis with edema, hyperemia, leukocytic infiltration and vascular thrombosis. Subsequently, these areas may coalesce to form patchy bronchopneumonia. Pulmonary lesions are same for all hydrocarbons diffuse hemorrhagic exudative alveolitis, bronchiolar necrosis, micro abscesses and alveolar thickening.<sup>1,2,5</sup> Kerosene can also cause partial obstruction in airways leading to air trapping phenomenon like emphysematous changes, pneumatoceles, pneumothorax and pneumomediastinum.

### Fatal Dose and Fatal Period

Ingestion of 10-15 ml of kerosene may be fatal, although recovery has been seen following ingestion of about 200-250 ml.<sup>1</sup> Kerosene and other petroleum products have low surface tension and as a result they spread over large surface areas, e.g. lung and cause severe pulmonary irritation. Fatal period is therefore a few hours. With other hydrocarbons, presence of benzene, heavy metals and pesticides markedly increase the toxicity.

### Clinical Features

The earliest sign with kerosene ingestion may be choking, gagging, coughing and gasping respiration. Cyanosis and tachypnea may develop, which may progress within minutes to severe respiratory distress in the form of nasal flaring, grunting and chest retractions. In some cases respiratory distress can take 2-6 hours to develop. Auscultation of the chest may reveal diminished breath sounds and varying combinations of wheezes, crepitations and crackles. Pulmonary symptoms usually progress over first 24 hours and then subside by 2nd to 5th day. Large aspirations can progress on to respiratory failure and intractable hypoxia. Pulse oximetry, if available is a very important tool for bedside monitoring and early detection of hypoxia.<sup>1,4</sup>

Vomiting usually occurs, as all hydrocarbons are highly irritant and may be the cause of aspiration. Other gastrointestinal features include nausea, abdominal pain and diarrhea. Tachycardia coincides with the degree of lung injury. Dysrhythmias are less common with kerosene poisoning and also less common in children. CNS effects are common and may be the initial symptoms. Fever may occur (up to 38-39°C) and can persist for as long as 10 days. Renal injury is uncommon but may manifest as tubular necrosis, hematuria,

**Table 49.1.3: Viscosity and aspiration potential**

Aspiration potential	SUS	Examples
Very high	< 35	Gasoline, naphtha
Moderate	< 60	Kerosene, turpentine, furniture polish and waxes
Low	> 75	Mineral pills, light fuel oil

proteinuria and glomerulonephritis. Hepatic injury is also uncommon with kerosene but common with halogenated hydrocarbons like carbon tetrachloride. Fatty infiltration has been described in children.<sup>5</sup>

### Laboratory Investigations

Leukocytosis with left shift (seen in 15% patients) can occur even within 1 hour of ingestion and may be misleading of infection. It may persist for up to one week. Intravascular hemolysis and hemoglobinuria has been reported with ingestion of gasoline. Nitrobenzene and aniline have known to cause methemoglobinemia. Chest X-ray is usually normal initially and findings develop within 6-8 hours. Earliest changes have been seen to develop within 30 minutes. X-ray findings include bilateral, fine, mottled densities usually perihilar and in mid lung region, which coalesce to form areas of consolidation. Obstructive findings like hyperinflation, emphysematous changes, pneumatoceles, pneumothorax and pneumomediastinum may be seen on serial radiography. Blood gas is an important investigation and may reveal significant hypoxia with normal CO<sub>2</sub> initially. If CNS depression is marked, hypercarbia may develop rapidly.

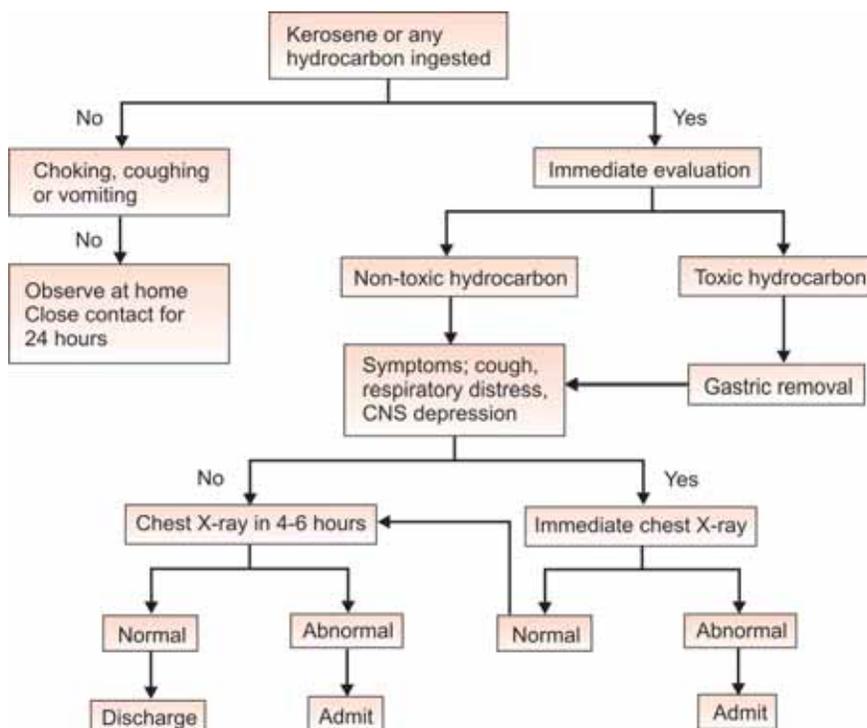
### Management

A poisoned child often represents an acute onset emergency and a systematic approach should be adopted for optimum care (Flow chart 49.1.1). The initial phase or 'primary survey' addresses support of vital functions and identification of the toxic agent wherever possible. The 'secondary survey' or 'evaluation and detoxification phase' aims at more specific evaluation followed by decontamination and neutralization of the poison along with supportive care.<sup>2</sup>

#### Primary Survey

In this phase the immediate priority is to maintain life. The general approach to evaluation and support of airways and cardiorespiratory function remains same as practiced in pediatric advanced life support ('ABCD' of resuscitation). In the context of kerosene poisoning some points deserve special attention. The pediatrician must pay special attention to any impaired airway protective reflexes. These children are at increased risk of aspiration for two reasons—first, because of high volatility and low viscosity of kerosene and second, they tend to vomit more as kerosene is highly irritant

Flow chart 49.1.1: Approach to child with kerosene poisoning



to the gastric mucosa. Children with kerosene poisoning may be agitated or depressed secondary to hypoxemia from aspiration. Hence early endotracheal intubation is indicated if these children develop severe respiratory distress or are neurologically depressed. If the child is conscious and has only mild respiratory symptoms, only oxygen to correct hypoxemia may be sufficient. Early efforts to obtain a secure intravenous line are also crucial.

### Secondary Survey

**Evaluation phase:** Once the primary steps of resuscitation have been accomplished, a brief and focused evaluation of the patient should be done. The primary goal is to determine the potential severity of toxin exposure. The focused physical examination should begin with a reassessment of the vital functions and complete recording of the vital signs including core temperature. Once this is done examination should focus on respiratory system, central nervous system, changes in skin and mucous membranes and odors. A thorough evaluation helps to assess the severity of the toxin exposure as well as follow the response to therapeutic interventions.

**Detoxification phase:** This phase involves removal of kerosene from the body. This includes cutaneous and gastrointestinal decontamination. Since kerosene is highly irritant to skin and mucous membranes any part of the skin exposed to kerosene must be thoroughly washed with soap and water. All possible sources of kerosene must be removed from the immediate vicinity of the patient. In gastrointestinal decontamination, emesis once thought to be useful, is contraindicated as it increases the risk of aspirations. Gastric lavage is also not indicated in kerosene poisoning as it increases the risk of aspiration. However, this is not universal for all hydrocarbons. The hydrocarbons for which lavage is indicated include those with high systemic toxicity due to low viscosity and good gastrointestinal absorption—Camphor containing hydrocarbons, Halogenated hydrocarbons, Aromatic hydrocarbons, heavy Metal containing hydrocarbons and Pesticide containing hydrocarbons ('CHAMP' mnemonic). Similarly activated charcoal is also not indicated for use in kerosene poisoning unless there is concomitant ingestion of other toxins or kerosene with toxic contaminants.<sup>1</sup>

**Supportive care:** The final step in optimizing the treatment for kerosene poisoning is meticulous attention to the supportive care, including close monitoring of the respiratory symptoms and signs, level of consciousness, urine output and fluid and electrolyte

status. For aspiration pneumonitis, usually O<sub>2</sub> alone is sufficient to correct hypoxemia. Development of ARDS like picture necessitates high-pressure ventilation. Ventilator therapy may require use of high PEEP to prevent atelectasis, to prevent V/Q mismatch and to maintain oxygenation.<sup>5,6</sup> Bronchodilators such as aerosolized salbutamol help to relieve the bronchospasm. Steroids have been used to reduce the inflammatory response but have not been found to be useful in kerosene poisoning. Antibiotics are usually not indicated and should not be given prophylactically. Fever and leukocytosis may be due to the pyrogenic effect of kerosene.<sup>1,2</sup>

### Prognosis

If the child improves from immediate hospitalization of aspiration, the prognosis is good. Most of the patients with kerosene poisoning recover without any residual effect, but in some, pulmonary functions may be abnormal for years.<sup>7</sup>

### Prevention

The aim of treating pediatrician is not only to treat the poisoned but also to provide **anticipatory guidance**<sup>8</sup> to parents in order to prevent any such further episodes. Parents should be guided to keep harmful substances, likely to cause poisoning, away from the reach of children. Kerosene and other such substances should be properly stored in capped containers. Use of beverage bottles or colorful containers, which attract children, should be avoided. More than that parents should be made aware of the danger signs of poisoning and in such circumstances, to rush to nearby hospital as early as possible.

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## 49.2 Datura

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*Datura stramonium* (Jimson weed, thronapple, locoweed) an annual plant grows to about 4 feet with tubular white flowers and green fruit covered with thorns. The leaf edges are serrated and the plant has a foul odor.<sup>1</sup>

The entire plant including the nectar is toxic. The pollen can cause unilateral mydriasis (Cornpickers Pupil).<sup>2</sup> The whole plant especially the foliage, seeds contain anticholinergic tropane alkaloids, also known as the belladonna alkaloids include, scopolamine, L-hyoscyamine, hyoscyamine and traces of atropine. Seeds contain highest amount of atropine (0.1 mg per seed). These toxins produce an anticholinergic poisoning syndrome characterized by the phrase “mad as the hatter, hot as a hare, dry as a bone, red as a beet, blind as a bat. Intoxication occurs by ingesting the seeds, drinking a brewed tea, or smoking the plant. In children accidental poisoning may occur due to ingestion of Datura fruits, mistaking them for edible fruits. A teenager can be a victim who ingests the seeds for hallucinogenic effects.<sup>3,4</sup> Accidental cases are also seen from use of Datura seeds by quacks for treatment of various ailments. The lethal dose for alkaloids is 4 mg though fatality is on record due to consumption of 4-6 seeds. Death usually occurs within 24 hours.

### Pathophysiology

On ingestion of Datura fruits or seeds its alkaloids get absorbed from intestine and antagonize the muscarinic action of acetylcholine (Anticholinergic syndrome). The chief sites of action of these alkaloids are cholinergic muscarinic receptors.<sup>5</sup> These are the postganglionic receptors for the parasympathetic nervous system as well as sympathetic system supplying sweat glands and smooth muscle tissue. The peripheral signs of anticholinergic syndrome because of Datura poisoning result almost entirely from blockade of these receptors.

CNS muscarinic receptors are located in the spinal cord, extrapyramidal system, reticular activating

system, vestibular system and cerebral cortex.<sup>6</sup> Nicotinic receptors are much less sensitive to anticholinergic action of belladonna alkaloids and do not play significant role in Datura poisoning, Scopolamine and atropine possess a tertiary amine group and cross blood brain barrier producing central effects.

### Clinical Features

On ingestion, clinical features appear usually within half an hour. They may be broadly divided into peripheral and central antimuscarinic effects.<sup>7</sup>

**Peripheral antimuscarinic effects:** Peripheral antimuscarinic poisoning syndrome results from the blockade of postganglionic muscarinic receptors in the parasympathetic nervous system. First affected are the function of salivation, sweating and bronchial secretion, followed by pupillary function, ocular accommodations and heart rate. At higher doses, bladder and intestinal motility are affected.

There is excessive thirst, blurring of vision and dysphoria. The skin and mucous membranes are dry. Inability to lose heat through perspiration is the major cause of hyperthermia in these patients. Temperature may become dangerously elevated (up to 40-43°C) and it may persist for days until normal thermoregulation returns. Skin and mucous membranes are dry. There is flushing of skin and symmetrical pupillary dilatation.

Tachycardia is a universal cardiovascular finding of Datura poisoning. Mild hypertension is commonly present along with sinus tachycardia. Significant hypotension may be seen with volume depletion. Rare unstable supraventricular dysrhythmias, or circulatory collapse are features of severe poisoning. Ingestion of large quantities are also associated with urinary retention and ileus.

**Central antimuscarinic effects:** The usual clinical course is one of CNS stimulation followed by depression. The children usually present with agitation, confusion and disorientation. Ataxia, tremors and clonic movements are

common. Visual incoordination may occur. Picking at clothes, bedsheets and imaginary insects is also a classic central motor sign. Patients keep on muttering indistinct words (muttering and delirium). Patient may be noisy and violent and can have dreadful hallucination. Hallucinations are usually visual but may be auditory or tactile. The child sees animals in his room, closets and drawers. Lilliputian hallucinations of tiny animals or people may be present. The patients often speaks to pets, friends or relatives that are not present.<sup>8</sup>

The acute delirium begins to wane off in an hour and is followed by a state of drowsiness. Coma is also seen as a complication of Datura poisoning and may have a prolonged, cyclical course with the patient partially awakening to periods of severe agitation and hallucinations. If anticholinergic toxicity progresses untreated, medullary respiratory depression and cardiorespiratory arrest eventually occur in fatal cases.

### Diagnostic Evaluation

The diagnosis is made clinically based on history of ingestion and typical physical findings. There is no laboratory test to confirm the diagnosis of an anticholinergic poisoning. Electrolyte and blood sugar should be obtained. Arterial blood gas determination should be done to assess acid-base and respiratory status, especially in severely poisoned patients. Chest radiograph is advised in cases of suspected aspiration pneumonitis. Examination of gastric contents may assist in confirmation of the presence of plant products and alkaloids.

### Treatment

Any patient with Datura poisoning should be admitted. All children with mild poisoning exhibiting only peripheral features should be observed in hospital for 24-48 hours. Patients with severe effects should be placed in monitored intensive care setting. Important initial measures in emergency department include assessment of airway and respiration, cardiac rhythm and blood pressure as well as immediate and accurate measurement of core temperature. Serial assessment of vital signs including temperature and mental status should be done. Cases with severe poisoning require gastrointestinal decontamination appropriate supportive care and use of specific antidotes to reverse the action of alkaloids.<sup>7</sup>

**5 Gastric decontamination:** Gastric decontamination with normal saline is useful up to 48 hours after ingestion because of delayed drug absorption from slowed gastric

emptying and decreased intestinal motility. Large doses of activated charcoal 1 gm/kg in slurry form have been recommended. On completion of lavage, activated charcoal in a dose of 1-2 g/kg, is left in the stomach. Agitated delirious patients may require endotracheal intubation prior to gastric decontamination. Ipecac is contraindicated because of the potential for altered mental status and seizures.

**Supportive care:** Supportive care includes care of airways, breathing, monitoring cardiac rhythm, core temperature and fluid status. A urinary catheter allows reliable monitoring of urine output and is usually required because of relaxed bladder musculature. An intravenous line for fluids and drugs should be secured. Hyperpyrexia is managed by cold sponging. Since hypertension is usually transient, it does not require any antihypertensive drug. Hypotension is managed by IV fluids and vasopressor amine like dopamine. Seizures should be treated with benzodiazepines and/or phenobarbital. Ventricular dysrhythmias may respond to standard doses of lidocaine. Forced diuresis and dialysis have no role in the management of Datura poisoning.<sup>5</sup>

### Specific Antidote

The specific antidote of Datura poisoning is physostigmine.<sup>8,9</sup> It is a cholinesterase inhibitor that increases amount of acetylcholine at cholinergic nerve endings. It crosses blood brain barrier because of its tertiary ammonium structure, thereby reversing both the peripheral and central anticholinergic effects of Datura alkaloids. However, it is indicated only for the patients with severe hallucinations, refractory seizures and hemodynamic instability. It has no role in tachycardia but may be indicated in some instances in which supraventricular tachycardia with hypotension is not reversed by conservative measures. Dose of physostigmine is 0.02 mg/kg (not to exceed 0.5 mg) intravenously over 5-10 minutes. Beneficial effects may take up to 20 minutes to occur. And a common pitfall is repeating the dose too often. Dose may be repeated after 20 minutes, if patient remains clearly anticholinergic until 2.0 mg have been given or reversal of toxic effects is noted. The shorter duration of action (45-60 minutes) may necessitate frequent repeated dose. Continuous infusion of physostigmine is not recommended.

Side effects are uncommon but may include excessive salivation, lacrimation, bradycardia, vomiting, abdominal cramps bronchorrhea and bronchospasm. These are effectively controlled with atropine in doses of

.01 mg/kg IV (up to 2 mg) or glycopyrrolate bromide in dose of 4-8 µg/kg IV every 2-3 minutes as needed. Cardiac monitoring is essential during its administration.<sup>9,10</sup>

### Disposition

Any case of significant toxicity with alteration of mental status or with dysrhythmias is observed overnight in an intensive care setting. Patient usually respond well to treatment within 24-48 hours. Psychiatric evaluation is warranted in cases of intentional ingestion with suicidal intention or drug abuse. In cases of possible non accidental ingestion or exposure, parental counseling is required.

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## 49.3 Opioids

Sanjay Choudhary

Opioids are naturally occurring or synthetic compounds with morphine like actions or actions mediated through binding to opioid receptors. The term 'Opioids' is preferred to term "Narcotic" which connotes only the potential to induce sleep. The more specific term "Opiate" refers only to alkaloids agents derived from opium which is obtained from milky juice of poppy, *Papaver somniferum*.<sup>1</sup> The classification of natural and synthetic opiates is summarized in Table 49.3.1.

### Pharmacology and Pathophysiology

Opioids are readily absorbed from gastrointestinal tract, lungs and muscles. Intravenous administration produces most rapid and pronounced effect and less severe actions are seen after oral ingestion because of its first pass hepatic extraction and metabolism. Opioids are metabolized primarily in the liver through conjugation with glucuronic acid and small amounts are excreted directly in urine and feces. The plasma half-life ranges from 2.5-3 hours for morphine to more than 22 hours for methadone.

Opioids interact with stereospecific saturable opiate receptors located throughout body including central

nervous systems. Five different opioid receptors have been identified; mu, kappa, delta (each with its own sub-types), sigma and epsilon  $\mu$ ,  $\kappa$  and  $\delta$  receptors, mediate analgesia above spinal cord. Spinal analgesia is mediated by  $\kappa$  and  $\delta$  receptors while sigma receptors effect dysphoria or psychomemetic responses. Sub groups of  $\mu$  receptors  $\mu_2$  may mediate respiratory, gastrointestinal and cardiovascular manifestations.<sup>3</sup> Different opioids bind with different affinities to these receptors to exhibit variable agnostic and antagonistic actions (Table 49.3.1).

Endogenous opioid peptides enkephaline, endorphin and dymorphin are the neurotransmitters in complex pain inhibitory system. Tolerance and dependence on Opioids are mainly due to complex mechanism of endogenous opioid system and partly due to changes in intracellular modulators such as adenyly nucleotide, calcium related substances as well as alteration in neurotransmitters including acetylcholine, serotonin and catecholamine. The direct effect on opioid receptors located in medulla (vomiting), limbic system (euphoria) and reticular activating system (sleep) are responsible for the neurological manifestations.

**Table 49.3.1: Classification of opioids<sup>2</sup>**

1. Pure agonist
  - a. Natural morphine
    - Codeine
  - b. Semisynthetic
    - Heroin (diacetylmorphine)
    - Hydromorphone
    - Oxymorphone
    - Oxycodone
    - Hydrocodone
  - c. Synthetic
    - Propoxyphene
    - Diphenoxylate
    - Methadone
    - Meperidine (pethidine)
2. Mixed agonist-antagonist
  - Butorphanol
  - Levallorphan
  - Nalorphine
  - Pentazocine
3. Pure antagonist
  - Naloxone
  - Naltrexone

### Clinical Manifestations of Opioids

The major manifestations of opioids on various systems are as following:

#### Central Nervous System

Opioids produce characteristic triad of CNS depression, respiratory depression, miosis. CNS depression can follow initial period of excitation. Nausea and vomiting may develop early. Infants and children may present with seizures, which are usually generalized. An impaired gag reflex may predispose the patient to aspiration of oral or gastric contents, especially during vomiting.<sup>3,4</sup>

Most important, from a toxicological point of view, is potential for profound respiratory depression resulting from reduced sensitivity of the medullary respiratory centers to a rising PCO<sub>2</sub> and depression of brainstem center that control breathing rhythmicity. Respiratory depression may be heralded by a decreased respiratory rate or reduction in tidal volume. Hypercapnia and hypoxia follow. Complete cessation of respiration is not uncommon and is leading cause of death from opioids.

**Cardiovascular system:** Orthostatic hypotension caused by arteriolar and venous dilatation due to release of histamine and central inhibition of adrenergic tone.

**Gastrointestinal tract:** Decreased peristalsis, increased segmentation and constipation. Biliary colic and increased intrabiliary pressure.

**Respiratory system:** Bronchospasm due to histamine release. Noncardiogenic pulmonary edema possibly due to anaphylaxis, hypoxia, capillary injury as well as direct CNS stimulation.

**Urinary tract:** Urinary retention.

**Miscellaneous:** Sweating, pruritus, piloerection, decreased sex drive, and prolonged labor.

### Opioid Overdose

Opioid intoxication in children is frequently the result of the accidental or suicidal ingestion of potent opioids or by a large overdose of pain medications with potentially lethal outcome. Intravenous abuse is less common in pediatric patients. The typical manifestations occur immediately with intravenous route or within an hour with oral administration. The manifestations are analgesia, nausea, drowsiness, shallow respiration, miosis, bradycardia, hypothermia and decreased peristalsis. Urinary retention and absence of responsiveness to external stimuli develop. If patient is not managed immediately, cyanosis and death may occur from respiratory depression and subsequent cardiorespiratory arrest.<sup>3,4</sup>

### Opioid Withdrawal

The time of onset as well as severity and duration of acute withdrawal are influenced by a number of variables including drug half-life, dose and chronicity of administration. The initial manifestations of opioid withdrawal are dilatation of pupils, piloerection, profuse sweating, rhinorrhea, myalgias, cramps, lacrimation and anorexia. Later restlessness, insomnia, hyperthermia, tachycardia and tachypnea occur. In severe forms of withdrawal, vomiting, diarrhea, hyperactive bowel sound and hypertension occur. Twitching of muscles and convulsions may occur.<sup>5</sup>

### Opioid withdrawal in Newborn Infant

The newborns of opioid addicted mothers develop withdrawal in 80-90 percent babies and carry a mortality of 3-30 percent if not treated, when prominent signs are apparent. The clinical manifestations of opioid withdrawal usually begin on third day. The babies usually present with irritability, excessive crying, tremor (80%), increased reflexes, tachypnea, diarrhea,

hyperactivity (60%) and vomiting (30%). The babies usually have a low birth weight.<sup>4</sup>

### Diagnosis of Opioid Toxicity

A history of drug abuse, needle marks on skin, clinical manifestations and laboratory findings all are helpful in diagnosis.

#### Laboratory Tests

1. Positive toxicological analysis of blood and urine for drugs and their metabolites.
2. Arterial blood gas-hypoxia and hypercapnia.
3. Hyperglycemia/hypoglycemia and
4. Hyperamylasemia/hyperlipasemia.

### Treatment

Initial management must be directed towards maintenance of an airway, adequate ventilation, oxygenation and circulation. This may necessitate immediate endotracheal intubation for severe respiratory depression and loss of gag reflex. An intravenous line should be secured immediately and blood samples drawn for estimation of blood glucose, electrolytes, hematocrit and toxicological analysis.<sup>7</sup>

Cardiorespiratory support includes intravenous fluids in hypotensive patients. Blood pressure should be stabilized with intravenous crystalloids and vasopressors. Oxygen administration and if necessary positive pressure ventilation is required. Cardiovascular instability often resolves with correction of hypoxia.

#### Decontamination

Gastrointestinal decontamination is indicated for opioid ingestion after initial stabilization. Decontamination means are unnecessary after injection or nasal application of opiates. However, in case of oral ingestion induce emesis with syrup of ipecac or perform gastric lavage to remove any remaining drug. These are useful even after hours of ingestion due to decrease gastrointestinal mobility. Care should be taken to use a cuffed endotracheal tube to prevent aspiration in case patient is not alert. Administer activated charcoal in a dose of 1 g/kg in a slurry form with a cathartic while protecting the airway at all times. Activated charcoal binds most opioids. Saline cathartic or glycerol should be copiously provided until charcoal is apparent in stools. One to two g/kg of activated charcoal should be left in the stomach after completion of lavage to prevent further absorption of the drugs.

#### Specific Treatment

Naloxone (N-allyl noroxymorphone) is a specific opioid receptor antagonist capable of reversing the effects of opioid intoxication. Given an initial dose of 0.1 mg/kg for children 1 month to 5 years (or < 20 kg). In older children, a minimum dose of 2.0 mg is recommended. If there is no clinical response another 2.0 mg is given every 2 to 3 minutes until at least 10 mg. is given without a response.<sup>8</sup> Naloxone may be given by continuous infusion in the doses of 20 to 40 µg/kg/h<sup>9</sup>. Gold frank et al have provided a dosing normogram for continuous infusion.<sup>10</sup>

In a suspected case of opiate poisoning, at least three doses at three minutes interval should be tried before ruling out narcotic involvement. Any improvement in mental status or pupillary findings confirm this. Any patient who demonstrates improvement with naloxone should continue to receive the drug as often as required until mental status improves and respirations are normal and stable. This may require administration of drug every five minute, with continuation of the drug up to several days. Careful monitoring and maintenance of respiration and oxygenation must be continued until the depressant effects of the narcotic is clearly resolved.

The major complication associated with naloxone is withdrawal syndrome which occurs almost exclusively in narcotic dependent patient. Other antidotes are nalorphine, levallorphan and naltrexone. Naltrexane, a pure antagonist to opioid receptors is effective in rehabilitation of patients because of its longer duration of action (24 hours). For effective rehabilitation, the patients should be free of opiates for a minimum period of five days.

Convulsions and cardiac arrhythmias should be managed with appropriate anticonvulsants and antiarrhythmic drugs respectively. Appropriate antibiotics are given if there is any evidence of infections.

#### Dispensation

Admit all patients with severe respiratory depression for overnight observation, regardless of how completely their symptoms resolve after naloxone.

#### Management of Opioid withdrawal

Proper physical examination of the patient including neurological should be done. Attention should be directed to search for local and systematic infections. Proper nutrition is given and rest is advised. Patients with mild opioid withdrawal may be managed by

calming and reassurance alone. Moderate to severe withdrawal requires readministration of sufficient opiate on day one to decrease symptoms followed by a more gradual withdrawal of the drug usually over 5-10 days. Methadone is the opioid of choice and the first dose is estimated from the previous history of amount ingested. Methadone 1 mg is approximately equivalent to 3 mg of morphine, 1 mg of heroin and 20 mg meperidine (Pethidine). The equivalent dose of methadone is given in two divided doses. After several days of stabilization, the original dose of methadone is tapered by 10-20 percent each day.

Clonidine, an alpha-2-adrenergic agonist may be used in part to decrease sympathetic overactivity. It is effective in relieving discomfort and pain. Clonidine is often not well tolerated because it produces high levels of sedation and orthostatic hypotension. The dose of clonidine is 5 µg/kg to a maximum of 0.3 mg in 2-4 divided doses.

Successful patient management demands excellent psychiatric and social support for the patient. This requires comprehensive program for rehabilitation.

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## 49.4 Acetaminophen Poisoning

Utpal Kant Singh, Rajniti Prasad

Acetaminophen is the most widely used antipyretic and analgesic. It is a combination agent in approximately 125 medications that has been deemed safe and effective when used within recommended dosage. Its therapeutic safety in children has been directly related to absence of significant cumulative kinetics. In USA, 203,930 cases of acetaminophen over ingestion were reported to US poison centers between 1998 and 1999, making it the leading pharmacologic agent associated with toxicity.<sup>1</sup> It is freely available in the market and its use is widely known to general public. Careless approach of family members towards its use and storage results in high incidence of accidental overdose in children particularly below the age of 6 years, less common but potentially more devastating is the suicide attempt as manipulative episode in the adolescent.

Experience with acetaminophen overdoses further indicates a considerable difference between the child under age 6 years and adolescent.<sup>2</sup> Following ingestion

of sufficient acetaminophen to produce potentially toxic blood level, an adolescent is six times more likely to develop evidence of hepatotoxicity than in a child under age of 6 years.<sup>3</sup> Adolescents are two times more likely to develop potentially toxic blood levels. The course following overdose in adolescents is indistinguishable from that of adults.

### Pathophysiology

The prime target organ of acetaminophen toxicity is liver. In addition to hepatotoxicity, renal tubular damage and hypoglycemic coma may also occur due to toxic action of active intermediate metabolites. Acetaminophen is rapidly absorbed after therapeutic dose and produces peak plasma level in half of one hour. In overdose, this absorption may be delayed as long as 4 hours. The volume of distribution and half life of acetaminophen with normal liver function are 1 L/kg and 1 to 3 hours respectively. The drug is

metabolized in liver with less than 2% being excreted unchanged in urine.<sup>4</sup>

In children, between 9 to 12 years of age, acetaminophen is primarily metabolized in the liver to the sulfate or glucuronide conjugates which are metabolically inert. The remaining 2 to 4% is metabolized through cytochrome p-450 mixed functions oxidase system which conjugates it with glutathione to produce mercaptopuric acid, a non-toxic product. The lower incidence of toxicity in young children may be related to lesser metabolism via p-450.<sup>5</sup>

With acetaminophen overdose, when hepatic stores of glutathione are depleted to less than 70% of normal, the highly reactive intermediate toxic metabolites bind with hepatic macromolecules and cause hepatic necrosis.<sup>6</sup> Hepatic enzyme induction by barbiturates, narcotics, hydantoin and histamines may increase the formation of reactive metabolites, predisposing the patient to hepatic damage even if a minor overdose of acetaminophen is ingested.<sup>7</sup> Co-ingestion of ethanol and acetaminophen is cytoprotective in both adults and children, probably as a result of competition at P-450 site but ethanol is not recommended as therapy.<sup>8</sup>

Chronic acetaminophen poisoning is rare as approximately 98% of the drug is metabolized by liver, children receiving therapeutic doses of acetaminophen over a long time should have no difficulty in managing the small load of toxic metabolites with constantly regenerating glutathione stores in liver. Therapeutic accumulation to plasma levels of 40 µg/dl which is still under that required for hepatotoxicity may occur if the highest recommended dose of 15 mg/kg is given every 4 hours for extended period, child abuse or intentional overdose must be considered in children who develop high plasma levels at therapeutic overdose.<sup>9</sup>

### Clinical Features

Children with overdose of acetaminophen usually present with features of hepatic cell damage, renal tubular necrosis and hypoglycemic coma. They pass through following four stages of toxicity if left untreated.<sup>10</sup>

**Stage I:** This stage lasts for first 24 hours after ingestion. Average time of onset of symptoms is 6 hours after ingestion and children usually become symptomatic by 14 hours. In this stage child usually presents with anorexia, nausea, vomiting, malaise, pallor and diaphoresis, children less than 6 years of age rarely show diaphoresis but present with early vomiting. Laboratory investigations

such as ALT, AST, serum bilirubin and prothrombin time are normal in this stage.

**Stage II:** This stage lasts for next 24 hours after stage I. It is characterized by resolution of symptoms of stage I with upper quadrant abdominal pain and tenderness. Mild hepatomegaly and jaundice may also be present. Laboratory investigations show elevated serum bilirubin, AST, ALT and prothrombin time. Some children may develop oliguria.

**Stage III:** This stage is seen 48 hours to 96 hours after ingestion. Maximum liver functions abnormalities are seen during this period. Hepatotoxicity due to acetaminophen is characterized by elevated transaminases, increased serum bilirubin and prolonged prothrombin time.

Plasma AST level in excess of 1000 IU/L, prolongation of prothrombin time and serum bilirubin more than 4 mg/dL on 3rd to fifth day after ingestion are indicators of severe toxicity.<sup>11</sup> Acute renal failure may also occur in some patients. Anorexia, nausea, vomiting and malaise may reappear during this stage. Less than 1% of patients in stage III develops fulminant hepatotoxicity and eventually dies of hepatic failure, if left untreated. Liver biopsy in this stage reveals centrilobular necrosis of hepatocytes with sparing of periportal area.

**Stage IV:** This is the stage of resolution and extends from 4 days to two weeks. It is characterized by resolution of hepatic dysfunction although AST may remain elevated for few more days. On follow up of patients who had hepatotoxicity, usually revealed no sequelae either clinically or on liver biopsy, three months to one year later.

### Diagnosis

1. History of ingestion
2. Clinical features
3. Laboratory investigations
  - a. Plasma level of acetaminophen to assess the severity of hepatotoxicity: Serum concentrations greater than 200, 100 and 50 µg/ml at 4, 8 and 12 hours after ingestion respectively or any concentration above the values depicted on the Rumack Mathew normogram indicates a potential risk of hepatotoxicity.<sup>2</sup>
  - b. Plasma AST level greater than 1000 IU/L

- c. Bilirubin more than 4 mg/dL
- d. Prolonged prothrombin time.

### Management

1. **Assessment:** In children with acetaminophen overdose, efforts should be made to determine the amount of drugs or other co-ingestants which may also have been involved. Acetaminophen alone will not produce any alteration in the sensorium in first 24 hours and usually will not produce such an alteration unless patient develops hepatic encephalopathy. Thus, if a patient comes with a significant change in sensorium, some other agents should be considered in addition to or instead of acetaminophen care of airways, breathing and circulation should be done properly. A sample of blood should be drawn and sent for laboratory investigations including serum acetaminophen level.
2. **General measures:** When a child presents with a history acetaminophen overdose within 4 hours, gastrointestinal decontamination should be done. Emesis should be induced with syrup of ipecac to get rid of remaining acetaminophen. Gastric lavage must be done with normal saline. Activated charcoal is effective in adsorbing acetaminophen. In physiological pH range, adsorption is rapid and pH independent.<sup>12</sup> The dose of activated charcoal is 10 times the ingested dose of acetaminophen. Activated charcoal appears to reduce the number of patients who achieve toxic acetaminophen concentrations and thus may reduce the need for treatment and hospital stay.<sup>13</sup> For maximal effect, activated charcoal should be administered within 30 minutes of ingestion. However, *in vitro* experiments, activated charcoal effectively adsorbs both methionine and N-acetylcysteine, concurrent administration of both would markedly diminish their antidotal effectiveness.<sup>14</sup>

**Table 49.4.1: Biochemical and hematological abnormalities in paracetamol poisoning**

Biochemical	↑ ALT/AST
	↑ Bilirubin
	↓ Blood glucose
	↓ Lactase
	↑ Amylase
	↑ Creatinine
	↓ Phosphate
Hematological	Thrombocytopenia
	↑ Prothrombin time
	↓ Clotting factors II, V, VII

### Specific Measures

N-acetylcysteine is the specific antidote and drug of choice for prevention of hepatotoxicity. Other drugs like methionine, cysteamine are available but are not popular due to their side effect. Oral or intravenous N-acetyl cysteine mitigates acetaminophen induced hepatorenal damage as demonstrated by prevention of elevation of serum transaminases, bilirubin and prolongation of prothrombin time, if given within 10 hours but becomes less effective thereafter. *In vivo*, N-acetyl cysteine forms L-cysteine, cystine, L-methionine, glutathione and mixed disulfides; L-methionine also forms cysteine thus giving rise to glutathione and other products.<sup>15</sup> The beneficial effects of N-acetyl cysteine include improvement of liver blood flow, glutathione replenishment, modification of cytokine production and free radical oxygen scavenging.<sup>16</sup>

The oral dosage schedule of N-acetylcysteine is 140 mg/kg of body weight as loading dose followed by subsequent doses of 70 mg/kg body weight at 4 hourly intervals for an additional 17 doses.<sup>17</sup> If the patient vomits within an hour of administration of dose, it should be repeated. If there is persistent vomiting, a nasogastric tube should be inserted, preferably into the duodenum. The optimal route and duration of administration of N-acetylcysteine are controversial. On the basis of selected Post-hoc analysis, oral N-acetyl cysteine was found superior to intravenous route in presentations later than 15 hours. However, the differences claimed between oral and intravenous N-acetylcysteine regimes are probably artifactual and relate to inappropriate subgroup analysis. A shorter hospital stay, patient and doctor convenience and the concerns over the reduction in bioavailability of oral N-acetylcysteine by charcoal and vomiting make intravenous N-acetylcysteine preferable for most patients with acetaminophen poisoning (Table 49.4.1).<sup>18</sup> The administration of activated charcoal before oral N-acetyl cysteine in acetaminophen overdose does not reduce the efficacy of N-acetylcysteine and may provide additional hepatoprotective benefit. However, some workers have suggested increment of loading dose by 40% or from 140 mg/kg to 235 mg/kg body weight.<sup>19</sup>

As unpleasant odor and frequent vomiting is associated with its use, the concentration of N-acetylcysteine should be diluted to a final concentration of 5%(w/v) and to mask the unpleasant flavor, citrus fruit juices or carbonated beverages should be added with intravenous preparations loading dose should be given with 200 ml of 5% dextrose over 15 minutes followed by subsequent doses in 500 ml dextrose over 4-8 hours.

Nausea, vomiting and diarrhea may also occur as results of oral N-acetylcysteine administration. Anaphylactoid reactions including angioedema, bronchospasm, flushing, hypotension, hypokalemia, nausea/vomiting, rashes, tachycardia and respiratory distress may occur 15-60 minutes after N-acetylcysteine infusion in up to 10% of patients. A reduction in the loading dose of N-acetylcysteine may reduce the risk of adverse reactions while maintaining efficacy.<sup>15</sup> Oral therapy with N-acetylcysteine or methionine for acetaminophen poisoning is contraindicated in presence of coma or vomiting or if activated charcoal has been given by mouth. Hemodynamic and oxygen delivery and utilization parameters must be monitored carefully during delayed N-acetylcysteine treatment of patients with fulminate hepatic failure, as unwanted vasodilatation may be deleterious to the maintenance of mean arterial blood pressure.<sup>16</sup>

The administration of N-acetylcysteine for longer period might provide enhanced protection for patients in whom acetaminophen absorption or elimination is delayed. N-acetylcysteine may also have a role in treatment of toxicity from carbon tetrachloride, chloroform, 1, 2-dichloropropane and other compounds.<sup>15</sup>

Methionine acts by replenishing cellular glutathione stores or more probably through generation of cysteine and/or glutathione. It acts also as a source of sulfate and so unsaturates sulfate conjugation. Methionine is more effective when given orally than IV. The initial dose is 2.5 gm then 2.5 gm 4 hourly to a total of 10 gm over 12 hours.<sup>14</sup>

During the course of treatment, laboratory investigations should be repeated. If the liver function tests begin to become abnormal, proper measures should be taken. Once hepatic failure occurs, use of N-acetylcysteine is contraindicated<sup>15</sup> and patient should be managed along conventional line with lactulose, vit-K, 20% mannitol and appropriate IV fluids. Renal function should be evaluated periodically and necessary measures should be taken, if deterioration occurs.

Forced alkaline diuresis is of no therapeutic value. Hemodialysis or charcoal hemoperfusion enhances elimination of acetaminophen but not the toxic metabolites.

### Prognosis

The poor prognostic factors in established paracetamol induced hepatic failure are pH below 7.3, serum creatinine above 300  $\mu\text{mol/L}$  and prothrombin time above 100 seconds in grade III to IV encephalopathy. However, factor VIII to factor V ratio above 30 is the best poor prognostic indicator.<sup>16</sup>

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## 49.5 Organophosphorus Poisoning

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Organophosphorus (OP) compounds and carbamates are the two main classes of pesticides used for agricultural and domestic purpose. They together account for 80 percent exposure to insecticides. Organophosphates are the most widely used pesticide today (agriculture, industry, the home, gardens and in veterinary practice) and the cause of more incidences of pesticide poisoning than any other chemical class of pesticides.

There are more than 40 organophosphate pesticides in the market today and all can have acute and sub-acute toxicity.<sup>1,2</sup> The spectrum of toxicity varies according to the compound. The most toxic compounds include parathion, mevinphos, TEPP and disulfoton. Intermediately toxic are coumaphos, chlorpyrifos and trichlorfon, while the least toxic malathion, dichlorvos and diazinon are used for household and garden insects.<sup>3</sup> Exposure produces a characteristic syndrome in humans, though the classically described clinical syndrome in adults often is not found in young in children. Since the toxicity is treatable, recognition and timely intervention are of great importance.

### Epidemiology

Acute pesticide poisoning is an important cause of morbidity and mortality worldwide. It has been estimated that around three million severe cases of acute pesticide poisoning occur each year with some 220,000 deaths.<sup>4</sup>

Ninety-five percent of fatal pesticide poisonings occur in developing countries.<sup>5</sup> Children are particularly susceptible to poisoning because of their physiological and behavioral characteristics and are up to 10 times more vulnerable to chemical toxicities than adults because of larger surface area and limited detoxification mechanisms.<sup>6</sup> Given the same exposure, an outcome of poisoning is not dependent on sex.

### Pathophysiology

The primary mechanism of action of OP pesticides is inhibition of the neurotransmitter acetylcholinesterase (AChE) by irreversibly binding to it, causing its phosphorylation and deactivation. This inhibition leads to subsequent accumulation of acetylcholine at the neural synapses leading to an initial overstimulation, followed by eventual exhaustion and disruption of postsynaptic neural transmission in the CNS and

peripheral nervous system. Clinical manifestations are the result of muscarinic, nicotinic and CNS receptor stimulation.

Pathophysiology of cardiorespiratory failure in severe intoxication is multifactorial. Hypoventilation, leading to respiratory failure, occurs due to muscle weakness, seizures, CNS respiratory center depression or upper airway obstruction from accumulation of secretions and hypotonic weakened pharyngeal musculature. ARDS has been reported after severe poisoning.<sup>7</sup> As hydrocarbons are common solvents for OP, their aspiration can aggravate respiratory failure. Cardiac involvement can be divided into three phases; initial phase is manifested by tachycardia and hypertension due to nicotinic receptor stimulation, followed by the second phase of muscarinic receptor and parasympathetic discharge with sinus bradycardia and AV block. The third phase is characterized by prolonged QT interval, with TU waves, premature ventricular beats and ventricular tachycardia. This arrhythmia can occur in the early period or may even be delayed for several days causing delayed deaths.<sup>3</sup> The exact cause of this delayed effect is not clear. Other arrhythmias like supraventricular tachycardia SVT may also be seen.

Depression of respiration and pulmonary edema are the usual causes of death from organophosphate poisoning. Recovery depends ultimately on generation of new enzyme in all critical tissues. If the organophosphate-cholinesterase bond is not broken by pharmacological intervention within 24 hours, large amounts of cholinesterase are destroyed, causing long-term morbidity or death. After-effects of severe poisoning can last 1 to 3 weeks after the initial exposure. Some effects may last 1 to 3 months. The full long-term health effects of continued exposure to low doses over time are not well understood.

### Clinical Features

Organophosphates are efficiently absorbed from the skin, lungs and gastrointestinal tract. Hence poisonings occur by ingestion, inhalation, ocular exposure, dermal exposure (particularly at high temperature and in dermatitis), mucous membrane involvement, and parenteral exposures. The quickest symptoms occur with inhalation, followed by GI absorption and dermal exposure, with respiratory symptoms being the most critical.<sup>8</sup>

## Acute Effects

Onset and duration of symptoms depend on the nature and type of OP compound, the degree and route of exposure, lipid solubility, and rate of metabolic degradation. Most patients become symptomatic within 12 hours after exposure.<sup>3</sup> Symptoms may develop within minutes of massive ingestion or inhalation whereas on exposure to highly fat-soluble organophosphates (fenthion), clinical manifestations may develop after several days.<sup>9</sup>

All signs and symptoms of acute organophosphate poisoning are cholinergic in nature, and can be divided into 3 broad categories based on receptor types:

### 1. Muscarinic effects

- **Cardiac:** Bradycardia, hypotension, heart block, arrhythmia.
- **Respiratory:** Bronchorrhea, bronchospasm, dyspnea, cyanosis, pulmonary edema.
- **Gastrointestinal:** Anorexia, cramps, vomiting, nausea, diarrhea, fecal incontinence, tenesmus.
- **Salivary glands:** Excess salivation, increased sweating.
- **Eyes:** Miosis, lacrimation, blurred vision.
- **Bladder:** Urinary incontinence.
- **Others:** Garlic odor, hypothermia, pancreatitis.
- These can be remembered by the mnemonic SLUDGE/BBB (salivation, lacrimation, urination, diarrhea, gastrointestinal upset, emesis, bronchorrhea, bronchospasm, bradycardia).
- And DUMBELS (diaphoresis and diarrhea; urination; miosis; bradycardia, bronchospasm, bronchorrhea; emesis; lacrimation; salivation).<sup>10</sup>

### 2. Nicotinic effects (Effect on voluntary muscles)

- Skeletal muscle fasciculations, fatigue, paralysis, respiratory muscle weakness, diminished respiratory effort
- Sympathetic ganglia tachycardia, hypertension, mydriasis, pallor hyperglycemia.

3. **Central nervous system effects:** Anxiety, restlessness, delirium, psychosis, headache, dizziness, confusion, ataxia, seizures, insomnia, dysarthria, tremors, central respiratory paralysis, hypotonia, cardiovascular depression and coma.

With low doses of organophosphates, muscarinic symptoms are the most prominent. In more severe intoxication, nicotinic and central muscarinic activity may predominate. Thus, tachycardia and hypertension can be important signs of severe poisoning and the expectation of bradycardia should not cause delay in therapy.<sup>11,12</sup> Signs and symptoms in children are often different from those in adults. Children, particularly

younger ones, present with altered levels of consciousness including lethargy and coma (54-96%) and seizures (25%) rather than the classic SLUDGE syndrome observed more commonly in adults.<sup>13,14</sup>

### Delayed Effects

There are two delayed effects noted after OP poisoning as follows:

**Intermediate syndrome:** This syndrome occurs after resolution of a severe, acute cholinergic crisis, 24-96 hours after an exposure, and is not rare.<sup>15,16</sup> There is usually a period of apparent full recovery where the patient is free of cholinergic symptoms. It primarily involves acute respiratory and muscular paresis, especially of proximal limb muscles and those of the face and neck flexors, and also includes cranial nerve palsies and decreased deep tendon reflexes. This syndrome lacks muscarinic-type symptoms and appears to result from a combined pre- and post-synaptic neuromuscular dysfunction. It tends to occur in patients with prolonged exposure prior to treatment. It may persist for 4-18 days, can require intubation, and can be complicated by infections or cardiac arrhythmias. These symptoms do not respond well to atropine and oximes and treatment is mainly supportive.<sup>17</sup>

Organophosphate-induced delayed polyneuropathy (OPIDP) occurs 2-3 weeks after exposure to large doses of certain OPs. Patients also may have persistent CNS effects, weakness, lethargy, fatigue, and memory loss. Distal muscle weakness with relative sparing of the neck muscles, cranial nerves, and proximal muscle groups characterize OPIDP. Recovery can take up to 12 months, may be incomplete with residual neurological defects.<sup>18,19</sup>

### Differential Diagnosis

The full clinical symptoms present no diagnostic dilemma. A history of exposure combined with physical signs and symptoms consistent with organophosphorus poisoning often lead to the diagnosis. Coma with pinpoint pupils should bring to mind organophosphorus poisoning as one of the possibilities.<sup>20</sup> However, mild flu like symptoms from minimal exposures frequently are unreported or untreated. These symptoms may be falsely attributed to a viral etiology rather than poisoning.<sup>10</sup> Other differentials include sepsis, gastroenteritis with dehydration, reactive airway disease, acute respiratory distress syndrome, cardiogenic shock, septic shock, brain hemorrhage, hypoglycemia, severe pneumonia, status epilepticus and, other toxicity.

Post-ganglionic adrenal stimulation can lead to severe hyperglycemia and glycosuria and may be confused with DKA, but there is no ketonuria and ketoacidosis.<sup>21</sup> Presence of wheeze, coughing, fever and leukocytosis may mimic lower respiratory tract infection. Low-grade fever may persist for many days and should not be confused with infection.<sup>3</sup>

### Diagnosis

If there are strong clinical indications of acute organophosphate poisoning, the patient should be treated immediately, without waiting for laboratory confirmation. Depressions of plasma pseudocholinesterase and/or RBC acetylcholinesterase enzyme activities are the generally available biochemical indicators of excessive organophosphate absorption. Depression of the plasma enzyme generally persists several days to a few weeks; the RBC enzyme activity may not reach its nadir for several days, and usually remains depressed for up to 1-3 months, until new enzyme replaces that inactivated by organophosphate.<sup>22</sup> As individual variability of enzyme levels is common, laboratory normals must be used with caution. Mild, moderate and severe poisoning is associated with >20 percent, 10-20 percent, and < 10 percent activity respectively.<sup>23,24</sup> The sample should be taken before giving oxime therapy, as it will normalize red cells enzyme though pseudocholinesterase activity is not affected.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to 48 hours thereafter. Detection of intact organophosphates in the blood is usually not possible except during or soon after absorption of substantial amounts. In general, organophosphates do not remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is large or the hydrolyzing liver enzymes are inhibited.<sup>25</sup>

Other supportive laboratory tests include chest X-ray, serum electrolytes, BUN, creatinine, complete blood counts, arterial blood gases and ECG. Many retrospective studies have shown that a prolonged QTc interval is the most common ECG abnormality.<sup>26</sup> Elevation of the ST segment, sinus tachycardia, sinus bradycardia, and complete heart block (rare) may also occur (Sinus tachycardia occurs just as commonly as sinus bradycardia).

### Management

Therapy of patients with organophosphate poisoning depends on the severity. In the mildest cases only

observation is required, but aggressive cardiorespiratory support may be needed for the most seriously intoxicated patients. Pediatric patients with severe, life-threatening exposures should be transferred to a facility equipped with an intensive care unit and pediatric intensivist. The patients should be clinically stable prior to transfer. Identify the type of ingestion, time interval, and current symptoms, and relate the amount ingested to the patient's weight. If the quantity of liquid ingestion is unknown, it may be estimated that the average swallow of a young child is 5-10 ml and that of an older child or adolescent is 10-15 ml.<sup>27</sup> Persons attending to the victim must protect themselves from contact with contaminated skin, clothing and vomitus. Rubber gloves should be worn, as vinyl gloves provide no protection from organophosphates.<sup>28</sup>

#### *Airway, Breathing, Circulation*

The airway must be protected. Ensure a clear airway by aspiration of secretions. Intubate as necessary and improve tissue oxygenation as much as possible to minimize the risk of ventricular arrhythmias when administering atropine. Oxygen should be administered to maintain saturation above 90 percent. The patient may need mechanical ventilation, if respiration is depressed. In severe poisonings, this may be necessary for several days, since muscular weakness, excessive secretions, emesis and seizures all contribute to respiratory failure. Intubation with PEEP may be needed for pulmonary edema refractory to full atropinization.<sup>10</sup> However, for patients in respiratory distress, atropine is more helpful at controlling the secretions and bronchospasm than intubation with PEEP. Intravenous fluids are indicated for volume depletion following prolonged course of vomiting, diarrhea and increased secretions. As intubation may be necessary in cases of severe poisoning, succinylcholine should be avoided as it is metabolized by means of plasma cholinesterase, OPC or carbamate poisoning may cause prolonged paralysis. Increased doses of nondepolarizing agents, such as pancuronium or vecuronium, may be required to achieve paralysis because of the excess ACh at the receptor.<sup>29</sup>

#### *Skin Decontamination*

The patient must be thoroughly washed with soap and water, twice, since one washing only removes 50 percent of the toxin. Contaminated clothing should be promptly removed and properly discarded.

### *GI Decontamination*

Gastric lavage should be performed and activated charcoal may be given in cases of ingestion, although charcoal is not expected to bind well to organophosphates. The dose of activated charcoal for < 2 years is 1-2 g/kg PO, up to 15-30 g and for > 2 years is 1 g/kg PO, up to, 50-100 g. Dosage 0.5 g/kg may be repeated every 4 hours.<sup>10</sup> Many patients will have persistent vomiting and lavage will not be necessary.

### *Atropine Sulfate*

Atropine is the specific antidote for muscarinic effects and should be administered early. It has no effects against nicotinic actions and also does not reactivate the cholinesterase enzyme. Respiratory support is therefore vital. Despite these limitations, atropine is life saving agent. Favorable response to a test dose of atropine (1 mg in older children, 0.01 mg/kg in children under 12 years) can help, if necessary to differentiate poisoning by anticholinesterase agents from other conditions. Tachycardia is not a contraindication to atropine as it could be due to hypoxia and continuing autonomic stimulation.<sup>3</sup>

Where intravenous access is not available, atropine may be administered via the intramuscular, subcutaneous, endotracheal or intraosseous (<6 years) routes. In children >12 years the initial dose is 1-2 mg and in <12 years it is 0.05 mg/kg with a minimum dose of 0.1 mg to prevent reflex bradycardia. Repeat the dose every 10-15 minutes until atropinization is achieved. Large doses may be required, as much as several grams per day. The desired end-point is defined as clearing of secretions (reversal of muscarinic effects) and not pupillary changes.<sup>3</sup> Maintain atropinization with repeated dosage of 0.02-0.05 mg/kg body weight for 2-12 hours or longer depending on severity of poisoning. Doses should be given every 30-60 minutes because of the relatively short half-life of atropine. Rales in the lung bases indicate inadequate atropinization. Miosis, nausea, bradycardia, and other cholinergic manifestations also signal the need for more atropine. Severely poisoned individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested for lesser severity of poisoning may be needed. The dose of atropine may be increased and the dosing interval decreased as needed to control symptoms. Continuous intravenous infusion of atropine may be necessary when atropine requirements are massive and the dose is 0.02 to 0.08 mg/kg/h, depending on the degree and stage of intoxication.<sup>30</sup> The adjunctive use of nebulized atropine has been

reported to improve respiratory distress, decrease bronchial secretions and increase oxygenation.<sup>31</sup> Signs of improvement after 12-24 hours are indications to begin gradual tapering of atropine doses.

It should be noted that children only slightly or not poisoned by organophosphates may develop signs of atropine toxicity from such large doses manifesting with fever, muscle fibrillations or delirium. If these signs appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily, while the severity of the poisoning is re-evaluated.

### *Pralidoxime (2-PAM)*

Within 24-48 hours of the organophosphate binding to AChE, some phosphorylated AChE can be dephosphorylated (reactivated) by the oxime antidote 2-PAM. As time progresses, the enzyme-phosphoryl bond is strengthened in a process called aging. Traditionally, it was felt that 2-PAM was not useful after this time period. However, there are case reports of improvement with 2-PAM days after exposure.<sup>32</sup> When used early pralidoxime relieves the nicotinic as well as muscarinic effects of poisoning, so it should be administered as early as possible in cases of severe poisoning.<sup>3</sup> Increased muscle strength should begin in 30 min. This drug must not be used as an alternative or in preference to atropine, the use of which is essential.

Dosage of 2-PAM in patients over 12 years old is 1-2 g by IV infusion over 30 minutes. Children less than 12 years of age should receive 20-50 mg/kg (depending on severity of symptoms) IV over 30 minutes. 2-PAM may be given as a deep IM injection if necessary. The dosage in all patients may be repeated in 1-2 hours, then at 6-12 hour intervals as needed. Continuous infusion may be beneficial in some cases in the dose of 8 mg/kg/h until clinical recovery is observed and for at least 24 hours. Infusion should be slow, achieved by administering the total dose in 100 ml of normal saline solution over 30 minutes, or longer.<sup>33</sup> A more recent randomized study in patients with moderately severe anticholinesterase pesticide poisoning comparing continuous vs bolus pralidoxime showed that patients with the continuous pralidoxime infusion were found to have decreased atropine requirements and decreased need for intubation.<sup>34</sup>

Blood pressure should be monitored during administration in view of the occasional occurrence of hypertensive crisis. Side effects of 2-PAM are usually minimal, and include hypertension, blurred vision, and dizziness.

In case of large amount of ingestion or continuing transfer of highly lipophilic organophosphates from fat into blood, it may be necessary to continue administration of pralidoxime for several days beyond the 48 hours post-exposure interval.<sup>35</sup>

### *Glycopyrrolate*

It has been recently studied as an alternative to atropine and found to have similar outcomes using continuous infusion.<sup>36</sup> The apparent advantage was a decreased number of respiratory infections. It may represent an alternative when there is a concern for this due to excessive and difficult to control secretion and in the presence of altered level of consciousness where the distinction between atropine toxicity or relapse of OP poisoning is unclear. Dose in adolescents it is 1-2 mg IV, in children 0.025 mg/kg IV prn to control peripheral cholinergic effects (e.g., bronchorrhea).<sup>37</sup>

### *Contraindications*

The following medications are contraindicated in organophosphate poisonings: succinylcholine, morphine, theophylline and phenothiazines. Diazepam or lorazepam is a safe drug for sedation and for controlling seizures.

**Other treatments:** Prospective studies of both magnesium and fresh-frozen plasma as adjunctive therapy in OP poisoning have shown improved mortality rates with both treatments.<sup>38,39</sup> However, both must be evaluated further. Nebulized ipratropium bromide may also have therapeutic effects as an adjunct agent.

### *Inpatient Monitoring*

Most patients requiring therapy for organophosphate poisoning require hospital admission for continued monitoring and therapy. The patient should be observed for 24 hours after the last dose of atropine is given.<sup>40</sup> Reports of delayed respiratory arrest following inadequate treatment exist. Patients requiring continuous airway and neuromuscular monitoring will require intensive care unit (ICU) observation. Pulse, blood pressure, ECG, SaO<sub>2</sub>, respiration, and level of consciousness should be monitored. Close observation of the patient's progress should be made during treatment, as it may be required up to 10 days in severe cases. Arrhythmias may not respond to usual treatment and artificial pacing may be indicated. Monitor patient during administering atropine and 2-PAM until QT interval improves.

### **Sequelae**

Persistent CNS effects (e.g. irritability, fatigue, impaired memory, depression, psychosis) and peripheral neuropathies (e.g. weakness, paresthesia, ataxia, chronic pain) have been reported in survivors of significant organophosphate poisoning and in patients with multiple small exposures over prolonged periods.<sup>41,42</sup> Such sequelae may last for weeks or years.<sup>43</sup>

### **Prognosis**

Mortality rates depend on the type of compound used, amount ingested, general health of the patient, delay in discovery and transport, insufficient respiratory management, delay in intubation, and failure in weaning off ventilatory support. The primary cause of death in acute poisoning is usually respiratory failure with a contributing cardiovascular component. Worldwide mortality studies report mortality rates from 3-25 percent<sup>44</sup> compared to 0.3% in developed countries<sup>45</sup> OP poisoning has a high inpatient mortality and many patients have cardiorespiratory arrests after admission, 38% of patients requiring intubation in one study.<sup>46</sup> There are many scoring systems to assess severity of poisoning but has been seen in a study that simple scoring such as GCS may also be helpful. Patients who present with a GCS <13 need intensive monitoring and treatment but is crucial that the identity of the OP be taken into account because highly lipid soluble poisons such as fenthion can cause delayed effects and half of all patients that die from this type of poisoning only have mild symptoms at presentation. Patients poisoned with such OP, therefore, need close monitoring even if they are asymptomatic at presentation.<sup>47</sup>

Fatality usually occurs within 24 hours in patients with severe toxicity that is untreated. Aggressive and timely therapy usually leads to complete recovery within 10 days.<sup>48</sup> Repeated absorption of organophosphorus at significant dosage, but in amounts not sufficient to cause acute poisoning, may cause persistent weakness, anorexia and malaise.<sup>49</sup>

### **Medicolegal Pitfalls**

Since organophosphate poisoning can present in a variety of ways with atypical presentations, especially in the young child, physicians must consider and treat potential life-threatening complications even in the absence of confirmatory laboratory or diagnostic tests. Once the diagnosis of acute organophosphate poisoning is made, the patient should be admitted to an intensive care setting with experience dealing with critically ill children.<sup>10</sup> Physicians should be keenly aware of the

hospitals capabilities and transfer criteria to the tertiary center. Most organophosphate poisonings occur in the home and may be secondary to improper storage, illegal chemicals, or suicidal or homicidal behavior. All exposure should be investigated thoroughly to avoid missing cases of abuse or neglect. Potential exposures on children's play-grounds, fields, and gardens should be investigated to prevent exposure of other children.

## Prevention

As children are particularly susceptible to pesticides, it is imperative to minimize exposures. Strict legislation should be passed regarding the sale and storage of dangerous chemicals. Pediatricians should work for primary prevention of poisoning by supporting efforts at educating parents about properly storing and disposing toxic substances.

The following steps will help in a long way to prevent exposure to organophosphates: (i) Keep all pesticides out of reach of children, store them safely in a locked area; (ii) Keep pesticides in original containers with clear labels intact; (iii) Never re-use food or drink containers for pesticides; (iv) Dispose of unused pesticides properly; (v) Destroy any food (or other items) suspected to have been contaminated by pesticides; (vi) Do not eat or drink when pesticides are being used; and (vii) Provide good ventilation when using pesticides.

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## 49.6 Lead Poisoning

Tarun Dua

Lead poisoning is a common disease of toxic environmental origin. Lead is ubiquitous in the human environment as a result of industrialization. It has no known physiologic value. It affects both children and adults with children being more susceptible to lead's toxic effects. Lead poisoning can be either acute or chronic. It is usually chronic in childhood due to exposure to inorganic lead over a prolonged period. Because of their normal oral exploratory behavior, children absorb most of their lead by ingestion.<sup>1</sup> The usual sources of exposure leading to toxicity are lead from paints from walls of old houses either directly by

ingesting paint chips (pica) or indirectly by inadvertent ingestion of lead-contaminated house dust, food and water stored in lead containers, storage batteries, air borne lead from automotive and industrial emissions, home remedies and children of lead workers.<sup>2</sup>

Lead toxicity may be caused by organic or inorganic lead poisoning. The principal organic lead compound in gasoline is tetraethyl lead which is converted in the body into inorganic lead. Although lead use in gasoline has been markedly reduced, previous use has resulted in widespread contamination of soil and dust. Metallic lead and all its salts are poisonous. The principal salts

which produce toxic effects are: (i) Lead acetate (occurs as white crystals), (ii) Lead carbonate (occurs as a white crystalline powder), (iii) Lead chromate (a bright yellow powder), (iv) Lead monoxide (pale brick red masses), and (v) Lead tetroxide (red lead). Some salts of lead are also used as hair dyes.

### Pathophysiology

Lead is a highly reactive divalent cation with marked affinity for the sulfhydryl group. It exerts its toxic effects by its action on mitochondrial function where it interferes with oxidative phosphorylation. The target tissues involved in lead poisoning are the erythroid precursors in the bone marrow, renal tubular cells and cells of the central and peripheral nervous systems. The fatal dose is 20 g of lead acetate or 30 g of lead carbonate, and death usually occurs in 1 to 2 days.

### Clinical Features

Lead is well recognized to produce a wide range of toxicity. These toxic effects extend from acute, clinically obvious symptomatic poisoning to sub-clinical effects. The adverse effects of lead are summarized in Table 49.6.1.<sup>3</sup>

#### Acute Toxicity

Characteristics of this life-threatening syndrome are abdominal colic, constipation, fatigue, anemia, peripheral neuropathy and in most cases, alteration of central nervous function. In severe cases, a full-blown picture of acute encephalopathy with coma, convulsions and papilledema may be seen.<sup>4</sup> In many instances, persons who have suffered from acute lead encephalopathy are left with permanent neurologic and behavioral sequelae.<sup>5</sup>

#### Subclinical Toxicity

Subclinical toxicity denotes the concept that relatively low-dose exposure to lead can cause harmful effects that are not evident on a standard clinical examination. Thus, clinically obvious manifestations of lead poisoning such as anemia, neuropathy and renal failure lie at the upper end of the range, whereas covert effects such as impaired biosynthesis of heme, slowed nerve conduction and altered excretion of uric acid are their subclinical correlates.<sup>2</sup> It is important to note that these subclinical changes represent truly harmful outcomes and are not merely homeostatic or physiologic adjustments to the presence of lead.

**Table 49.6.1: Interpretation of blood lead test results and follow-up activities: Class of child based on lead concentration**

Class	Blood lead concentration ( $\mu\text{g}/\text{dL}$ )	Comments
I	$\leq 9$	A child in class I is not considered to be lead poisoned
IIA	10-14	Many children with blood lead levels in this range should trigger community wide childhood lead poisoning prevention activities. Children in this range may need to be rescreened more frequently
IIB	15-19	A child in class IIB should receive nutritional and educational interventions and more frequent screening. If the blood lead level persists in this range, environmental investigation and intervention should be done
III	20-44	A child in class III should receive environmental evaluation and remediation. Such a child may need pharmacologic treatment of lead poisoning
IV	45-69	A child in class IV will need both medical and environment interventions, including chelation therapy
V	$\geq 70$	A child with class V lead poisoning is a medical emergency. Medical and environmental investigation and intervention must begin immediately

The toxic effects of lead are evident principally in three organ systems: the central and peripheral nervous system, the erythrocytes and the kidneys.

#### Neurological Toxicity

Lead encephalopathy is the most dreaded manifestation of chronic lead poisoning. The onset is insidious. In the toddler, early manifestations are anorexia, irritability, refusal to play and vomiting. In the older child, abnormal behavior and headache are early features which usually appear 4-6 weeks before onset of altered sensorium, accompanied by persistent vomiting, ataxia and seizures. Stupor rapidly progresses to coma and may be similar in presentation to meningitis. Lead poisoning should be especially suspected in children presenting with a febrile encephalopathy. Lead encephalopathy may be associated with raised intracranial tension. If necessary, a

controlled lumbar puncture with a small bore needle should be done.

Peripheral neuropathy is a rare presentation in childhood. Muscle weakness and easy fatigability precede the onset of wrist drop, and less often foot drop. There is usually no sensory impairment.

Exposure to lead may produce a syndrome of developmental regression. These children have normal development during the first 12 to 18 months of life followed by a steady loss of motor skills and speech. They have hyperkinetic and aggressive behavior and poorly controlled convulsions. Clinically asymptomatic children with elevated body lead burdens have also 4-5 points deficit in verbal IQ compared with children with lower lead burden.<sup>6</sup>

The neuropsychological dysfunction at lower dose is also characterized by diminished intelligence, shortened attention span and slowed reaction time.<sup>7</sup>

#### *Renal Toxicity*

It occurs in two forms:

1. Reversible renal tubular disorder (usually seen in children with acute lead exposure).
2. Irreversible interstitial nephropathy (usually seen in adults after chronic lead exposure).

Clinically, a Fanconi like syndrome is seen along with proteinuria and hematuria. Hyperuricemia is a recognized association. Clinical manifestations of renal impairment consisting of elevations in blood urea nitrogen or serum creatinine levels do not ordinarily become evident until 50 to 75 percent of the nephrons have been destroyed.<sup>2</sup>

#### *Abdominal Syndrome*

Abdominal pain is an early manifestation of chronic lead poisoning. Anorexia, malaise and abdominal discomfort are usually associated with constipation. Diarrhea is not common. A persistent metallic taste in the mouth is an early feature of the syndrome. Attacks of abdominal colic are paroxysmal and extremely painful. The abdominal muscle become rigid and tenderness is maximum near the umbilical region.

#### *Hematologic Toxicity*

Anemia is the classic clinical manifestation of lead toxicity. It is caused primarily by an impairment of heme biosynthesis but an increased rate of erythrocyte destruction may also occur. The severity and prevalence of lead-induced anemia are correlated directly with the blood lead level. The anemia induced by lead may be either normochromic or hypochromic and may be

associated with an increased reticulocyte count. Erythrocytes also show basophilic stippling. The hemoglobin level usually does not decrease below 8-9 g/dl. The erythrocyte osmotic fragility is also decreased and the bone marrow shows erythroid hyperplasia with stippling of nucleated cells; some of these are ring sideroblasts.

Many other effects are seen at low blood lead levels, including decreased stature or growth, decreased hearing acuity and decreased ability to maintain a steady posture.<sup>1</sup> Lead's impairment of the synthesis of the active metabolite 1,25-(OH)<sub>2</sub> vitamin D is detectable at blood lead levels of 10-15 µg/dL.<sup>1</sup> Maternal and cord blood lead levels of 10-15 µg/dL also appear to be associated with reduced gestational age and reduced weight at birth.<sup>1</sup>

**Physical examination** of lead-exposed children includes blood pressure, pallor, lead (blue-black) lines on gums, abdominal tenderness, motor/sensory/cerebellar neurological deficits, tremor, cognitive function, and mood and affect.

#### **Laboratory Tests**

Measurements of blood lead level is the best indicator of recent lead absorption and is the current biological standard for lead exposure. Blood lead can be measured in whole blood by atomic absorption spectrophotometry or anodic stripping voltametry. Measurements of blood lead level is essential to decide the exact management. Epidemiological studies have identified harmful effects of lead in children at blood lead levels at least as low as 10 µg/dL.<sup>1</sup> The single, all purpose definition of childhood lead poisoning has been replaced with a multititer approach described in Table 49.6.1. The relationship of symptoms to inorganic lead levels is summarized in Figure 49.6.1 Free erythrocyte protoporphyrin or zinc protoporphyrin (ZPP) in blood reflect the effect of lead on the heme synthetic pathway and indicate lead exposure over the three months period prior to testing. ZPP levels begin to rise above the normal value of 35 µg/dL when blood lead concentration rise above 30 µg/dL.<sup>8</sup> Patients with elevated ZPP should have a complete blood count with a peripheral smear for RBC morphology and a serum iron level performed to rule out anemia, which can result in increase in ZPP level independent of lead's effect. Because iron deficiency can enhance lead absorption and toxicity and often coexists with it, all children with blood lead levels  $\geq 20$  µg/dL should be tested for iron deficiency.

Radiologic examination of the abdomen may show radiopaque foreign materials if the material has been

	150
Death	
	100
Encephalopathy Nephropathy Frank anemia Colic	
	50
↓ Hemoglobin synthesis	40
↓ Vitamin D metabolism	30
↓ Nerve conduction velocity	20
↑ Erythrocyte protoporphyrin ↓ Vitamin D metabolism	
Developmental toxicity	10
Transplacental transfer	

**Fig. 49.6.1:** Lowest observed effect levels of inorganic lead in children (in  $\mu\text{g}/\text{dL}$ ) (↑ Increased, ↓ decreased)

ingested during the preceding 24 to 36 hours. X-ray of the long bones may show lines of increased density in the metaphyseal plate of the distal femur, proximal tibia, and fibula caused by lead which has disrupted the metabolism of bone matrix. Although these lines are sometimes called lead lines, they are areas of increased mineralization or calcification and not X-ray shadows of deposited lead.

Nerve conduction velocity (NCV) is of value in documenting the presence of lead-related peripheral neuropathy. Impaired conduction rates may be an early sign of subclinical neurotoxicity. NCV should be considered when persistent symptoms and/or clinical findings suggest the presence of a peripheral neuropathy and especially if blood lead level exceed  $80 \mu\text{g}/\text{dL}$ .

Other tests include calcium sodium EDTA ( $\text{CaNa}_2\text{EDTA}$ ) challenge testing.  $\text{CaNa}_2\text{EDTA}$  is administered in a dose of  $500 \text{ mg}/\text{m}^2$  intravenously in 5 percent dextrose over 30 minutes followed by urine collection in a lead-free container of 8 hours duration. The urinary excretion of lead is measured and ratio of lead excreted (mg) by  $\text{CaNa}_2\text{EDTA}$  given (mg) calculated. A ratio greater than 0.6 is considered as positive provocative test. This suggests that treatment will be effective and is indicated. Use of such challenge testing

is declining due to questions raised about the possibility of redistributing lead from skeletal stores to the brain and other sensitive organs and precipitating features of acute toxicity.<sup>9,10</sup>

A relatively new technology to measure chronic lead exposure is measurement by X-ray fluorescence.<sup>11</sup> This is based on the observation that approximately 95 percent of absorbed lead ultimately is deposited in the skeleton, with only very slow release later. The technique, however, remains largely as a research tool till now.

### Diagnosis of Lead Poisoning

Lead poisoning must be considered in all cases of:

1. Altered sensorium with features of raised intracranial tension.
2. Wrist and foot-dropl.
3. Abnormal behavior of recent onset.
4. Regression of milestones after 12-18 months of age
5. Bluish-black line on gums.
6. Recurrent, poorly controlled seizures.
7. Recurrent abdominal pain.
8. Hypochromic microcytic anemia.
9. Pica.

### Management

The Center for Disease Control (CDC), Atlanta recommends a coordinated program of follow-up screening, education, case management, environmental investigation, lead hazard control and clinical evaluation.<sup>1</sup> The classification based lead level is useful for providing approximate management guidelines.

#### Removing the Source of Lead Exposure

This is the most important aspect of management. In most cases, this is the only necessary action. Removal of the source, however, must be complete.

#### Chelation Therapy

The decision to chelate is based on several considerations: the current blood level; evidence of current adverse clinical effect, including disabling, lead-related symptoms; the duration of excessive exposure (as determined by the exposure history or longitudinal blood lead data) and duration of symptoms.

#### Symptomatic Children and Children with Blood Lead Levels of more than $70 \mu\text{g}/\text{dL}$

Treatment consists of dimercaprol followed by edetate calcium-disodium. Dimercaprol or BAL is given in a dose of  $75 \text{ mg}/\text{m}^2$  every 4 hourly. It is available as

ampoules containing 50 mg/ml oily solution for intramuscular use. Side effects include a rise in both systolic and diastolic blood pressure accompanied by headache, sweating and tachycardia, nausea, vomiting, abdominal pain, fever, burning sensation in the lips, mouth and throat and sterile abscesses at injection sites.<sup>12</sup> These disappear on discontinuing therapy. BAL can also cause hemolysis in patients with G6PD deficiency.<sup>13</sup> Edetate calcium disodium is given in the dose of 1500 mg/m<sup>2</sup>/day by continuous intravenous infusion. Slow infusion is indicated as rapid infusion may precipitate encephalopathy. It is important to start with BAL and to initiate CaNa<sub>2</sub>EDTA only 3-4 hours later. Treatment with CaNa<sub>2</sub>EDTA should be accomplished in a hospital setting and only after adequacy of renal function is established. Adequate hydration along with strict urine output recording and other renal function monitoring is essential with CaNa<sub>2</sub>EDTA as the chelator-lead complex is nephrotoxic.<sup>10</sup> It is available as calcium disodium versenate for parenteral use in ampoules of 200 mg/ml. This chelation agent should not be confused with disodium edetate which can cause fatal hypocalcemia. The maximum daily dose should not exceed 500 mg/kg. With this therapy, symptoms of lead poisoning resolve in 4-5 days. Blood lead levels are determined at the outset and conclusion of the five-day course.

Treatment should be continued for 5 days. BAL is stopped as soon as blood lead level falls below 60 µg/dL. A second course of CaNa<sub>2</sub>EDTA alone is recommended if blood level rebounds to 45 to 69 µg/dL. The use of CaNa<sub>2</sub>EDTA in combination with BAL is recommended for rebound blood lead level higher than 70 µg/dL. The CDC recommends waiting five to seven days between the end of the first course and the beginning of a second course. Repeated courses of treatment may be necessary for these children until their blood lead level falls below 20 µg/dL.

#### *Management of Encephalopathy*

This includes:

- Chelation therapy (as described earlier).
- Treatment of seizures with diazepam followed by long-term phenytoin.
- Treatment of raised intracranial tension with careful fluid management, intravenous mannitol and dexamethasone.

#### *Asymptomatic Children with Blood Lead Levels of 45-69 µg/dL*

The treatment may consist of EDTA (as described above). When the intravenous route is not possible,

EDTA may be given intramuscularly; however, by this route, it is extremely painful, and the pain is only partially alleviated if the drug is mixed with procaine. If blood lead level does not fall below 20 µg/dL, course of EDTA can be repeated after a 2 days interval.<sup>10</sup>

An alternative therapy consists of DMSA (Succimer). DMSA can be given orally, and has minimal side effects. Outpatient DMSA should never be used unless there is absolute certainty that the child's environment is perfectly clean. DMSA is administered for 5 days at a dose of 350 mg/m<sup>2</sup> every 8 hourly followed by 2 weeks of therapy every 12 hourly for a total of 19 days (5+14). Additional courses may be given after a 2 weeks interval if blood lead remains above 20 µg/dL.<sup>10,14</sup>

#### *Symptomatic Children with Blood Lead Levels of 20-45 µg/dL*

CaNa<sub>2</sub>EDTA challenge test should be performed. If positive, either CaNa<sub>2</sub>EDTA or DMSA can be used in the regimen described above.

#### *Asymptomatic Children with Blood Lead Levels of 20-45 µg/dL*

No treatment is necessary at the level. Only general education is recommended.

#### *Other Chelating Agents*

D-penicillamine is another oral chelating agent available. Because of the toxicity of penicillamine, this agent is used to treat lead poisoning only when unacceptable reactions have occurred to DMSA and CaNa<sub>2</sub>EDTA and continued therapy is considered important. The dose is 20-30 mg/kg/day to be taken for 4-12 weeks. Complete blood count and urinalysis should be monitored routinely throughout treatment. Penicillamine therapy is contraindicated in children with known penicillin allergy.<sup>15</sup>

#### *Supportive Therapy*

In treating the acute intestinal overdose, gastric lavage should be used for recent ingestions. Whole bowel irrigation or a cleansing enema should be considered if a leaded object such as a weight or bullet is found on an abdominal radiograph but is generally not indicated for lead paint chips. Iron, zinc and calcium supplementation is advocated along with chelation therapy as the other metals are also chelated along with. Moreover, diet rich in vitamin C, iron and calcium reduces the absorption of lead into the body.

## Prognosis

The mortality rate of untreated lead encephalopathy is 65 percent and neurological sequelae are frequent in survivors. With adequate treatment, mortality rate in lead encephalopathy can be decreased to 25 percent with 40 percent of survivors having neurological sequelae like intellectual impairment, seizures which are poorly controlled with anticonvulsants, cerebral palsy, optic atrophy and dystonia musculorum deformans.

In acute poisoning, death usually occurs due to gastroenteritis and subsequent shock. In chronic cases, malnutrition, intercurrent infection, hepatic failure, respiratory or renal failure and lead encephalopathy can be directly responsible for causing death.

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## 49.7 Iron Poisoning

Utpal Kant Singh, Rajniti Prasad

Iron is an essential nutrient that is a common content of numerous vitamin preparations and tonics. Accidental iron ingestion is not uncommon in children and has become a leading cause of unintentional pharmaceutical ingestion fatality.<sup>1</sup> Accidental ingestion of iron is the leading cause of poisoning deaths in children under 6 years in United States despite child resistant packaging. Since 1986, over 110,000 such incidents have been reported leading to 33 deaths. Almost 17% of children's death reported to poison control centers in USA between 1988 and 1992, were due to iron poisoning.<sup>2</sup> Though there have been several reports of acute iron poisoning in children in India, the exact incidence and mortality is not known either

due to scarcity of reports or lack of effective reporting system.

### Why Iron Poisoning is Common?

Accidental iron poisoning in children is common because of the following facts about iron.

- Iron supplements are found in many homes with small children. Iron is freely available in numerous over-the-counter and prescription tablets and liquids. It is also found in many multivitamins preparations of both children and adults. Pregnant women are often prescribed prenatal vitamins that have high amounts of iron and often kept around house even after stops taking them.

- Unawareness of people that iron can be dangerous.
- Attractiveness of iron tablets: Various chewable children tablets of Vitamins with iron are often in cartoon shapes with various colors and fruit flavors. The much more dangerous adult formulations contain more iron and often look like brightly colored candies to young children.
- Illiteracy and carelessness of parents.

### Pathophysiology

Although iron is an essential mineral physiologically but in excess it acts in the body as metabolic poison. Normally it is absorbed in ferrous form into mucosal cells of duodenum and jejunum by saturable, carrier mediated uptake. Further it is oxidized to ferric form, transported by protein transferrin and utilized for synthesis of hemoglobin, myoglobin, catalase, cytochrome oxidase or stored in liver and bone marrow, binds to proteins as ferritin or hemosiderin. In acute overdose, normal mechanisms of absorption are exceeded and iron is absorbed by a passive first order process.<sup>3</sup> Factors that enhance iron absorption from gastrointestinal tract are presence of valine and histidine, ascorbic acids, succinate, pyruvic acid and citric acid in diet. Furthermore iron toxicity is also influenced by serum copper, phosphorus and Vitamin-E level, and associated diseases such as primary hemochromatosis, thalassemia, liver diseases that in turn enhance toxicity.

Ferritin is a unique iron storage protein, the production of which is directly related to amount of iron in the body. Ferritin is abundant in heart and livers, therefore large amount of accidentally ingested iron rushes in to these organs for storage. Excess build up of iron in these organs causes tissue destruction. With acute iron poisoning much of damage to gastrointestinal tract and liver may be a result of high localized iron concentration and free radical production leading to hepatotoxicity via lipid peroxidation and destruction of hepatic mitochondria.<sup>3,4</sup> Various mechanisms of iron toxicity have been suggested.

- It exerts a direct corrosive effect on gastrointestinal tract leading to hemorrhagic necrosis and cause nausea, vomiting diarrhea and abdominal pain. The ferrous remains stable in acid pH and cause direct irritation of gastric mucosa whereas in duodenum it gets converted into insoluble iron complexes causing further mucosal damage.
- Free iron crosses cellular membranes and at sub-cellular level tends to concentrate around mitochondrial cristae and may act as an "electron sink" shunting electron away from electron transport

system. A switch to anaerobic metabolism and increased lactic acid production results in metabolic acidosis.<sup>4</sup>

- Reduction-oxidation reactions of excess iron may lead to excessive production of free radicals in the body which cause damage to cells of various organs by peroxidation of lipids and proteins. The pulmonary damage manifests as ARDS, respiratory failure and acidosis.



Free iron also acts on vascular system causing post-arteriolar dilatation and increased capillary permeability leading to venous pooling, decreased blood volume and reduced cardiac output due to release of histamine and serotonin.<sup>3,4</sup>

- Excess free iron leads to functional, reversible and concentration dependent impairment of coagulation within first few hours, probably as a consequence of susceptibility of serine proteases to nontransferrin bound ferric ion.<sup>5</sup>

Acute iron intoxication exerts its primary effects on GI tract, liver and cardiovascular system. Pathological changes in various organs are mentioned in Table 49.7.1.

**Table 49.7.1: Pathological changes in iron poisoning**

- Esophagus:* Ulceration, edema, hemorrhage
- Stomach:* Early—Ulceration, venous thrombosis, gastritis, necrosis tab and perforation  
Late—Stricture/obstruction
- Liver:* Swelling, hemorrhagic periportal necrosis, iron deposition in Kupffer or parenchymal cells
- Lung:* Vascular congestion, edema, atelectasis
- Heart:* Fatty degeneration of cardiac muscles
- Kidneys:* Fatty degeneration of renal tubules
- Pancreas:* Hemorrhagic necrosis

### Toxic Dose Range

The lowest reported lethal dose for children was 600 mg. However iron ingestion less than 20 mg/kg body weight though considered subtoxic will rarely produce even mild symptoms, 20-60 mg/kg body weight is considered potentially serious and more than 60 mg/kg body weight, potentially lethal.

### Clinical Presentation

The presentation of severe iron poisoning has been separated into five stages depending on clinical and pathological evolution although patients may not follow this pattern precisely (Table 49.7.2).<sup>6</sup>

**Table 49.7.2: Clinical manifestations of iron poisoning**

*Gastrointestinal:* Anorexia, nausea, vomiting, hematemesis, diarrhea, tarry stools, scarring of stomach and bowel in serious cases

*Cardiovascular:* Hypotension, tachycardia

*Nervous system:* Drowsiness, lack of desire to do anything, coma

*Respiratory:* Tachypnea, pulmonary edema, adult respiratory distress syndrome, respiratory failure

*Skin:* Bluish colored lips and finger nails, jaundice

*Other:* Dehydration, hypothermia, hypoglycemia, oliguria

### Stage I (Gastrointestinal)

This stage usually appears 30 minutes to 2 hours after ingestion of iron containing preparations. The clinical manifestations during this phase are the result of local necrosis and hemorrhage at the site of contact. The usual manifestations during this stage are nausea, vomiting, bloody diarrhea, abdominal pain and hematemesis. Sometimes pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis and severe hypotension or cardiovascular collapse may occur.

### Stage II (Stage of apparent recovery)

This is a poorly defined stage during which child appears better. In this stage iron accumulation continues in mitochondria and various organs. The careful observations reveal ongoing problems which are manifested as hyperventilation, oliguria, poor tissue perfusion and vague gastrointestinal symptoms.

### Stage III (Stage of circulatory failure)

This stage is characterized by shock which is usually multifactorial in origin. Gastrointestinal fluid or blood loss, increased capillary permeability, loss of post-arterial and venous tone are the main contributing factors. These are further exacerbated by coexisting metabolic acidosis and coagulopathy. The clinical manifestations during this stage are tachycardia, pallor with cold extremities, decreased central venous pressure and later hypotension, oliguria, depressed sensorium and severe acidosis. Acute tubular necrosis, pulmonary hemorrhage and pancreatic necrosis may occur in severe cases.

### Stage IV (Stage of hepatic necrosis)

This stage, usually seen 2-4 days after ingestion, is rarely encountered and is characterized by severe hepatic necrosis with elevation of AST, ALT, prothrombin time and serum bilirubin.

### Stage V (Stage of Gastric scarring)

This stage usually seen 2 to 4 weeks after ingestion and clinical manifestations are those of gastric outlet or intestinal obstruction secondary to scarring from corrosive effects of the iron. An overgrowth of *Yersinia enterocolitica* sepsis is an infrequent complication.

### Problems Resulting from Iron Toxicity

There are many problems that may result from iron toxicity. These include anorexia, diarrhea, hypothermia, diphasic shock, metabolic acidosis and death. In addition to these, the patient may experience vascular congestion of GI tract, liver, kidneys, heart, brain, spleen, adrenals and thymus.

As a result of iron storage disease, the liver becomes cirrhotic and incidence of hepatoma, primary cancer of liver increases several fold. Also when siderosis becomes severe in young people, myocardial disease is a common cause of death. Impotence may occur in young male and amenorrhea may occur in adolescent girls. Both of these sexual related problems are due to iron loading in the anterior pituitary.<sup>7</sup>

### Management

When a child presents with acute iron intoxication, the clinician is faced with two important management queries:

1. Does the child warrant intervention?
2. If yes, how exactly should he manage the patient?

These questions are answered in the algorithm shown in Flow chart 49.7.1. Every attempt must be made to calculate the elemental iron dose ingested.

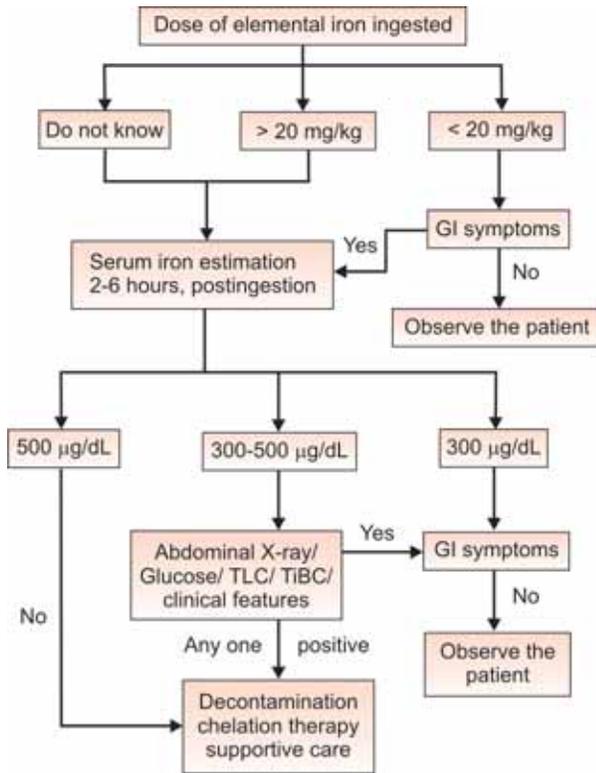
### Laboratory Evaluation

Serum iron; total and free, and total iron binding capacity should be carried out to aid in the diagnosis and delivery of supportive care. Free serum iron is the best way to determine the potential for toxicity.

1. If free serum iron is less than 50 µg/dL – toxicity unlikely.
2. If free serum iron is 50 µg/dL or more – toxicity manifests.
3. Total serum iron 350 µg/dL or more – toxicity evident.

A hematocrit, total leukocyte counts, arterial blood gases and electrolytes, serum glucose and a plain X-ray of the abdomen comprise the minimal essential laboratory workup in iron poisoning. The presence of radio-opaque shadow in radiograph, total leukocyte count greater than 15,000/cumm, metabolic acidosis and increased anion gap in ABG and blood glucose

Flow chart 49.7.1: Management of iron poisoning



more than 150 mg/dL warrants urgent interventions. Individual cases of severe poisoning may require monitoring of coagulation profile and serum calcium. Transaminase determinations are useful only after 24 hours to indicate possible hepatic damage.

### Therapeutic Modalities

When a child presents in emergency with iron poisoning, the following measures should be promptly started.

1. **Decontamination:** This should be done as rapidly as possible. Emesis may be induced with ipecac syrup, if patient is alert and co-operative and ingestion occurred within 30 to 60 minutes or if an abdominal X-ray shows the presence of tablets in the stomach. However, ipecac does not consistently remove all iron tablets from stomach. Gastric lavage should be done in all cases irrespective of previous vomiting either spontaneous or induced.

Gastric lavage should be done with a large bore tube using saline. Following lavage, 100 ml of milk of magnesia<sup>8</sup> or 50-100 ml of 5% sodium bicarbonate solution may be left within the stomach.<sup>9</sup> These compounds will form complex iron to prevent

further absorption and also decrease the corrosive effects of stomach acid upon a denuded gastric mucosa.<sup>8,9</sup> Oral administration of desferrioxamine has been shown experimentally in humans and in some animal models to promote the absorption of iron from GI tract and therefore, this should not be used.<sup>6</sup>

Whole bowel irrigation using PEG-ELS solution should be used as an alternative to emesis, lavage and cathartics, particularly if large numbers of tablets are visible on X-ray past the stomach.<sup>10</sup> Activated charcoal does not bind iron and should not be given unless co-ingestants are involved that may be bound by charcoal. An abdominal X-ray should be performed to determine the presence of any remaining tablets following GI decontamination.

In a small number of cases where X-ray has shown as bezoars of iron tablets in GI tract, surgical removal of the tablets (gastrotomy) may be done. This should be considered if a clump of tablets can be seen on X-ray and they fail to move or break-up with the usual procedures.<sup>11</sup> Endoscopy has rarely been successfully used to break-up clumps of tablets in the stomach.

2. **Definitive therapy:** The definitive therapy of iron poisoning is chelating agent desferrioxamine. Desferrioxamine a chemical produced by siderophore bacteria with high affinity for iron in the plasma resulting in excretion of ferrioxamine complex via urine which typically becomes Vinrose (pink) in color.<sup>6,10,12</sup> It can bind free iron at subcellular level by crossing the cell membrane.

#### Indications of chelation therapy<sup>12,13</sup>

- Clinical manifestation like lethargy, hypotonia, tachypnea and tachycardia.
- If free serum iron more than 50 µg/dL or total serum iron more than 350 µg/dL.
- Abdominal radiograph showing large mass of remaining tablets.
- Total leukocyte count more than 15,000/cumm.

### Routes and Dosage of Desferrioxamine

For acute cases, continuous intravenous infusion is preferred while in less severe cases it can be given intramuscularly. The dose of desferrioxamine is 15 mg/kg/hour for intravenous infusion and 50 mg/kg (maximum 1 g per dose) given every 4 hours by intramuscular route. Total dose of desferrioxamine should not exceed 6.0 g i.v. or i.m. For practical purposes, it is useful to remember that 1 g of desferrioxamine chelates about 90 mg of elemental iron. It is available as inj. Desferal, a white powder in doses

of 500 mg. It is diluted by adding 5 ml of distilled water for injection to each 500 mg vial to produce 10% solution. It is further diluted with normal saline or one fifth glucose saline and administered as a continuous infusion. The clinical improvement can be seen in an hour or two.

### Effectiveness and Duration of Therapy

The effectiveness of chelation therapy is judged by passage of red colored or port wine urine. The duration of continuous infusion still remains a debatable issue. Traditionally, a change in urine color to pink or vin rose is interpreted as an indicator of high iron load and treatment is continued till urine is clear for 24 hours. However, urine color may not change despite serum iron level of more than 500 µg/dL.<sup>6,13</sup> Therapy is continued till the urine color becomes normal or serum iron falls to less than 300 µg/dL. In severe poisoning, additional 12-24 hours chelation therapy is recommended.<sup>14</sup> Recently, Yatscoff RW et al have suggested an objective criteria for cessation of desferroxamine therapy based on urinary iron to creatinine ratio, if facilities are available.<sup>15</sup>

Acute reactions such as hypersensitivity reactions and anaphylaxis may develop. In higher dose, hypotension may occur due to histamine release. Pulmonary edema and ARDS have been reported in patients receiving desferroxamine infusion for more than 65 hours. Optic neuropathy, hearing loss and cataracts have been reported after long term use.<sup>16</sup>

### Supportive Therapy

Attention to airway and ventilation is important in patients who developed altered sensorium. Shock must be treated with i.v. fluid and inotropic support with frequent monitoring of CVP. Blood transfusion may be given if there is significant hemorrhage. Persistent acidosis may require correction with sodium bicarbonate. Liver and renal failure should be managed as per hospital standard protocols. Dyselectrolytemia and hyperglycemia associated with stage III and IV should be managed effectively. Sometimes patient may develop gram negative septicemia especially due to *Yersinia enterocolitica* or *Listeria monocytogens* either due to free iron induced mucosal damage or desferroxamine induced growth of these organism.<sup>17</sup>

### Other Measures

Hemodialysis as such has no role to play but is indicated in patients with oliguria to remove ferrioxamin.<sup>18</sup> Exchange transfusion along with desferroxamine may

increase clearance of free irons as much as 30 fold as compared to desferroxamine alone.<sup>19</sup> However, it is indicated only in cases where serum iron levels exceed 1000 µg/dL and no response to routine treatment.<sup>6</sup> Charcoal hemoperfusion may not be very useful since charcoal has poor affinity for iron. Experimental modalities of therapy include i.v. administration of liposomal encapsulated desferroxamine<sup>2</sup> and high molecular weight derivatives of desferroxamine, i.e. desferroxamine covalently attached to high molecular weight carbohydrates such as dextran and hydroxyethyl starch.<sup>21</sup>

### Prognosis

Children with iron poisoning usually respond very well to conservative management and chelation therapy. The prognosis is directly related with development of shock and hypotension. Untreated children with shock have almost 100% mortality compared to those who received chelation;10%.<sup>4</sup>

### Prevention

The prevention of iron poisoning in children requires a multifaceted approach. Education of parents, restriction on over-the-counter prescription of iron, safe and child resistant packaging, unit-dose packaged product in original containers, storage of product out of children's reach and conspicuous warning about dangers of accidental over ingestion in children are all essential steps of prevention. Simultaneously, additional resources should be directed towards the identification, testing and marketing of improved antidotes.<sup>1</sup>

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## 49.8 Barbiturate Poisoning

Rajesh Mehta

Barbiturates are substituted derivatives of barbituric acid. These are used in pediatric practice mainly for seizures control. Phenobarbitone is also used as enzyme inducer in the treatment of Crigler-Najjar syndrome type II. Poisoning is uncommon in children.<sup>1</sup>

### Pharmacological Actions

Barbiturates appear to act primarily at GABA-BZD receptor-CI channel complex and potentiate GABA-ergic inhibition by increasing life time of CI channel opening and at high level they directly increase CI conductance (GABA Mimetic action) and inhibit calcium dependent release of neurotransmitter. At very high level they also block Na<sup>+</sup>/K<sup>+</sup> channels.<sup>1</sup>

Barbiturates may be classified as (i) Long acting barbiturates (duration of action 8-16 hours), e.g. barbitone and phenobarbitone, (ii) Intermediate acting barbiturates (duration of action 4-8 hours), e.g. amylobarbitone and butobarbitone, (iii) Short acting barbiturates (duration of action 3-6 hours), e.g. cyclobarbital and pentobarbital, and (iv) Ultrashort acting barbiturates, e.g. pentothal sodium).<sup>1,2</sup>

### Actions on Various Systems

These can be summarized as below:

1. **Central nervous system (CNS):** Barbiturates cause dose dependent CNS depression ranging from

sedation, sleep, anesthesia and finally to coma. REM phase and stages III and IV of sleep are decreased. REM/NREM sleep cycle is disturbed. Phenobarbitone has high anticonvulsant sedative ratio, i.e. it has specific anticonvulsant action independent of general CNS depression.<sup>1,2</sup>

2. **Respiratory system:** Respiratory depression occur at relatively higher doses. Neurogenic, hypercapnic and hypoxic drives are decreased in succession.
3. **Cardiovascular system:** Slight decrease in the blood pressure is seen at hypnotic doses. Toxic dose produces marked fall due to ganglionic blockade, vasomotor depression and direct cardiac toxicity.
4. **Skeletal muscles:** Large doses cause decreased muscle contraction by decreasing excitability of neuromuscular junction.
5. **Smooth muscle:** Tone and motility are decreased.
6. **Renal functions:** Barbiturates may decrease urine output by decreasing BP and increasing ADH release.<sup>1</sup>

### Pharmacokinetics

Barbiturates are weak acids with pKa around 7.24. They are rapidly absorbed from the gastrointestinal tract, including the rectum and from subcutaneous tissues. Their protein binding is 45-70 percent and they are mainly metabolized in the liver. In contrast to short

acting barbiturates, long acting ones undergo renal excretion, e.g. 95 percent in barbital and 25-33 percent in phenobarbital. The lethal blood levels have been described for various classes of barbiturates as follows: (i) Long acting barbiturates—10 mg/dL; (ii) Intermediate acting barbiturates—7 mg/dL; and (iii) Short acting barbiturates—3 mg/kg.

### Acute Poisoning

Barbiturate poisoning is specially seen in those children who are on treatment for epilepsy and hence have an easy access to the drug. Barbiturates have a narrow therapeutic index (ratio of therapeutic level compared to the lethal level).

Manifestations of barbiturate poisoning are due to excessive CNS depression. The patient is flabby and comatose with shallow and failing respiration. There may be a fall in BP and cardiovascular collapse, renal shut down and pulmonary complications may occur. In some cases bullous eruptions are observed. They most typically occur on hands, buttocks and knees. Bullous lesions are not specific for barbiturate toxicity and can also be seen in carbon monoxide and ethchlorvynol poisoning.<sup>3</sup> Pupils are generally constricted but may dilate in terminal stages. There can be nystagmus and disconjugate eye movements also. Similar findings can be seen in glutethimide poisoning.<sup>4</sup>

**Mild poisoning:** The patient becomes drowsy but can be aroused easily. He may show other signs of CNS depression like disorientation, confusion, slurred speech, and mild ataxia. The blood pressure and respiration are not affected.

**Moderate poisoning:** The patient shows further CNS depression in the form of stupor-coma, he can only be made to respond by vigorous physical stimulation. Respiration becomes shallow and general reflexes become slow. Corneal and pharyngeal reflexes are still intact.

**Severe poisoning:** The patient slips into deep coma and is not arousable at all. The respiration is seriously depressed, is shallow and slow. Cheyne-Stokes character may be seen. Marked hypotension may develop. Because of ineffective respiratory effort, cyanosis may develop and cerebral hypoxia leads to cerebral edema and the signs of raised intracranial pressure. The patient may develop hypothermia. Aspiration pneumonia may complicate the situation. Usually, the cause of death is respiratory failure.

### Management

The management of acute barbiturate poisoning depends on the severity of poisoning. Mild and moderate poisoning does not require vigorous treatment. The patients need to be monitored for respiratory and hemodynamic parameters and state of sensorium. Subjects with signs of severe intoxication need to be admitted in the intensive care unit for urgent vigorous treatment. After due attention to the ABCs (airway, breathing and circulatory status), the following steps may be undertaken as needed.

1. Gastric lavage helps if performed within 4-6 hours of ingestion.
2. Administration of activated charcoal and magnesium sulfate help to decontaminate the gut and decrease drug absorption.
3. Care of airway is important as aspiration pneumonia often complicates barbiturates poisoning due to obtundation with loss of gag reflex.
4. The primary intervention in barbiturate poisoning is respiratory monitoring and ventilatory support when needed (positively before the respiratory failure/ arrest develops) since the death is caused by respiratory failure. As soon as there are signs of inadequacy of ventilation, mechanical ventilation is resorted to.
5. The mechanism of shock is due to drug-induced dilatation of capacitance vessels with consequent pooling of blood and reduction in effective circulatory volume. So, fluid replacement therapy should be used rather than previously recommended vasopressors. If shock persists in face of normal CVP, a trial of dopamine/dobutamine may be instituted.
6. Renal elimination of the drug is hastened by forced alkaline diuresis in case of phenobarbitone, which has 30-50 percent urinary excretion. Alkalanization of urine to maintain a pH of 7.5-8.0 is helpful. Intravenous sodium bicarbonate is given as repeated boluses of 1 mEq/kg till arterial pH is 7.45 to 7.5. Urine output is maintained above 2.0 ml/kg/hour.
7. Hemodialysis and charcoal hemoperfusion are effective in removing the drug from circulation but are rarely needed.<sup>1,2,4</sup>

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## 49.9 Phenothiazine Toxicity

Rajesh Mehta

Phenothiazines are neuroleptic agents and are used primarily in functional psychoses (like mania and anxiety), as anti-emetic, in tetanus to control spasms and sometimes to control intractable hiccups. Various preparations of these drugs are available for therapeutic use—chlorpromazine, prochlorperazine, promazine, trifluoperazine and thioridazine. Although mortality due to these drugs is negligible, the symptoms are disturbing and frightening to the patient as well as the doctor. Safety is due to flat dose response curve. The therapeutic index is lowest for thioridazine.<sup>1,2</sup>

### Pharmacokinetics and Mechanism of Action

Phenothiazines show unpredictable gastrointestinal absorption. Peak levels are obtained 2-6 hours after ingestion of the drug. Protein binding in the plasma is 92-98 percent. The metabolism is primarily hepatic; 3 percent of drug is excreted unchanged.

These compounds have effect on various receptors in body like blockage of post-synaptic dopamine receptors, blockage of peripheral and central  $\alpha$ -adrenergic receptors, blockage of cholinergic muscarinic receptors, quinidine like antidysrhythmic and myocardial depressant effect, lowering of convulsive threshold and an effect on temperature regulatory center.<sup>1</sup>

Phenothiazines cross the placenta into the breast-milk. Therefore they should be used with caution in pregnancy and lactation.

Toxic amount is not established but the maximum daily therapeutic dose may result in significant side effects and twice the amount is potentially fatal. Chlorpromazine cause hypotension and CNS depression at around 200 mg or 17 mg/kg in children.

### Clinical Features

#### *Idiosyncratic Dystonic Reactions*

Dose-independent idiosyncratic reactions seen in some individuals even after a single dose of a phenothiazine

are really frightening for the child as well as the parents. Typical manifestations are torticollis, stiffening of the body, cogwheel rigidity, rhythmic movements of the tongue, speech and swallowing difficulty, oculogyric crises, and inability to communicate. These episodes usually last for a few seconds to a few minutes but rarely cause death. These extrapyramidal crises may be aggravated by dehydration.<sup>1,2</sup>

Metoclopramide, which is not a phenothiazine may also present with an identical clinical picture.

#### *Dose Dependent Toxic Manifestations*

**Anticholinergic effects:** Namely miosis (pupillary constriction) is seen in 80 percent of cases. Agitation, delirium and coma may also occur in some patients in high doses, phenothiazines can cause vascular collapse and arrhythmias, which are seen mainly with thioridazine. **Neuroleptic malignant syndrome** is rarely seen with high doses of potent phenothiazines. The common features are fever, rigidity, and fluctuating blood pressure and heart rate. This lasts 5 to 10 days after drug withdrawal and may be fatal.<sup>1</sup>

### Diagnosis

The diagnosis is made basically on clinical grounds. If laboratory facilities are available, tests can be performed to detect the products since they are excreted in the urine. The urine sample of the patients is acidified with dilute nitric acid and 10 drops of tincture of ferric chloride are added to it. If phenothiazine is present, a reddish purple color develops. Haloperidol can be picked up on X-ray abdomen as the drug is opaque. The differential diagnosis includes meningitis, metoclopramide induced dystonia, tetanus, conversion reaction and chorea.

### Management

**Vital stabilization:** Immediate attention should be given to airway, breathing and circulation (ABC) and

necessary interventions started immediately to stabilize the child. Cardiac and respiratory monitoring, and temperature charting are instituted. Intravenous glucose, naloxone (0.01 mg/kg), and thiamine (100 mg) should be administered in a comatose patient as a general measure common to all poisonings caused by CNS depressants.

**GI decontamination:** Gastric lavage is useful but not necessary if cathartic has been given promptly after ingestion of the drug.

**Seizures:** Intravenous diazepam or lorazepam is given to control the seizures.

**Dysrhythmias:** Unstable rhythms need to be treated with cardioversion. Anti-arrhythmics like procainamide and quinidine are contraindicated. Hypokalemia, if present should be treated aggressively.

For torsades de pointes an intravenous bolus of 2 mg of magnesium sulfate (20% solution) is given over 2 min; if there is no response, repeat the dose and start continuous infusion at the rate of 5-10 mg/min for 2 hours.

**Hypotension:** Hypotension when present should be aggressively treated by administering normal saline or Ringer's lactate. The patient is put in the Trendelenburg's position. Vasopressors may be needed. Vasopressor of choice is norepinephrine and is given

as an intravenous infusion at the rate of 0.1-0.2 µg/kg/min and the dose is titrated to the response. Epinephrine and dopamine are not to be used.

**Hyperthermia:** If there is hyperthermia, treat with external cooling; antipyretics are to be avoided.

**Malignant neuroleptic syndrome:** The offending agent must be stopped promptly. Antiparkinsonian anticholinergics are of no help. Dantrone at dose of 2-5 mg/kg IV may help. Bromocriptine at large doses (2.5-7.5 mg) may also be useful.

**Treatment of dystonic reactions:** The drug of choice is inj. diphenhydramine. It is given in the dose of 1.0 mg/kg IV or IM. The symptoms resolve immediately following an IV injection but it takes about half an hour for resolution after an IM injection. If this drug is not available, Injection Promethazine can also be used with good effect in the dose of 0.5 mg/kg. If the symptoms do not get controlled promptly, alternate diagnoses like conversion reaction, encephalitis, meningitis, tetanus, etc. should be considered.<sup>1</sup>

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## 49.10 Corrosive Poisoning

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Corrosives are strong acids or alkalis. The acidic agents usually implicated are toilet bowl cleaners and automobile battery fluids which contain hydrochloric or sulphuric acid. The alkaline agents most commonly involved are laundry detergents and soaps. Sodium and potassium chloride are corrosive agents widely used in industry and also as drain cleaners in homes. Most of these agents are liquids and those at greatest risk are toddlers. The incidence varies from 3-5 percent.<sup>1</sup>

### Pathophysiology

The acid and alkali corrosives differ in their predisposition to affect portions of the gut. Alkali burns mainly involve the esophagus in contrast to acid burns, which have a predilection for the stomach, and this difference can be explained by their mechanisms of

action. On contact with the esophageal mucosa, strong alkalis combine with protein and fat resulting in liquefaction necrosis. Loss of mucosal integrity exposes the deeper tissues to the same effect causing full-thickness burns of the esophagus, which may result in perforation.

Acids cause coagulative necrosis and exert a superficial effect on esophageal epithelium during transit to the stomach, after reaching the stomach they are transported along the major rugal folds in the lesser curvature of the stomach to produce tissue destruction. This causes pylorospasm, which results in antral pooling of acid, and this is the portion of the stomach where maximum tissue destruction occurs. The coagulum prevents the acid from penetrating deeper tissues and exerts a protective effect to some extent. Fullthickness burns of the stomach with perforation are

not uncommon following acid ingestion<sup>2</sup> and fibrosis starts by 3 weeks in areas of necrosis, leading ultimately to strictures.

### Clinical Features

The child is usually brought to the casualty with a history of ingesting caustics and is found to be irritable and pulling at the mouth due to pain. Burns of the lips and tongue may be observed. There may be excessive drooling and refusal to drink. Dysphagia occurs due to spasm of the esophagus as well as inflammatory edema. Aspiration pneumonia may result. Hematemesis and perforation of the esophagus or stomach may cause mediastinitis, perforation and shock. Renal failure, convulsions and coma may be terminal manifestations.

A child who ingests acid presents with severe burning in the mouth, pharynx and abdomen followed by bloody vomiting and diarrhea. Shock and death may occur in up to 50 percent of these patients.<sup>3</sup> In individuals who survive the insult, damage to esophagus and stomach usually progresses for the next 2-3 weeks and as high as 95 percent of them may develop esophageal strictures. Acid burns produce extensive scarring which may necessitate skin grafting. Pyloric stenosis has been described following acid ingestion.<sup>3</sup> Inhalation of fumes causes coughing and choking, followed 6-8 hours later by pulmonary edema, hemoptysis and hypotension.<sup>4</sup>

Zinc chloride is a powerful corrosive agent. Reports of zinc chloride ingestion have described severe gastric corrosion caused by local caustic action. Antral strictures have been described. Laboratory findings may include hyperglycemia, hyperamylasemia and renal insufficiency.<sup>5</sup> Careful long-term follow-up is required because there is a potential risk of development of malignancy in the damaged stomach.<sup>6</sup>

A 40 percent solution of formaldehyde in water is known as formalin. Formalin is irritating, corrosive, toxic and absorbed from all surfaces of the body. Ingestion is rare because of alarming odor and irritant effect but has been documented in accidental, homicidal and suicidal attempts. Acute ingestion can lead to immediate deleterious effects on most organ systems predominantly gastrointestinal tract, central nervous system, cardiovascular system and hepatic and renal complications and may manifest as gastrointestinal hemorrhage, cardiovascular collapse, coma, convulsions and severe metabolic acidosis.<sup>7</sup> No specific antidote is available. Treatment of toxicity is supportive and requires a multidisciplinary approach.

### Complications

The complications following corrosive poisoning may be early or late.

#### *Early Complications (within 72 hours of ingestion)*

- Esophageal perforation and mediastinitis following alkali ingestion.
- Stomach perforation and peritonitis following acid ingestion.
- Severe glottic edema with respiratory obstruction
- Circulatory collapse.

#### *Late Complications (after 72 hours of ingestion)*

- Esophageal stricture following alkali ingestion.
- Pyloric stenosis following acid ingestion.

The late complications may not appear for several weeks following the corrosive ingestion.

### Investigations

The best method of evaluating alkali poisoning is immediate esophagoscopy and this should be performed under general anesthesia within 48 hours of alkali ingestion. Poor correlation has been observed between the presence of oral burns and the extent of esophageal involvement and this is the reason why esophagoscopy is mandatory in every patient with suspected corrosive poisoning. The endoscope should not be passed beyond the first area of ulceration and perforation is carefully looked for and documented.

If respiratory distress is marked, X-rays of the chest and soft tissues of neck are required. Following treatment and before discharge, a baseline barium swallow and upper gastrointestinal contrast series is performed. This is useful in documenting subsequent esophageal stricture or pyloric stenosis.

### Management

All children with suspected corrosive poisoning should be hospitalized. The use of neutralizing agents, such as vinegar for alkali and sodium bicarbonate for acid burns are no longer recommended. Emesis or lavage is contraindicated and the use of prophylactic antibiotics should be avoided.

#### First Aid Measures<sup>8-10</sup>

- Dilute acid immediately with 500 ml of water or milk.
- Follow this up with a demulcent drink like barley water, olive oil or melted butter. Alkaline substances

like bicarbonates should not be used as they evolve carbon dioxide which will increase respiratory distress and may cause perforation by suddenly distending the stomach.

- In alkali ingestion, neutralize by giving vinegar, lemon or orange juice mixed with 500 ml of water.
- This should be followed by ingestion of demulcents like olive oil, white of egg, milk or butter.
- A piece of ice should be given to suck.

### Specific Treatment for Acid Ingestion

- A nasogastric tube is gently inserted and the gastric contents are aspirated as rapidly as possible after the diagnosis is made. No lavage is performed.
- Emergency laparotomy is indicated if signs of peritonitis appear.

### Specific Treatment for Alkali Ingestion

- At esophagoscopy, in the absence of perforation, the caustic agent can be washed off the esophagus with water.
- If no esophageal burns are documented, the child may be observed at home.
- If esophageal perforation is present, the patient should be taken up for an emergency surgery.
- If there are esophageal burns without perforation, parenteral steroids are started (dose equivalent to 2 mg/kg prednisolone/day) and as the condition of the patient improves, parenteral steroids are discontinued and oral prednisolone is started which is continued for a total duration of 3 weeks. Steroids should be started immediately after esophagoscopy for the maximum benefit to reduce inflammation and scarring.
- The child is put on maintenance intravenous fluids until he demonstrates the ability to swallow his oral secretions. Subsequently, oral fluids are started and gradually a normal diet is introduced.
- Feeding gastrostomy is indicated in a child with a severely burnt esophagus who is unable to swallow.
- Antibiotics will be required to prevent secondary infection for 10 days. Ampicillin or methicillin are the drugs of choice because the infective agents are usually Gram positive cocci.

- Blood transfusion will be required in case of bleeding or shock.
- If there is severe laryngeal edema, tracheostomy may be required.

### Prognosis and Follow-up

The incidence of late complications following significant tissue necrosis with corrosive ingestion is high and immediate mortality is higher with acid ingestion.

Repeated barium studies of the esophagus are performed after 3 weeks. If significant stricture is seen, dilatation is initiated with esophageal bougies. If no stricture is present, then a monthly follow-up for one year is indicated. If the strictures do not respond to dilatation, esophageal replacement is done by interposition of colon or jejunum.

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## 49.11 Naphthalene Poisoning

S Gopalan, Panna Choudhury

Naphthalene poisoning occurs mainly in the pediatric age group and the substance is present in a 100 percent concentration in mothballs.<sup>1</sup> The toxic effect of naphthalene is due to the hemolytic activity of its toxic metabolite alpha-naphthol. The parent compound, however, is devoid of hemolytic properties.

### Toxicity

The commonest presentation of acute naphthalene toxicity is acute hemolytic anemia.<sup>2</sup> Toxic effects are known to occur within 24 hours of ingestion and include fever, nausea, abdominal pain, vomiting, diarrhea, convulsions, jaundice, dark urine and anemia. In North Indian patients, severe intravascular hemolysis leading to acute renal failure has been reported.<sup>3</sup>

Individuals with G6PD deficiency are more susceptible to the effects of naphthalene toxicity.<sup>4</sup> The presence of a fatty meal in the stomach at the time of naphthalene ingestion aggravates the effects of toxicity. Severe toxicity with a fatal outcome following dermal or inhalation exposure has been described in neonates and infants.<sup>5</sup> High performance liquid chromatography (HPLC) has been shown to be very useful in the evaluation of infants with unexplained neonatal jaundice, anemia, acute hemolytic jaundice and hemoglobinuria if naphthalene poisoning is suspected.<sup>6</sup> Daily oil massage of a neonate can enhance dermal absorption of naphthalene, which is lipophilic. The usual sequence of acute toxicity in neonate is an acute hemolytic reaction with anemia and jaundice terminating in kernicterus.<sup>2,4,5</sup>

Naphthalene balls usually weigh between 0.5-3.5 g.<sup>7</sup> There is a wide variability with regard to toxic effects seen after naphthalene exposure but a dose of as little as 0.25 g in infants and toddlers may prove to be toxic.

### Treatment

1. A single small mothball ingestion is managed by induced emesis with ipecac syrup provided the

ingestion was within 2 hours. Larger quantities cannot be removed by emesis or gastric lavage. Use of cathartics and activated charcoal is indicated in this situation. Milk and fatty meals should be avoided for 2-3 hours following naphthalene ingestion in order to minimize the risk of enhancing absorption.

2. Close monitoring for hemolysis must be continued for at least 7 days after exposure. Severe hemolysis may require transfusion and exchange transfusions might be needed in neonates.
3. Use of adequate intravenous fluids along with alkalinization of the urine may prevent acute renal failure resulting from precipitation of hemoglobin in renal tubules.
4. In patients presenting with methemoglobinemia, treatment with methylene blue is indicated in the presence of hypoxemia and also when methemoglobin level in blood exceeds 30 percent.

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S e c t i o n

6



# Neonatal Emergencies in Delivery Room

Amit Upadhyay, Ashok K Deorari

According to WHO estimates, around 3% of approximately 120 million infants born every year in developing countries develop birth asphyxia requiring resuscitation. Nevertheless, there is one single intervention for dealing with asphyxia at birth that is resuscitation. Effective resuscitation will revive more than three-quarters of newborns with birth asphyxia and decrease neuromotor disability in survivors.

All hospital personnel involved with delivery of newly born infant should be able to identify the infant in need of any assistance and quickly establish normal vital functions in babies who need help. Reversal of asphyxia, normalization of cardiac function and correction of shock are the major considerations in initial management of the compromised newly born in the delivery room. An accurate assessment of the baby is important. Overzealous treatment may cause injury to a healthy newly born infant, and failure to initiate proper management in a newly born in need may cause perpetuation of injury to vital organs.

In the delivery room, some foreseen and some unforeseen emergencies occur. Prompt and skilled interventions help in saving many newly born lives. Readiness with skilled manpower and equipment of resuscitation are the key to success. So, each and every birth must be considered a potential emergency. All necessary equipment should be available in working condition. There are certain high-risk situations in which emergencies at birth are more likely to occur. With careful consideration of risk factors, more than half of all newly born who will need resuscitation can be identified prior to birth. If we anticipate need for resuscitation at birth, we can call for additional skilled personnel to be present and prepare necessary equipment. To manage such high-risk emergency situation, all the personnel involved in delivery room must be adequately trained in neonatal resuscitation. Frequent drills and practice session will help in improving performance of delivery room personnel.

## NEONATAL EMERGENCIES WHICH CAN PRESENT IN LABOR ROOM

These are enumerated in Table 50.1.

### Prenatal Alert

Assessment of fetal well-being by use of count of fetal movement, auscultation for fetal bradycardia, non-stress test, Manning score and continuous electronic fetal

**Table 50.1: Neonatal emergencies which can present in the labor room**

#### Medical

- i. Birth asphyxia (most common)
- ii. Meconium stained liquor in a depressed baby
- iii. Shock and hypovolemia
- iv. Mother with opiate injection in past 4 hours of delivery
- v. Hydrops fetalis
- vi. Conditions with impaired lung function
  - Pneumothorax
  - Massive ascites/pleural effusion
  - Birth of an extremely low birth weight (ELBW) baby
  - Fetal sepsis/fetal pneumonia
- vii. Accidental injection of local anesthetic in baby's scalp
- viii. Congenital heart diseases: Cyanotic congenital heart disease, complete heart block

#### Surgical

- a. *Mechanical blockade of airways*
  - i. Bilateral choanal atresia
  - ii. Pierre-Robin sequence (pharyngeal airway malformation)
  - iii. Airway malformations
    - Tracheal agenesis
    - Laryngotracheoesophageal cleft
    - Laryngeal atresia, laryngeal webs
  - iv. Cystic hygroma
  - v. Congenital goiter
- b. *Impaired lung function*
  - i. Congenital diaphragmatic hernia
  - ii. Eventration of diaphragm
  - iii. Bilateral pulmonary hypoplasia
  - iv. Congenital cystic adenomatoid malformation

monitoring leads to early diagnosis of fetal compromise. Prompt measures to deliver the fetus with speed and safety are crucial in prevention of perinatal hypoxia.

Ultrasonography is a useful modality to diagnose various congenital lethal malformations in the fetus. In presence of polyhydramnios in mother, fetus should be screened *in utero* for tracheoesophageal fistula, meningomyelocele and airway malformations; while oligohydramnios in mother may be associated with pulmonary hypoplasia and renal anomalies. Many a time antenatal diagnosis of congenital diaphragmatic hernia, hydrops fetalis and thoracic masses is made. This helps in alerting the pediatrician to make arrangements for postnatal management of these emergency conditions.

## MANAGEMENT OF NEONATAL EMERGENCIES

### Preparation for Delivery

**Personnel:** At each delivery, there should be at least one person whose primary responsibility is to take care of the baby, and is capable of initiating resuscitation. A second person who is capable of all steps, like intubation and chest compressions should be present in immediate vicinity, and should be called if required.

In case of an anticipated high risk birth (Table 50.2), two persons are usually required. In case of multiple births, one team of two persons should be there for each baby. In more serious cases like hydrops, three or even four persons with varying degree of resuscitation skills may be needed at delivery. One of them, with complete resuscitation skills, would serve as the leader of the team and take care of “initial steps”, including positioning and airway. Second will assist in bag and mask ventilation and intubation, and thoracocentesis, if required. Third person is required for giving chest compressions and fourth one for medications and accurate documentation of events.

**Equipment:** Appropriate equipment should be ready to use (Table 50.3). All equipment must be tested before each delivery.

### BABY NOT BREATHING AT BIRTH<sup>1-4</sup> (FLOW CHART 50.1)

Careful assessment of each neonate should be done after birth and then decide which baby needs resuscitation. Apgar score is not a pre-requisite for resuscitation. The following four should be assessed immediately after birth<sup>3</sup>:

**Table 50.2: Conditions with anticipated high-risk birth**

<i>Antepartum factors</i>	
Maternal diabetes	Post-term gestation
Pregnancy-induced hypertension	Multiple gestation
Chronic hypertension	Size-dates discrepancy
Anemia or isoimmunization	Drug therapy, e.g. lithium carbonate, magnesium, adrenergic-blocking drugs
Previous fetal or neonatal death	Maternal substance abuse
Bleeding in second or third trimester	Fetal malformation
Maternal infection	Diminished fetal activity
Maternal cardiac, renal, pulmonary, thyroid, or neurologic disease	No prenatal care
Polyhydramnios	Age < 16 or > 35 years
Oligohydramnios	
Premature rupture of membranes	
<i>Intrapartum factors</i>	
Emergency cesarean section	Fetal bradycardia
Forceps or vacuum-assisted delivery	Non-reassuring fetal heart rate patterns
Breech or other abnormal presentation	Use of general anesthesia
Premature labor	Uterine tetany
Precipitous labor	Narcotics administered to mother within 4 hours of delivery
Chorioamnionitis	Meconium-stained amniotic fluid
Prolonged rupture of membranes (> 18 hours before delivery)	Prolapsed cord
Prolonged labor (> 24 hours)	Abruption placentae
Prolonged second stage of labor (> 2 hours)	Placenta previa

**Table 50.3: Neonatal resuscitation supplies and equipment****Suction equipment**

Mechanical suction and tubing  
Suction catheters, 5F, or 6F, 8F, 10F or 12F  
8F feeding tube and 20 mL syringe  
Meconium aspirator (De Lee trap)

**Bag and mask equipment**

Neonatal resuscitation bag with a pressure-release valve or pressure manometer (the bag must be capable of delivering 90 to 100 percent oxygen)  
Face masks, term newborn and premature sizes (cushioned-rim masks, preferred)  
Oxygen source with flow meter (flow rate up to 10 L/min) and tubing  
Laryngeal mask airway (LMA)

**Intubation equipment**

Laryngoscope with straight blades, No. 0 (preterm) and No. 1 (term)  
Extra bulbs and batteries for laryngoscope  
Endotracheal tube: 2.5, 3.0, 3.5, 4.0 mm internal diameter (ID)  
Scissors  
Tape or securing device for endotracheal tube  
Alcohol sponges

**Medications**

Epinephrine 1:10,000 (0.1 mg/mL) 2 mL or 10 mL ampoules  
Isotonic crystalloid (Normal saline or Ringer's lactate) for volume expansion  
Naloxone hydrochloride (0.4 mg/mL) 1 mL ampoules, or 1.0 mg/mL, 2 mL ampoules  
Dextrose 10 percent  
Feeding tube, 5F (optional)  
Umbilical vessel catheterization supplies  
Sterile gloves  
Scalpel or scissors  
Povidone-iodine solution  
Umbilical tape  
Umbilical catheters 3.5F, 5F  
Three-way stopcock  
Syringes, 1, 3, 5, 10, 20, 50 mL  
Needles 25, 21, 18 gauge

**Miscellaneous**

Radiant warmer or other heat source  
Firm, padded resuscitation surface  
Clock (timer optional)  
Warmed linen  
Stethoscope  
Tape, 1/2 or 3/4 inch  
Cardiac monitor and electrodes and/or pulse oximeter with probe (optional for delivery room)  
Oropharyngeal airways

- Is amniotic fluid clear of meconium and no evidence of infection?
- Is baby breathing or crying?

(i) If answer to any of the questions is 'No', take the baby under radiant warmer and begin the **initial steps of resuscitation**:

**1. Provide Warmth**

Place the baby under pre-warmed radiant warmer. Dry with pre-warmed linen and remove the wet linen. Drying provides sufficient stimulation of breathing in mildly depressed newborns. VLBW babies likely to be hypothermic despite use of conventional techniques. Additional wrapping techniques should be used like plastic wrapping using polyethylene bags and monitoring for the development of hypothermia.<sup>6</sup> The goal is to achieve normothermia and to avoid iatrogenic hyperthermia in infants who require resuscitation.

**2. Clear Airway**

- Gentle suction of mouth, oropharynx and nose (mouth before nose). Pressures during suction should not exceed 100 mm Hg (or 130 cm of H<sub>2</sub>O). Deep suction should be avoided, as it can induce vagal stimulation, resulting in apnea and bradycardia. However routine suction of the newly born vigorous baby is not recommended.
- Position the baby with head held in midline and semi-extended.

**3. Use of Oxygen during Neonatal Resuscitation**

Current evidence is insufficient to resolve all questions regarding supplemental oxygen use during neonatal resuscitation.

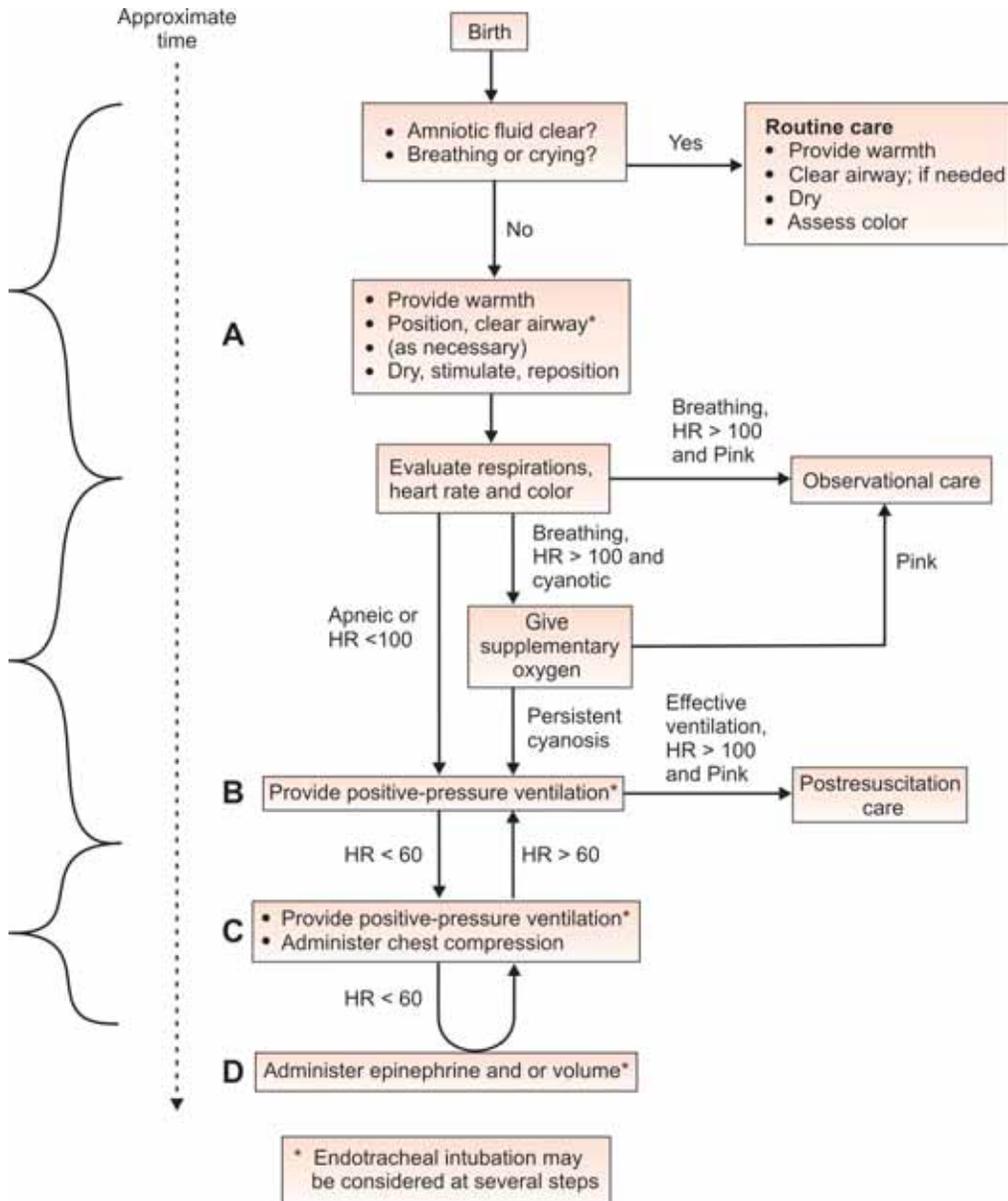
**For babies born at term:**

- Positive pressure ventilations can be initiated with room air. It can be as successful as 100% oxygen. However, back up oxygen should be available if there is no appreciable improvement within 90 seconds following birth.<sup>7</sup>
- If supplemental oxygen is unavailable, continue positive-pressure ventilation using room air.<sup>8</sup>

**For babies born preterm (< 32 weeks):**

- Use an oxygen blender and pulse oximeter during resuscitation.<sup>9</sup>
- Begin PPV with oxygen concentration between 30-40% oxygen. No studies justify starting at any particular oxygen concentration.

Flow chart 50.1: Algorithm for resuscitation of the newly born infant



- Titrate oxygen concentration up or down to achieve an oxygen saturation of 85%. Decrease the oxygen concentration as saturations rise over 95%. If the heart rate does not respond by increasing rapidly to > 100 beats per minute, correct any ventilation problem and use 100% oxygen.

If your facility does not have an oxygen blender and pulse oximeter in the delivery room, and there is insufficient time to transfer the mother to another facility, then initiate assisted ventilation with 100% oxygen. There is no convincing evidence that a brief

period of 100% oxygen during resuscitation will be detrimental to the preterm infant.

#### *If necessary*

- Place a shoulder roll (1/2 to 3/4 of inch) beneath the scapula, so as to open the airways.
- Rub the back or thighs gently; avoid continued use of tactile stimulation in an apneic baby, as this will waste valuable time.

Promptness and skill, both are equally important. These initial steps should be done in no more than 20 to 30 seconds.

Now evaluate the baby for respiration, heart rate and color, simultaneously (if two persons present), and sequentially, in the order mentioned, if only one person is present. Heart rate should be assessed by auscultation. Count the heart beats for 6 seconds and multiply by 10 to get the heart rate/minute. Palpation of pulse of umbilical vessels or brachial artery is also acceptable.

Begin positive pressure ventilation (PPV) by a bag and mask using oxygen guidelines mentioned earlier:

- i. Baby is apneic/gasping, or
- ii. Heart rate is < 100 beats per minute 30 seconds after administering initial steps, or
- iii. Central cyanosis is present despite free flow oxygen (at 5 L/min).

### Technique of Positive Pressure Ventilation

1. Place a small towel under the neonate's shoulder to extend the neck slightly-sniffing position (optional).
2. Select an appropriate size mask, connect it to the bag and place over baby's face to include the chin, mouth and nose.
3. Ensure a good seal, and compress the bag enough to cause a **visible chest expansion** at the rate of about 40-60 breaths/minutes. The initial inflating pressure of 20 cm of H<sub>2</sub>O may be effective, but 30-40 cm of H<sub>2</sub>O may be required in some term babies without spontaneous respiration.
4. **Checklist** in case of non-expansion of chest:
  - a. Airway → Yes → Oropharyngeal suction blocked check neck position
  - b. Leak in → Yes → Reapply face mask with mouth seal
  - c. Insufficient → Yes → Check leak in bag, inflation increase pressure applied
5. **Check effectiveness**
  - a. Primary measure of improvement is increase in heart rate.
  - b. If heart rate is not improving, assess chest movements and breath sounds.

If despite these corrective measures, the chest does not expand, consider intubation of the baby.

6. **Indications** to intubate baby at birth include:
  - a. Meconium stained baby who is not vigorous.
  - b. Non-response to bag and mask ventilation.
  - c. Suspected congenital diaphragmatic hernia.
  - d. When chest compressions are performed.
  - e. When endotracheal administration of drugs is required.

Capnography is the recommended method of confirming tube placement.<sup>5,10</sup> This may have no

role in brief period of intubation for clearing meconium from trachea. During cardiac arrest, if exhaled CO<sub>2</sub> is not detected, tube placement should be confirmed with direct laryngoscopy.

7. Response to assisted ventilation is assessed 30 seconds after initiating ventilation. **Good response to assisted ventilation** (it is also an indication to discontinue assisted ventilation) is indicated by:
  - a. Appearance of spontaneous respiratory effort.
  - b. Heart rate > 100 beats/min.
  - c. Pink color.

After 30 seconds of bag and mask ventilation, evaluate heart rate:

- a. If HR is >100 bpm, assess respiration and if
  - Adequate—gradually wean off PPV by decreasing the rate and pressure of PPV.
  - Apneic/gasping—continue PPV.
- b. If heart rate is between 60 and 100 bpm, continue PPV, and re-evaluate after 30 seconds.
- c. If heart rate is less than 60 bpm, begin chest compressions at rate of 90/min in ratio of 3:1 with positive pressure ventilation (from this step onwards, *you definitely need at least two persons; one for PPV and other for chest compressions*).

### Devices for Assisted Ventilation

Flow-controlled pressure limited mechanical devices (e.g., T-piece resuscitators) are recognized as an acceptable method of administering positive-pressure ventilation during resuscitation of the newly born and in particular the premature infant.<sup>11</sup> However, self-inflating and flow inflating bag-and-mask equipment and techniques remain the cornerstone of achieving effective ventilation in most resuscitations.

### Laryngeal Mask Airway<sup>12</sup>

The laryngeal mask airway has been shown to be an effective alternative for assisting ventilation of some newborns who have failed bag-and-mask ventilation or endotracheal intubation. However there is insufficient evidence to recommend use of the laryngeal mask airway as the primary airway device during neonatal resuscitation or in the settings of meconium-stained amniotic fluid, when chest compressions are required, or for the delivery of drugs into the trachea.

### Assisted Ventilation of Preterm Infants

Evidence from animal studies indicate that preterm lungs are easily injured by large-volume inflations immediately after birth.<sup>13</sup> Additional animal studies indicate that when positive-pressure ventilation is

applied immediately after birth, the inclusion of positive end-expiratory pressure (PEEP) protects against lung injury and improves lung compliance and gas exchange.<sup>14</sup> When ventilating preterm infants after birth, excessive chest wall movement may indicate large-volume lung inflations, which should be avoided. Monitoring of pressure may help to provide consistent inflations and avoid unnecessary high pressures. If positive-pressure ventilation is required, an initial inflation pressure of 20 to 25 cm H<sub>2</sub>O is adequate for most preterm infants. If prompt improvement in heart rate or chest movement is not obtained, higher pressures may be needed. If it is necessary to continue positive-pressure ventilation, application of PEEP may be beneficial. Continuous positive airway pressure in spontaneously breathing preterm infants after resuscitation may also be beneficial.<sup>15</sup>

## TECHNIQUE OF CHEST COMPRESSION

### Indication

If heart rate is < 60 bpm despite adequate ventilation with supplementary oxygen for 30 seconds:

1. Place the baby on a firm surface.
2. Identify the lower one-third of the sternum (area between the inter-nipple line and the xiphisternum).
3. Use (a) Two finger (index and middle finger) technique or (b) Two thumbs with fingers encircling hands technique for compression.

Because the 2 thumb encircling hands technique may generate higher peak systolic and coronary perfusion pressure than 2 finger technique, the 2 thumb-encircling hands technique is recommended.<sup>16</sup> However, the 2 finger technique may be preferable when access to the umbilicus is required during insertion of an umbilical catheter. Compress sternum by one-third of anteroposterior diameter of chest at a rate of 90 times/minute.

4. Ensure coordination between ventilation and cardiac massage for every three chest compression after one assisted ventilatory breath in a ratio of 3:1. (Ensure compression ratio by counts cadence—"one-and-two-and-three-and-breathe-and....")
5. Assess response to cardiac massage and ventilation as per Flow chart 50.1.
6. Chest compression can be discontinued when the heart rate rises to above 60/min.

After 30 seconds of PPV and chest compressions, reassess heart rate:

- a. If > 60 bpm—omit chest compressions and continue PPV till HR >100 bpm.
- b. If < 60 bpm—continue chest compressions and give adrenaline.

*Description of technique of intubation and umbilical vessel cannulation is beyond the scope of this chapter.*

## USE OF DRUGS

Drugs are seldom needed in resuscitation of the newly born infant. Bradycardia in the newborn infant is usually the result of inadequate lung inflation or profound hypoxemia, and establishing ventilation is the most important step to correct it. But if the heart rate remains < 60 bpm despite adequate ventilation with 100% oxygen and 30 seconds of chest compressions, administration of epinephrine or volume expansion, or both, may be indicated.

1. **Adrenaline:** Adrenaline is indicated whenever the heart rate remains < 60/min in spite of 30 seconds of chest compression and assisted ventilation. Past guidelines recommended that initial doses of epinephrine be given through an endotracheal tube because the dose can be administered more quickly than intravenous route. Given the lack of data on endotracheal epinephrine, the IV route should be used as soon as venous access is established.<sup>17</sup> Do not give high doses of intravenous epinephrine.<sup>18</sup> The recommended IV dose is 0.1 to 0.3 mL/kg of 1:10,000 solution. Draw up in 1-mL syringe (0.1 ml adrenaline and 0.9 ml normal saline). ET dose is 0.3 to 1.0 mL/kg of 1:10,000 solution. Draw up in 3-mL or 5-mL syringe.

2. **Sodium bicarbonate:** The previous guidelines indicated that bicarbonate may be given IV as 2 ml/kg if ventilation is adequate and the pCO<sub>2</sub> is in the normal range. Examining the evidence revealed no experimental neonatal animal studies have been carried out. One small randomized trial of NaHCO<sub>3</sub> in neonatal resuscitation showed no benefit on survival.<sup>19</sup> Several studies show deleterious effects of depression of myocardial function, paradoxical intracellular acidosis, reduction in cerebral blood flow and increased risk of IVH in preterms. Current guidelines do not recommend the use of bicarbonate in delivery room resuscitations.

3. **Naloxone:** Administration of naloxone is not recommended as part of initial resuscitative efforts for newly born with respiratory depression. If administration of naloxone is considered, heart rate and color must be first restored by supporting ventilation. It should be avoided in babies whose mothers are suspected of having had long term exposure to opioids. **Dose** is 0.1 mg/kg for naloxone. **Route** of administration is intravenous (or IM) or subcutaneous. It should not to be given by endotracheal route<sup>5</sup> (For details see Drug Depression given later in this chapter).

4. **Normal saline:** It is indicated when blood loss is suspected or infant appears to be in shock as judged by pale skin, poor pulses, peripheral cyanosis and cold extremities. It is the solution of choice for volume expansion in the delivery room. **Dose** is 10 ml/kg of normal saline intravenously, over 5 to 10 minutes (For details, see shock given later).

If despite all above steps baby is not improving consider the conditions mentioned in Table 50.4.

Flow chart 50.1 summarizes in an algorithm, the recommended steps for resuscitation of a newborn.

### Resuscitation Practices that are not Effective or are Harmful

These include:

- Routine aspiration (suction) of the baby's mouth and nose as soon as the head is born, or later when the amniotic fluid has been clear;
- Routine aspiration (suction) of the baby's stomach at birth;
- Stimulation of the newborn by slapping or by flicking the soles of its feet;
- Holding the newborn's head down by holding the baby by the legs has been proved fatal;
- Postural drainage and slapping the back;
- Squeezing the chest to remove secretions from the airway;
- Routine giving of sodium bicarbonate to newborns who are not breathing;
- Intubation by an unskilled person.

**Table 50.4: Common problems interfering with effective resuscitation**

- a. *Improper Performance*
  - Head and neck position is not proper
  - Airway patency not adequate
  - Mask size and application not appropriate
  - Adequacy of bag compression not enough
  - Sternal placement of fingers not correct
  - Adequacy of sternal compression not enough
- b. *Mechanical Difficulties*
  - Oxygen not turned on
  - Airway connectors loose or unconnected
  - Oxygen tubing unconnected/leaking
- c. *Endotracheal Tube Problems*
  - Far too into one bronchus
  - Into esophagus
  - Occluded
- d. Hypovolemia is persisting
- e. Pneumothorax has developed during resuscitation
- f. Maternal medication (opiate, anesthetic) depression
- g. Congenital anomaly of airway, lung, heart or diaphragm
- h. Birth trauma (leading to internal bleed)

### WHEN TO STOP RESUSCITATION

Discontinuation of resuscitative efforts is deemed appropriate if heart rate is absent after 10 min of effective resuscitation.<sup>20,21</sup> This indicates that death or severe disability is almost inevitable in these babies. Guidelines should always be 'interpreted according to regional outcomes and societal principles'.

### WITHHOLD RESUSCITATION<sup>20</sup>

If the newborn has a severe malformation that is lethal, resuscitation should not be attempted. These include:

- Severe hydrocephaly
- Anencephaly
- Holoprosencephaly
- 13 Trisomy syndrome
- 18 Trisomy syndrome
- Sirenomelia
- Short-limb dwarfism syndromes
- Multiple defects syndromes
- Renal agenesis (Potter Syndrome).

Extreme prematurity (gestational age < 23 weeks or birth weight < 400 g). However, this lower limit has to be individualized according to set up. In most units in India, gestational age less than 26 weeks and weight less than 750 grams might qualify to withhold resuscitation.

### MECONIUM STAINED LIQUOR

Aspiration of meconium before delivery, during birth, or during resuscitation can cause meconium aspiration syndrome. One obstetrical technique to try to decrease aspiration has been to suction meconium from the infant's airway after delivery of the head but before delivery of the shoulders (intrapartum suctioning). Although some studies suggested that intrapartum suctioning might be effective for decreasing the risk of aspiration syndrome, subsequent evidence from a large multicenter randomized trial did not show such an effect.<sup>22</sup> Therefore, current recommendations no longer advise routine intrapartum oropharyngeal and nasopharyngeal suctioning for infants born to mothers with meconium staining of amniotic fluid. Traditional teaching recommended that meconium-stained infants have endotracheal intubation immediately following birth and that suction be applied to the endotracheal tube as it is withdrawn. Randomized controlled trials have shown that this practice offers no benefit if the infant is vigorous.<sup>23</sup> A vigorous infant is defined as one who has strong respiratory efforts, good muscle tone, and a heart rate 100 beats per minute (bpm). Endotracheal suctioning for infants who are not vigorous

should be performed immediately after birth. These guidelines remain same whether meconium is viscid or thin.<sup>1,24</sup>

## SHOCK

Shock should be recognized and promptly treated in delivery room. Events such as maternal bleeding during third trimester, blood loss due to *placenta previa* and *abruptio* or cord rupture, smaller of the twins in monozygotic twinning, or delivery by cutting through an anteriorly placed placenta, should alert the pediatrician to potential problem of hypovolemic shock. Cardiogenic shock may accompany severe asphyxia. Ideal is to have a invasive BP (IBP) through umbilical artery and if it is 10 mm Hg less than expected for gestation, it should be treated. Invasive BP is however rarely, if ever available. In the setting of blood loss, if a baby who is not recovering from asphyxia or the baby is pale and has poor pulses and tachycardia, volume expansion should be given. Initial dose of volume expansion is 10 ml/kg infused over 5-10 minutes.<sup>4</sup> If baby shows only minimal improvement, give another dose of 10 ml/kg. The ideal replacement fluid for shock due to blood loss is whole blood. If such a situation is anticipated, O negative packed cells with AB negative plasma, crossed matched with maternal serum should be arranged at time of delivery. However, more often than not, it is unanticipated, and no blood is pre-arranged. Then, the recommended fluid for emergency treatment is normal saline or Ringer's lactate. Randomized, controlled trials in neonates showed that isotonic crystalloid is as effective as albumin for the treatment of hypotension.<sup>25</sup> In consideration of cost and theoretical risks, an isotonic crystalloid solution rather than albumin should be the fluid of choice for volume expansion in neonatal resuscitation. The recommended route of volume replacement in emergency is through umbilical vein (finding a peripheral vein in a baby with asphyxia and shock can be very difficult).

Preterm babies have very fragile network of capillaries in germinal matrix of brain. They are at high risk of developing intraventricular hemorrhage from too rapid volume expansion. It is therefore advisable to give fluid bolus slowly, over ½ to 1 hour, depending on severity of blood loss.

**Use of vasopressors in shock:** It is rarely, if ever indicated in labor room. It should be started only if baby has documented hypotension despite 2 boluses of 10 ml/kg of volume expanders. The most common cause of such a scenario is persistent hypoxia and second is underestimation of blood loss. Dopamine

should not be started till adequate volume replacement is done (shown by a CVP > 8 cm H<sub>2</sub>O). It is started in dose of 5 microgram/kg/min. It requires infusion pump for controlled drug delivery, so it should preferably be started once baby is brought to NICU. Adrenaline and dobutamine are the other vasopressors that are commonly used. No one drug is superior to other.

## DRUG DEPRESSION

Drugs used in mother for analgesia or tocolysis within 3-4 hours of delivery may cause respiratory depression in neonates.

Such drugs include:

- i. **Opiates**-e.g. Morphine, pethidine, fortwin (Pentazocin)
- ii. **Benzodiazepines**-e.g. Diazepam
- iii. Tocolysis with **Magnesium sulphate**.

If the depression of baby is solely related to the drug, with no overlying asphyxia the infant usually has a good heart rate and poor or no respiratory effort. For resuscitation, he just needs adequate ventilation. The action required is to provide initial steps of resuscitation, then establish airway and initiate positive pressure ventilation. Only then should one use specific antagonists for reversal of respiratory depression.

- i. **Opiates have been given to mother:** Give Naloxone-0.1 mg/kg intravenous, as absorption through IM and subcutaneous route may be delayed. Naloxone should be given only if respiratory depression is associated with history of opiate use in mother, within 4 hours prior to delivery.
- ii. **Magnesium sulphate given to mother:** Absent respiration with areflexia are the hallmark. No specific antidote is available. But IV calcium gluconate 2 ml/kg over 10 minutes can be tried.
- iii. **Diazepam:** Flumazenil is a specific antidote. The dose is 200 µg/kg/min. Repeat doses to a maximum of 1 mg may be required for complete reversal of symptomatology.

## HYDROPS FETALIS

Hydrops fetalis is defined as fluid collection in two or more serous cavities of baby or skin edema with any one serosal site involvement. In India, Rh isoimmunization is still the most important cause of hydrops. Once a hydropic baby is about to deliver, some extra preparedness is required in delivery room.

- a. **Personnel:** Three pediatricians, trained in resuscitation and umbilical venous and arterial cannulation should be present at delivery. Two nurses in delivery room

should be present for baby care. One to provide equipment and other to give drugs, blood and packed cells. Staff nurse in NICU should be alerted and asked to prepare warmer bed with necessary life saving equipments.

- b. **Equipment:** In addition to equipment present otherwise, additional arrangement should be made for (i) Umbilical cannulation, (ii) Abdominal thoracentesis—20 ml syringe with needle (18G/20G), 24G cannula or angiocath, three way and IV sets, and (iii) Pneumothorax drainage set (as for 'centesis' plus under water seal). Blood and blood products should be available in delivery room at time of birth—50 ml/kg of O Negative packed red cells and 200 ml/kg of O Negative packed red cells mixed with AB plasma in ratio of 70 and 30, percent respectively.

### Resuscitation of a Hydropic Baby

- Temperature maintenance is of utmost importance and all precautions should be taken to avoid hypothermia.
- Initial steps should be done as detailed earlier.
- It is better to electively intubate a hydropic baby as bag and mask ventilation may not be effective. Intubation may be difficult due to generalized edema. It can be aided by using endotracheal tube of 1 size less (for that gestation and weight), and applying gentle but continuous pressure. The usual guide of tip to lip distance may be misleading due to edema, so the tube should be fixed where air entry is good and bilaterally equal.
- During bagging, high peak pressures may be required.
- Indications for chest compression and medications are as per above guidelines.
- Paracentesis is indicated if despite appropriately positioned endotracheal tube, positive pressure ventilation and chest compressions, air entry in lungs is poor, the heart rate is <100 bpm and saturation does not increase.<sup>26</sup> Abdominal centesis should be done first because it is easier, associated with less complications and does not interfere with ventilation or chest compressions. It should be done with 18G/20G needle, in a zig-zag fashion, at lateral 1/3rd and medial 2/3rd junction of line joining umbilicus to anterior superior iliac spine. No more than 20 ml/kg should be aspirated at one time, and it should not be done more than twice.

If after adequate resuscitation and abdominal centesis, response to resuscitation is poor, thoracentesis is indicated. It is done in 4th to 5th intercostal space at midaxillary line, with needle directed

posteriorly. About 10-20 ml/kg of fluid should be drained and this should preferably not be repeated on that side. It may not help as such, because pulmonary disease could be due to surfactant deficiency, pulmonary edema, pulmonary hemorrhage and pulmonary hypoplasia.

The saturation of oxygen may not improve despite all this due to severe anemia or shock. Umbilical venous line should then be inserted. Samples should be drawn for hematocrit, bilirubin, blood group, direct Coombs' test, peripheral smear, reticulocyte count. Central venous pressure (CVP) should be measured. Shock should be treated by standard guidelines (*vide supra*).

**Treatment of anemia:** (a) If CVP is low (<6 cm) or patient is in shock, packed cell transfusion should be given directly. (b) If hematocrit is <35 percent with normal or high CVP, partial exchange transfusion (PET) with packed red cells should be done. Double volume exchange transfusion is required for hyperbilirubinemia and helps in removing the antigen-antibody complexes already formed. It is rarely, if ever needed in labor room. It should be done in NICU under more aseptic and safe environment after the stabilization of the baby.

### IMPAIRED LUNG FUNCTION

#### Medical Disorders

- Pneumothorax:** Air leak into the pleural spaces can occur spontaneously, but it is more likely to occur in babies who have received positive pressure ventilation. Small leaks are not dangerous, but once it is large enough to cause mediastinal shift or even a small leak in already compromised neonate, this can be life-threatening. It leads to failure of resuscitation, hypoxia and bradycardia. The classical picture is a baby who was recovering after PPV, and then suddenly deteriorates with worsening bradycardia, cyanosis and has asymmetric breaths sounds. The side with decreased air entry appears slightly bulging. A definitive diagnosis is made by chest X-ray, but the treatment should not await X-ray confirmation. Fast bedside diagnosis can be made by transillumination by a cold light source. It is an emergency and it should be immediately relieved by inserting a 22G/24G angiocath on the side with decreased air entry, in 4th intercostal space, just above the lower rib, at anterior axillary line. The spinal needle or the angiocath should be attached through a three way, to a 10/20 ml syringe, which is half filled with saline. If there is a pneumothorax, air bubbles will

be seen gushing through the saline into the syringe, which is accompanied by improvement in the baby. This provides confirmation of diagnosis.

- ii. **Pleural effusion:** Congenital hydrothorax is usually a part of hydrops and has been dealt in detail earlier. Isolated hydrothorax can occur. It is suspected, by decreased air entry on one side. It rarely causes problems in delivery room; if it does, it should be drained by a procedure as described with hydrops fetalis.
- iii. **An extremely premature baby:** Extra precaution for maintaining temperature should be taken, as risk of hypothermia is higher due to less subcutaneous fat, thin and fragile skin, increased insensible water loss, higher body surface area per kg of body weight and faster respiration. One should be gentle in drying and suctioning, else intracranial hemorrhage can occur. Despite being smaller, with lower tidal volume, such babies may require more pressure than even term babies during positive pressure ventilation. This is because they have stiffer lungs due to surfactant deficiency. It is better to electively intubate babies <1000 grams if they require PPV. Sodabarbonate or fast boluses of other medications should be avoided because their germinal matrix is very fragile and intraventricular hemorrhage can occur.

### Surgical Disorders

- i. **Congenital diaphragmatic hernia (CDH):** Most cases can be diagnosed antenatally by a level II ultrasound, although it may be completely unanticipated especially in unbooked cases. A baby with CDH may have respiratory distress since birth, cyanosis, unusually flat (scaphoid) abdomen and decreased breath sound on side of hernia (usually left sided). Such a baby deteriorates rapidly if bag and mask ventilation is started after birth. Baby should be intubated and then provided PPV, if required. PPV with bag and mask is *contraindicated* in babies with CDH. An orogastric tube should be inserted immediately to decompress the gut in the thoracic cavity; this allows room for lung expansion. CDH is said to be a physiological emergency and not a surgical emergency. The baby should be first medically stabilized in nursery by maintaining temperature, sugar, electrolytes and blood gases. Only then he should be shifted for a semi elective surgery.
- ii. **Bilateral pulmonary hypoplasia:** This is characterized by absence of air entry or any lung expansion

despite use of high airway pressures. Presence of oligohydramnios and renal agenesis are important clues to its existence. X-ray chest showing bilateral white out lungs with low lung volume is highly suggestive of lung hypoplasia. Some babies have small chest. The outcome of such babies is very poor.

### ACCIDENTAL INJECTION OF LOCAL ANESTHETIC<sup>27</sup>

Local anesthetic can get inadvertently injected into infants scalp, at the time of placement of paracervical or pudendal block or local anesthesia for episiotomy. Clinical features are depressed Apgar scores at 1 and 5 minutes, apnea, bradycardia and hypotonia, followed by seizures. The condition mimics birth asphyxia. However, two distinguishing features aid in differential diagnosis: (1) Pupils are fixed to light and often dilated and (2) Fixed doll's eye reflex (absent extraocular movements). Management depends on prompt recognition. Vigorous respiratory support is essential. Removal of drugs is better accomplished by diuresis with acidification of urine than by exchange transfusion. The outcome is good if hypoxic complications do not occur.

### AIRWAY ANOMALIES IN DELIVERY ROOM RESUSCITATION<sup>28,29</sup>

- i. **Nasal areas:** Mild mid face hypoplasia can cause critically compromised airway by narrowing of anterior portion of bony nose.
- ii. Bilateral choanal atresia.
- iii. Macroglossia, glossoptosis, in conjunction with hypoplastic mandible, including Pierre-Robin sequence, can cause obstruction to airflow after birth.
- iv. Laryngeal atresia, vascular malformation (sub glottic hemangioma).
- v. Tracheal agenesis, tracheomalacia, vascular rings.
- vi. Large neck masses compressing or distorting the airways; e.g. congenital goiter, cystic hygroma.

Cyanosis that disappears with crying and reappears when baby stops to cry (so called cyclic cyanosis) is classical presentation of bilateral choanal atresia. It is diagnosed by closing the babies mouth, and looking for cyanosis and respiratory distress. Diagnosis is confirmed if the catheter fails to pass more than three to four cm in both the nostrils.

Examination of tongue and its relationship to mandible, pharynx and hyoid give information needed to assess the difficulty of endotracheal intubation.

Glossoptosis will result in airway obstruction either immediately, or few hours later. The degree of obstruction is variable and related to baby's position. Intubation becomes difficult in babies with decreased temporomandibular joint mobility and limited cervical spine extension (both of which can occur in babies with airway malformation).

Stridor, a sound of intense turbulence from compromised airflow, has a variety of causes. A few associated findings may suggest possible diagnosis. There are certain diagnostic clues. Active chest wall motion with no cry and no air movement should lead to suspicion of laryngeal atresia, a condition requiring immediate tracheostomy. Cutaneous vascular malformation in a baby with stridor should alert for a possibility of vascular malformation, particularly subglottic hemangioma. If there are subcostal and intercostal retractions during inspiration, with prolonged expiration on auscultation, the possibility is of intrathoracic airway obstruction (e.g. vascular ring encroaching on the trachea).

### Management of Airway Anomalies

- i. **Positioning:** Lateral decubitus or prone positioning may be all that is required in newborns with mild obstruction. If this is unsuccessful, a nasopharyngeal tube should be inserted. The tip of nasopharyngeal tube is best placed posterior to base of tongue and just superior to epiglottis. Positioning of tube is also guided by relief of symptoms in the baby.
- ii. **Mask ventilation:** May be required when preparing for intubation. Key to success is appropriate size of mask (covers both nostrils, mouth and chin), airtight seal of mask on face by gentle pressure on the face. Care must be taken to place one's fingers on the margin of the mandible; placing the fingers, by mistake, on the floor of mouth, on soft tissues under the mandible, will collapse the floor of mouth and tongue into oral lumen, and further compromise the airway. If baby has nasal obstruction (e.g. nasal mass, choanal atresia), PPV with open mouth or after inserting an oral airway is very helpful.
- iii. **Laryngeal mask airway (LMA):** This is a newer form of airway maintenance device. LMA is particularly useful when airway obstruction is related to glossoptosis, macroglossia, hypoplastic mandible or cervical immobility which prevent visualization of larynx for tracheal intubation. It can be inserted till a more stable airway is achieved.
- iv. **Intubation of trachea:** It is indicated when above maneuvers do not give a satisfactory airway. However, it may be very difficult or impossible in some conditions. Emergency tracheostomy at that time may be a life saving maneuver. In order to provide optimal care to mothers during delivery and ensure intact survival of newborn babies, it is desirable that delivery room should be provided with necessary physical infrastructure, equipment, staff and facilities. The health professionals working in this area should have adequate knowledge and skill to resuscitate a newly born baby. To improve the management and outcome of sick newborn babies with emergencies at birth, the pediatrician should establish close collaboration with a large number of specialists especially obstetricians, pediatric surgeons and pediatric radiologist. Each of these subspecialty constitute an important and crucial link for optimal management of neonatal emergencies at birth, but cooperation and interaction with obstetrician is most vital to improve neonatal outcome.

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Most deaths amongst sick infants brought to hospitals occur within the first 24 hours. Many of these deaths can be prevented if very sick infants are identified soon after they arrive at the hospital and appropriate treatment is started immediately. A survey of district and teaching hospitals from 7 developing countries revealed that two-thirds of the hospitals lacked an adequate setting for priority screening (or triage).<sup>1</sup> This was evidenced by poor initial patient assessment and delay in treatment. Most emergency treatment areas were poorly organized and lacked essential supplies (families being required to buy essential drugs before they could be given). It was also observed that most personnel had inadequate knowledge and skill for managing these children. There is thus a need for initial triage, emergency care, assessment and monitoring if mortality amongst sick infants is to be reduced. The next few sections will outline how to prioritize infants in need of immediate care and the care to be provided to them.

### INITIAL ASSESSMENT

Every infant on arrival at the hospital should be assessed for symptoms and signs that are indicative of serious illness and adverse outcome and thus form the criteria for immediate hospitalization of these infants. There have been several studies that have evaluated the sensitivity and specificity of clinical signs in predicting serious illness and the need for hospitalization. In a study by Singhi et al<sup>2</sup> in sick young infants less than 2 months old, decreased activity, abnormal cry, presence of pallor, fast breathing, decreased consolability and consciousness level had a sensitivity of > 90 percent and negative predictive value of > 95 percent for prediction of an adverse outcome. Altered consciousness level followed by poor feeding and color were the most important predictors of outcome. In an attempt to identify the simplest symptoms and signs for use as a triaging procedure in young infants for identifying those in need of hospital intervention, Hewson et al<sup>3</sup> observed that the presence of any one

of the following markers: drowsiness, significant chest retraction, generalized pallor, history of poor feeding or decreased activity, had a sensitivity of 91 percent and a specificity of 72 percent. Another recent study has also affirmed that drowsiness, breathing difficulty, pallor and fever identified 82 percent of babies deemed to be subsequently seriously ill.<sup>4</sup>

Table 51.1 provides the list of symptoms or signs when present alone or together that suggests serious illness and the immediate need for hospitalization.

**Table 51.1: Clinical symptoms/signs suggesting serious illness**

- Drowsiness/coma
- Convulsions
- Shock
- Breathing difficulty (apnea, gasping, fast breathing > 60/min, severe chest retractions)
- Decreased feeding, decreased activity
- Severe jaundice (palms and soles stained)
- Severe pallor

These signs therefore could be used for emergency triage assessment and treatment. Tamburlini et al<sup>5</sup> evaluated a simplified algorithm for emergency triage assessment and treatment (ETAT). The ETAT assessment algorithm had a group who had an emergency condition needing immediate treatment (the signs included in this group were severe respiratory distress, shock, coma and convulsions). The other group were those with priority signs requiring hospitalization but not emergency treatment (the signs included were non-severe respiratory distress, severe pallor, lethargy, irritability, severe wasting or edema). It was observed that about 3 percent infants attending the emergency room had signs of an emergency condition and they constituted 37 percent of all in-patient admissions. There were 17 percent infants who had priority signs and this group made up about 48 percent of all in-patient admissions. When this algorithm was administered by nurses in infants < 1 month of age, it had a sensitivity of 82.2 percent and specificity of

89.2 percent in identifying those in need of emergency treatment and those needing priority assessment.

## EMERGENCY TRIAGE

### Emergency Signs

All infants must be initially assessed for signs needing emergency care. These signs include:

1. Gasping breathing or apnea
2. Severe respiratory distress
3. Central cyanosis
4. Shock (poor perfusion indicated by cool peripheries with capillary refill longer than 3 seconds and weak, fast pulse)
5. Coma (these infants are unconscious and do not respond to stimuli)
6. Convulsions

The presence of these signs requires immediate emergency treatment. Figure 51.1 gives the outline on how to carry out an emergency assessment and treatment.

### Emergency Treatment

Treatment that must be urgently initiated in the emergency room is outlined in Flow chart 51.1.

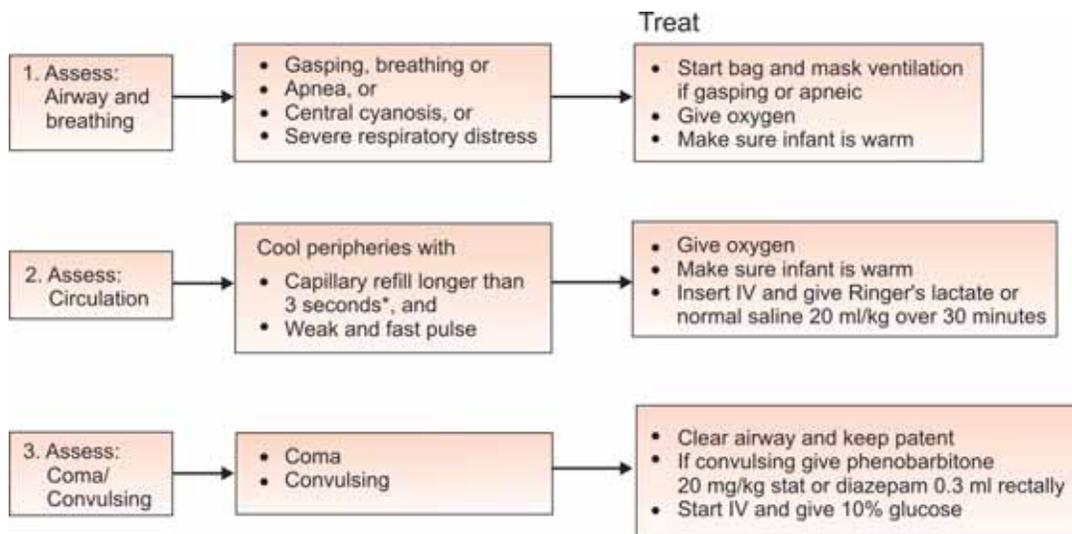
**Bag and mask ventilation:** In infants with gasping respiration or apnea, immediate bag and mask ventilation with supplemental oxygen must be initiated to establish and maintain adequate ventilation. If the infant

does not establish adequate spontaneous respiration, it would be necessary to intubate the infant and continue assisted ventilation till the infant is stabilized and can be transferred to an intensive care facility.

**Oxygen therapy:** In infants with cyanosis, severe respiratory distress and shock, supplemental oxygen therapy must be initiated with a facemask, head box or nasal cannula. Care must be taken to ensure that the oxygen is humidified and warmed. If oxygen is being bubbled through a bottle of warm water, care must be taken to ensure that the water is frequently changed with warm water. If oxygen is being administered by head box, the minimum oxygen flow in the head box needs to be atleast 2-3 L/min to prevent accumulation of exhaled carbon dioxide. With a head box, oxygen concentration delivered can be up to 80-90 percent. When oxygen is administered by a nasal cannula, a flow rate of 0.5 L/min provides about 25 percent oxygen, while 2 L/min can deliver up to 40 percent oxygen. Provide sufficient oxygen till the baby becomes pink or if a pulse oximeter is available to raise the oxygen saturation up to 88-95 percent.

**Clear airway:** In infants who are comatose or those who are convulsing, it is important that the airways are kept patent. This is achieved by suctioning out secretions and appropriately positioning the infant with slight neck extension (facilitated by placing a one inch thick shoulder roll). Placing the baby in a lateral position can also help by preventing obstruction due to falling back of tongue or pooling of secretions.

Flow chart 51.1: Emergency assessment and treatment



\* Capillary refill is assessed over the sternum

If any signs are positive: Give treatment, call for help into the emergency room and take blood samples for laboratory investigations (glucose, hemoglobin, blood group, smear).

**Establishment of vascular access and fluids:** Once ventilation and oxygenation have been stabilized, it is important that a vascular access is established. If the baby is in shock, then 20 ml/kg of Ringer's lactate or normal saline should be infused over 20-30 minutes. If there is no response to volume expansion and there is an obvious cause for hypovolemia such as diarrhea, persistent vomiting or bleeding, further volume administration can be attempted (up to 2 more doses of volume expansion with 10 ml/kg over 20-30 minutes). If shock persists in spite of adequate volume expansion, inotrope administration with dopamine or dobutamine must be considered.

If there is no perfusion problem, fluids must be initiated with 10 percent dextrose with a volume appropriate for the infant's age.

**Maintain warmth/Rewarming:** Record the baby's temperature on arrival and assess for hypothermia (< 36°C) or fever (temperature > 38°C). Hypothermia may be a sign of cold environment or a sign of serious systemic infection in the infant. It is essential to rewarm a baby with hypothermia as soon as possible.

- Rewarming can be achieved by placing a baby under a thermostatically controlled radiant warmer or heated mattress set at 36.5 to 37°C.
- Before rewarming, the infant's cold clothing should be removed and replaced with pre-warmed clothes and a cap/bonnet.
- If these electrical heating devices are not available, then the baby can be rewarmed in cot by placing the fully clothed baby over an adequately padded hot water bottle to prevent burns.
- The infant's temperature should be monitored every half-hour till it returns to normal.

**Control of convulsions:** The initial control of convulsions requires an immediate check of the blood sugar. If that is not possible or blood sugar < 40 mg/dl, administer 2-4 ml/kg of 10 percent glucose IV (200-400 mg/kg) as a bolus. If blood sugar is normal or convulsions are not controlled with bolus glucose, then phenobarbitone at a dose of 20 mg/kg can be infused slowly over 20 minutes for seizure control. If there is no control, the drug can be repeated in a dose of 10 mg/kg. If there is no response another anticonvulsant such as phenytoin can be used in dose of 10 mg/kg or diazepam (dose 0.3 mg/kg IV or rectally) can be used.

If neonatal tetanus is suspected then diazepam is the drug of choice and may be required in dose of 5 mg/kg every 6 hours.

## Laboratory Investigations

The investigations that may be useful in the emergency room management include:

- **Blood sugar** should be done in all sick newborns because it may be the cause of some of the emergency signs such as convulsions or lethargy, or may be an associated feature in any sick newborn. Treatment of hypoglycemia is important because of its association with poor long-term outcome especially in symptomatic newborns.
- When bacterial infections are suspected the helpful laboratory investigations are:
  - **Blood examination** of the peripheral blood smear may be useful if increased number of immature polymorphs (> 20%) are seen along with leukopenia or leukocytosis. One can also assess the adequacy of platelets by detecting platelet clumps on peripheral smear. A total leukocyte count, micro-ESR and C-reactive protein may be useful in detecting a positive sepsis screen.
  - **Lumbar puncture** for CSF examination and culture should be carried out if meningitis is suspected.
  - Blood culture should be taken in all cases before antibiotics are started.
- **Chest skiagram** is required especially in infants with respiratory distress. This may help in diagnosing hyaline membrane disease, pneumonia, some congenital heart diseases or other congenital defects such as a diaphragmatic hernia.
- **Hematocrit/hemoglobin** to diagnose anemia especially in infants with pallor or those with clinical bleeding.
- **Blood grouping** for those in need of blood transfusion or exchange transfusion.
- **Serum bilirubin** in severely jaundiced newborns, because it helps in deciding the need for exchange transfusion or phototherapy.
- **Arterial blood gas analysis** can be useful in critically sick newborns if the facilities are available. It helps in assessing the extent of metabolic and respiratory acidosis. This would optimize further treatment of these infants.

## DIFFERENTIAL DIAGNOSIS

After the initial assessment has been completed, consider the various conditions that could cause the infant's illness. The most common presenting acute problems in a young infant presenting in the emergency room usually are:

- *Unconscious, lethargic or convulsing*
- *Respiratory distress*
- *Diarrhea or blood in stools:* In neonates blood in stools in the first 5 days could be due to hemorrhagic disease of the newborn which is due to vitamin K deficiency, after 7 days it could be due to surgical conditions such as necrotizing enterocolitis.

The common conditions presenting with an alteration in sensorium, activity or convulsions are listed in Table 51.2. The most common conditions in the first week of life include birth asphyxia/trauma, kernicterus, hypoglycemia, intracranial hemorrhage and infections (especially tetanus, sepsis and meningitis). After the first week, infections dominate the conditions causing these signs.

Table 51.3 provides a brief differential to infants presenting with respiratory distress. The most common conditions in the first week include respiratory distress syndrome, pneumonia and sepsis. After the first week, infections (especially pneumonia) are the predominant cause.

**Table 51.2: Differential diagnosis of infant presenting with lethargy, unconsciousness or convulsion**

Diagnosis or underlying cause	Supporting information
Birth asphyxia	• Onset in first 3 days of life
Hypoxic ischemic encephalopathy	• Abnormal labor
Birth trauma	
Intracranial hemorrhage	• Onset in first 3 days in low birth weight or preterm infant
Hemolytic disease of newborn	• Onset in first 3 days
Kernicterus	• Jaundice
	• Pallor
	• Serious bacterial infection
Hypoglycemia	• Onset in first 3 days
	• Low birth weight baby
Neonatal tetanus	• Onset at day 3-14 days
	• Irritability
	• Difficulty in breastfeeding
	• Trismus
	• Convulsions
Meningitis	• Lethargy
	• Apneic episodes
	• Convulsions
	• High-pitched cry
	• Bulging fontanelle
Sepsis	• Fever or hypothermia
	• Shock
	• Seriously ill with no apparent cause

**Table 51.3: Differential diagnosis of infant with respiratory distress**

Diagnosis or underlying cause	Supporting information
Respiratory distress syndrome (hyaline membrane disease)	<ul style="list-style-type: none"> <li>• Preterm birth</li> <li>• Onset within 1 hour of birth</li> <li>• Lower chest in-drawing</li> <li>• Grunting</li> <li>• Fast breathing</li> </ul>
Sepsis/Pneumonia	<ul style="list-style-type: none"> <li>• Lethargy</li> <li>• Hyper or hypothermia</li> <li>• Difficulty in breastfeeding</li> <li>• Difficult breathing</li> </ul>
Meningitis	<ul style="list-style-type: none"> <li>• Lethargy</li> <li>• Apneic episodes</li> <li>• Convulsions</li> <li>• High-pitched cry</li> <li>• Bulging fontanelle</li> </ul>
Neonatal tetanus	<ul style="list-style-type: none"> <li>• Onset at day 3-14 days</li> <li>• Irritability</li> <li>• Difficulty in breastfeeding</li> <li>• Trismus</li> <li>• Convulsions</li> </ul>

## BREASTFEEDING PROBLEMS PRESENTING IN THE EMERGENCY ROOM

Early discharge of newborns from the hospital by 48 hours often results in mothers bringing in their newborns with breastfeeding problems to the emergency room.<sup>6</sup> Any difficulty mentioned by the mother is important. Breastfeeding difficulties mentioned by the mother may include her infant feeds too frequently, not frequently, she does not have enough milk, her nipples are sore, she has flat or everted nipples, or infant does not want to take to the breast. The other common complaints with which they present include excessive crying by the baby (often due to colic) and failure to thrive. If a mother says that the infant is not able to feed, assess breastfeeding or watch her try to feed the infant with a cup to see what she means by this. An infant who is not able to feed may have a serious infection or other life-threatening problem and needs immediate hospitalization. Most often the problem of insufficient milk is more a 'maternal perception' than a reality. It requires careful assessment of breastfeeding (Table 51.4). Observe the baby's attachment, position and sucking at the breast. Most often these problems are related to faulty feeding techniques, insufficient feeding frequency and

**Table 51.4: Assessment of an infant's breastfeeding**

Ask:

- Has the infant breastfed in the previous hour?

If the infant has not fed in the previous hour, ask the mother to put her infant to the breast. Observe her breastfeed for 4 minutes

If the infant was fed during the last hour, ask the mother if she can wait and tell you when the infant is willing to feed again

- Is the infant able to attach? Classify as:

*No attachment at all, Not well attached, Good attachment*

To check attachment, Look for:

- *Chin touching breast*
  - *Mouth wide open*
  - *Lower lip turned outward*
  - *More areola visible above than below the mouth*
- (All of these signs should be present if the attachment is good)

- Is the infant suckling effectively (that is, slow deep sucks, sometimes pausing)? Classify as:

*not suckling at all, not suckling effectively, suckling effectively*

Clear a blocked nose if it interferes with breastfeeding

- Look for ulcers or white patches in the mouth (thrush)

inadequate emptying of both breasts during feeding. Rarely, it can also be due to a blocked nose or oral thrush. These problems are seen both in term and preterm babies, but are probably more common amongst low birth weight babies who are born at home or have been discharged from hospital prior to 72 hours. Careful assessment and counseling in the emergency room can solve most of these problems. The rest may require hospitalization.

## CONCLUSION

All sick newborns presenting in the emergency room must be immediately assessed using a triage system to help identify those in need of emergency treatment, assessment and hospitalization. Investigations and diagnosis should be delayed till the infant is stabilized. This approach can prevent delay in institution of therapy and save many lives.

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Respiratory failure is an acute emergency requiring prompt and effective treatment. It is characterized by the development of hypoxia or hypercarbia or both. Newborns are particularly vulnerable to develop respiratory failure. It is particularly important to have a good understanding of the underlying pathophysiology as this influences treatment. Moreover the underlying process contributing to respiratory failure is a dynamic one and is influenced by many factors such as differing stages of lung development, changing status of the lung disease, secondary complications, unique interactions of neonatal heart and lungs, and the maturity of the central respiratory drive.

The act of breathing requires the development and maturation of the various components of the breathing apparatus. The respiratory apparatus is made up of a gas exchanging organ (the lung) and the conducting system (upper airways). These are driven by a pump. The pump consists of the thoracic cage, the muscles of respiration (diaphragm and the intercostal muscles), and the respiratory center in the brain.

Maturation of the airways, chest wall, respiratory muscles and respiratory center is integral to the optimal functioning of the breathing apparatus. This maturation continues after birth well into childhood. There must be sufficient gas exchange surface of a structurally stable nature for effective ventilation to occur. Pulmonary vasculature must also develop to transport the oxygen and carbon dioxide. Effective functioning of the respiratory system also requires good cardiac function. At birth the placental circulation is cut off and the peripheral resistance and aortic pressure rise. Simultaneously as the lungs expand with infant breathing, the pulmonary vasculature opens and the pulmonary pressures fall. The foramen ovale and the ductus arteriosus close soon after birth and the postnatal circulatory pattern is established.

#### CAUSES OF RESPIRATORY FAILURE IN THE NEWBORN

The causes of respiratory failure in the newborn can be broadly classified into:

- *Central causes:* Due to lack of drive for respiration
- *Peripheral causes:* Associated with
  - Upper airway pathology.
  - Lung pathology.
  - ‘Pump’ failure.
- *Mixed:* Where both central and peripheral causes play a part.
- *Failure of cardiopulmonary adaptation at birth.*

The important causes of respiratory failure in the newborn are listed in Table 52.1.

**Table 52.1: Causes of respiratory failure in newborn**

Affected area	Causes
Brain	Apnea of prematurity Neonatal encephalopathy Intracranial hemorrhage
Lung	RDS Pneumonia Pulmonary hemorrhage Pneumothorax Aspiration Chronic lung disease Diaphragmatic hernia Congenital lung malformation
Airway	Laryngomalacia Tracheomalacia Subglottic stenosis Choanal atresia
Muscular	Congenital myopathies Werdnig-Hoffmann syndrome Spinal cord lesions Myasthenia gravis
Miscellaneous	Persistent pulmonary hypertension Cardiac impairment Congestive heart failure, e.g. patent ductus arteriosus Tetanus neonatorum Hydrops fetalis

## MECHANISMS OF RESPIRATORY FAILURE

Respiratory failure occurs when there is an abnormality of gas exchange leading to *hypercarbia* (raised  $PaCO_2$ ), *hypoxemia* (low  $PaO_2$ ) or a combination of both.

*Hypoxemia* can result from:

1. *Ventilation perfusion (V/Q) mismatch*: This typically improves with supplemental oxygen and occurs in conditions such as RDS, meconium aspiration, pneumonia and chronic lung disease.
2. *Extrapulmonary shunting of blood*: Characterized by lack of improvement with supplemental oxygen despite the absence of congenital heart disease as seen in persistent pulmonary hypertension (PPHN).

*Hypercarbia* can result from: The presence of reduced tidal volume and/or frequency of respiration (i.e. minute ventilation). Usually hypercarbia accompanies hypoxemia but it can occur on its own. Hypoventilation leading to hypercarbia may be due to:

1. *Reduced respiratory compliance* as seen in RDS or pneumonitis.
2. *Atelectasis and reduced lung volume* as seen in RDS and pulmonary hypoplasia.
3. *Compressed lung* as in pneumothorax, lobar emphysema and pleural effusion.
4. *Ventilatory pump failure* as in apnea of prematurity, intracranial hemorrhage.
5. *Impaired muscular function* as in congenital myopathies.

## ASSESSMENT OF RESPIRATORY FAILURE

This should be based on the composite of clinical examination, blood gas assessment and radiography.

### Clinical Examination

The following aspects need to be borne in mind:

1. *Respiratory rate*: There may be tachypnea with respiratory rates greater than 60 per minute or slow irregular breaths with or without gasping as seen in more advanced cases of respiratory failure. Apnea and irregular respiration also occurs due to lack of central drive.
2. *Accessory muscles* of respiration may be used causing chest wall retractions and flaring of alae nasi.
3. *Grunting* is a feature of neonatal lung disease as the infant attempts to raise intra-alveolar pressure by exhaling against a closed glottis. *Stridor* may also be noted in conditions compromising the upper airway.

4. The baby appears unwell with tachycardia or has episodes of bradycardia. Persistent bradycardia is an ominous sign and a terminal event. There may be evidence of impaired cardiac performance with poor peripheral perfusion and shock.
5. *Cyanosis* occurs if more than 5.0 g/dL desaturated hemoglobin is present. This must be confirmed using pulse oximetry, as clinical signs are unreliable.
6. Percussion and palpation have a limited role in neonatal respiratory examination.
7. Auscultation may reveal general reduction in air entry as in any severe lung disease like respiratory distress syndrome. Unilateral decrease in air entry may occur in air leaks, pneumonia or misplaced endotracheal tube. Crepitations may be heard but are nonspecific.
8. Transillumination of the chest using a fiberoptic light source may be used to detect a pneumothorax.
9. *Cardiac evaluation* is part of assessment of respiratory system. Significant murmurs are more likely to be heard after 48 hours of age. Murmurs that are pansystolic/diastolic, grade 3/6 or more, accompanied by abnormal pulses are likely to be significant. Absence of a murmur does not exclude significant heart disease. Echocardiographic evaluation of the cardiac structure and function is a useful tool in the management of infants with respiratory failure.

### Radiography

Radiography has an important role in management of respiratory failure in newborn.

Chest X-ray is one of the most useful tools that a clinician can use in neonates with respiratory failure. Some important radiographic patterns are outlined below:

- *Ground glass appearance* of surfactant deficiency with air bronchograms. In the very premature infant this may present as a fine hazy appearance on the radiograph. Extreme premature infants with minimal alveoli may have clear lung field.
- In term babies transient tachypnea may be associated with mild haziness with fluid in the right minor fissure. Meconium aspiration may be seen with irregular pulmonary opacities and hyperinflated lungs.
- *Airleaks*: Pneumothorax, pneumomediastinum and pulmonary interstitial emphysema (PIE). PIE is seen as streaks of air dissecting towards the hilum. A pneumothorax may be difficult to detect in the supine film and may require a lateral decubitus view.

- Infants with bronchopulmonary dysplasia may show *cyst like areas* in addition to pulmonary opacities in both lungs.

Radiological appearances may be non-specific and it may be difficult to distinguish surfactant deficiency, chest infection, pulmonary edema from patent ductus and early chronic lung disease. Computed tomography of the chest may be needed to identifying lung malformations such as cystic adenomatoid malformation and lobar emphysema, which can be present despite normal X-ray appearances.

### Blood Gas Evaluation<sup>1</sup>

Oxygenation of blood is dependent on matching of ventilation and perfusion. Ventilation perfusion mismatch causes hypoxia. This can occur at the level of the lungs due to intrapulmonary shunt if atelectatic alveoli are perfused as in respiratory distress syndrome or at the level of the patent ductus or foramen ovale as in pulmonary hypertension.

Ventilation, which is the movement of carbon dioxide from the blood to alveoli, is dependent on alveolar ventilation. Alveolar ventilation is the product of tidal volume (minus dead space) and respiratory rate.

Respiratory failure leads to accumulation of carbon dioxide causing respiratory acidosis. If PaCO<sub>2</sub> is persistently elevated, as in chronic lung disease, the pH may return to normal as a result of compensatory metabolic alkalosis.

If an infant has severe hypoxemia and/or decreased tissue perfusion, metabolic acidosis results from anaerobic metabolism and the accumulation of lactate.

Oxygen is carried in the blood in two main forms dissolved in plasma and bound to hemoglobin. The former is trivial and it is hemoglobin that is the principal carrier of oxygen. The amount of oxygen carried in the blood depends on the hemoglobin level and the hemoglobin saturation. The PaO<sub>2</sub> that is needed to fully saturate hemoglobin is dependent on the oxygen hemoglobin dissociation curve which varies depending on the relative amount of fetal hemoglobin, which is fully saturated at a lower PaO<sub>2</sub> than adult hemoglobin. For this reason arterial oxygen saturation is a better indicator of amount of oxygen in the blood than PaO<sub>2</sub>, but is an unreliable method to detect hyperoxia (PaO<sub>2</sub> > 80 torr or 10 kPa). This is due to the sigmoid nature of the oxygen hemoglobin dissociation curve.

Interpretation of blood gases must be done with caution and taking into account the overall clinical picture.

1. *Is a recent change in blood gas an artefact or is it real*  
The following points can help in making this decision:

- An air bubble in the sample will lower the PCO<sub>2</sub> and move the PO<sub>2</sub> closer to partial pressure of O<sub>2</sub> in room air.
- Blood gas sample left for long period in room temperature will have higher CO<sub>2</sub> as cells continue to metabolize oxygen and produce CO<sub>2</sub>.
- Capillary blood gases should be interpreted with caution and may vary markedly from arterial sample.
- Gas machines derive SaO<sub>2</sub> from PaO<sub>2</sub> assuming all hemoglobin to be adult. In an infant with significant fetal hemoglobin, the derived SaO<sub>2</sub> will be lower than the measured SaO<sub>2</sub>.
- Dilution of gas sample with fluid will cause both O<sub>2</sub> and CO<sub>2</sub> to diffuse out of blood into fluid and hence PaO<sub>2</sub> and PaCO<sub>2</sub> will be artificially lowered.

### 2. *Clinical status of infant*

Normal blood gas in a struggling infant is not reassuring. High CO<sub>2</sub> in an infant with chronic lung disease with a normal pH is not necessarily concerning.

### 3. *Where the infant is in the natural history of the disease*

An elevated CO<sub>2</sub> is more concerning in the early stages but may be acceptable in chronic lung disease. Other indices have been used in clinical trials to assess the severity of respiratory failure in ventilated patients. These include:

- *Alveolar-arterial oxygen differential (A-aDO<sub>2</sub>):* Normal values are 5-6 kPa (40-50 mm Hg). A-aDO<sub>2</sub> can be calculated directly by blood gas machines.
- *Oxygenation index (OI):* This is obtained from the formula: OI = Mean airway pressure × FiO<sub>2</sub>/PaO<sub>2</sub> (mm Hg).

OI values above 25 imply severe respiratory failure and values above 40 have been used as an indication for ECMO because they predict very high mortality.

## TREATMENT OF RESPIRATORY FAILURE

### Oxygen Therapy

For mild respiratory failure this may be all that is required to maintain oxygenation till the underlying pathology improves either on its own or as a result of treatment.

### Continuous Positive Airway Pressure (CPAP) and Positive End Expiratory Pressure (PEEP)<sup>2-4</sup>

CPAP is positive pressure applied throughout the respiratory cycle of a spontaneously breathing baby

while PEEP is pressure applied during the expiratory phase of artificial ventilation.

#### *Mechanism of Action of CPAP and PEEP*

- Mechanical splinting of upper airways keeps them open.
- Improves tidal volume in atelectatic lung and increases functional residual capacity.
- Improves compliance and decrease airway resistance with resultant decrease in work of breathing.
- Increases diaphragmatic activity.
- Decreases alveolar edema.
- Conserves surfactant on the alveolar surface.
- Increases mean airway pressure.

#### *Indications of CPAP*

- Increased work of breathing as shown by respiratory distress and increased oxygen requirements.
- Atelectatic lungs as shown on X-ray for example surfactant deficient lung disease (Respiratory distress syndrome).
- Apnea of prematurity.
- Post extubation. Babies are more likely to be successfully extubated if CPAP is applied immediately after extubation.
- Unstable upper airways as in tracheomalacia.

### Methods of Giving CPAP

#### A. Interface

1. *Nasal prongs*: This is the best method. One or two prongs are inserted into the baby's nostril. Binasal prongs have been shown to be better than single prongs. Prongs can be short (1-2 cm into the nostril) or long into the pharynx (cut endotracheal tube), although the latter have not been shown to be of additional benefit, indeed there is some evidence to show that shorter prongs are better because they offer less resistance. Problems with this method include loss of pressure when the prong slips out or gets blocked. Pressure is also lost when the baby cries. Soreness and deformity of the nose can also occur.
2. *Face masks* have been used but are less effective as it is difficult to have an effective seal and it is difficult to have access to baby's face.
3. *Endotracheal tube* has been used to deliver CPAP but this is not recommended, as the baby has to work against the resistance of the endotracheal tube to breathe.

Pressures used are typically 4-6 cm of water but can vary according to the underlying pathology. Pressures as high as 8-10 cm have been used provided baby has atelectatic low volume lungs. CPAP can cause CO<sub>2</sub> retention and if CO<sub>2</sub> levels rise, lowering the pressure may help. For PEEP, pulmonary graphics which show the opening pressures of the lungs, may be useful in determining the pressure to be used.

#### B. Devices Used to Deliver CPAP

##### *Bubble CPAP*

This system uses an underwater blow off system; sufficient flow creates continuous bubbling from the end of the underwater tube which is placed at a specified depth underwater. This system is simple and relatively inexpensive to set up. A recent study comparing its efficacy in preventing extubation failure in preterm babies found it as effective as the flow driver system.<sup>5</sup>

##### *Infant Flow System*

The "expiratory" limb of the flow driver system is open to the atmosphere. Theoretically this means that the baby can inspire with a higher flow than that set. This extra gas can be drawn from the expiratory limb (variable flow). This theoretically decreases the chance of the pressure falling with large inspirations.

##### *Ventilator*

Flow is usually set at about 6 liters/minute when the ventilator is used to deliver CPAP.

##### *Contraindications*

These include:

1. Need for mechanical ventilation due to respiratory failure.
2. Frequent apneas and bradycardia.
3. Upper airway abnormalities-cleft palate, tracheoesophageal fistula.
4. Cardiovascular instability.

##### *Complications*

These are:

1. Blockage of nasal tube.
2. Overdistension of lung leading to air leaks.
3. CO<sub>2</sub> retention.
4. Impaired venous return leading to decreased cardiac output.

5. Gastric distension.
6. Nasal irritation and damage to the septum.

### MECHANICAL VENTILATION

This combines artificial support at a predetermined level set by the clinician with the patient's own spontaneous breathing. There are two main forms of mechanical ventilation—*tidal ventilation* (also called conventional ventilation) and *high frequency ventilation*, which utilizes subphysiological tidal volumes.

#### Indications

1. Hypoxemic respiratory failure  $\text{PaO}_2 < 50$  torr (6.7 kPa) while receiving  $\text{FiO}_2 > 0.5$ .
2. Hypercapnia— $\text{PaCO}_2 > 60$  torr.
3. Impaired respiratory drive.
4. Unstable cardiovascular status-hypotension.
5. Increased work of breathing.

Factors affecting oxygenation and carbon dioxide elimination in conventional mechanical ventilation are summarized in Table 52.2.

**Table 52.2: Factors affecting oxygenation and carbon dioxide elimination**

Aim	Ventilator parameter change				
	PIP	PEEP	$\text{FiO}_2$	Rate	I:E ratio
1. Increase $\text{PaO}_2$	↑	↑	↑	-	↑
2. Decrease $\text{PaO}_2$	↓	↓	↓	-	↓
3. Decrease $\text{PaCO}_2$	↑	↓	-	↑	-
4. Increase $\text{PaCO}_2$	↓	↑	-	↓	-

Oxygenation is a function of the mean airway pressure which is affected by the peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) and inspiratory time. Carbon dioxide elimination is dependent on minute ventilation which is the product of tidal volume and respiratory rate.

With development in technology, mechanical ventilation has been increasing sophistication with time and various methods of delivering mechanical ventilation are now available.<sup>6,7</sup> Mechanical ventilation can be done by 'conventional' tidal method or by high frequency ventilation.

Pulmonary mechanics monitoring is also available and consists of direct online visualization of three fundamental vectors—pressure, volume and flow.<sup>6</sup> Pulmonary mechanics testing enables transition of care of ventilated patients from 'good judgement' to 'informed judgement' and is increasingly becoming an essential element in the assessment of patient status,

therapeutic evaluation and management guidance of infants with ventilator dependence.

*Conventional tidal* ventilation has traditionally been done using time cycled pressure ventilation primarily because of its efficacy, perceived safety and ease of application. peak inspiratory pressure (PIP) and positive end expiratory pressure (PEEP) are set by the clinician. The tidal volume delivered depends on the peak inspiratory pressure set by the clinician but varies at a set pressure depending on the compliance of the lung and may also vary depending on the synchrony between the patient and the ventilator. As the compliance of the lung varies considerably during the course of the disease the clinician has to alter the pressures accordingly to prevent hypo or hyper-ventilation. Weaning is done by reducing the PIP till 12-14 cm of water as compliance improves.

Volume controlled ventilation on the other hand delivers a set tidal volume set by the clinician irrespective of the compliance of the lung. This mode was not feasible for neonates till recently because of the small tidal volumes needed to ventilate them. With availability of microprocessor technology it is now possible to deliver this mode of ventilation to newborns. Inspiration ends when a preset volume determined by the clinician is delivered.<sup>7,8</sup> Tidal volume can be monitored at the ventilator but preferably at the proximal end of endotracheal tube. Levels of 4-7 ml/kg are targeted. Some tidal volume is, however, lost due to leak from uncuffed tube. There is some evidence that it is volutrauma from overdistension that damages lungs rather than barotrauma so it would be more useful to give known tidal volumes. Weaning of pressure occurs automatically as compliance improves in volume controlled ventilation. Adjustments in set tidal volume are done to maintain desired tidal volume delivery.

Modes that can utilize volume controlled or pressure limited ventilation include IMV, SIMV, assist control and also certain other newer modes.<sup>6,7</sup> These are summarized below.

1. *Intermittent mandatory ventilation (IMV)*: Mandatory breaths are delivered at a rate determined by the clinician. The patient can breathe spontaneously in between the mandatory breaths from a flow of gas with a predetermined level of oxygen. Weaning is done by reducing PIP or set tidal volume. When on minimal settings the rate is reduced till about 10 breaths/min then the patient is extubated. This mode can place the infant at a disadvantage as the baby is required to breathe against the resistance of the endotracheal tube for unsupported breaths.

2. *Assist control ventilation (also called synchronized intermittent positive pressure ventilation)*: In this mode, mechanical breaths are either patient (assist) or ventilator (control) initiated. This is also called patient trigger ventilation (PTV). If patient effort exceeds the trigger threshold a mechanical breath is delivered. If the patient does not breathe, the ventilator delivers a breath depending on the set control rate which is essentially a back up IMV (usually 40-60). Thus the patient controlled variables are respiratory rate and inspiratory time (if ventilator flow cycled), the clinician variables are PIP (if pressure limited), tidal volume delivery (if volume cycled), inspiratory time (if time cycled), flow and control rate. Suggested advantages of trigger ventilation over IMV include synchrony between patient and ventilator decreasing the need for sedation and paralysis although some trials have shown no benefits. Minimal assist sensitivity should be used to decrease the work of breathing. Weaning is done primarily by reducing the PIP because as long as patient breathes above the control rate weaning on rate has no effect. Patients can be weaned directly from A/C or switched to synchronized intermittent mandatory ventilation (SIMV). Problems with this mode include autocycling from endotracheal tube leaks (flow triggers), or cardiac impulses (chest impedance trigger). Inadequate inspiratory time (flow cycling) may result in inadequate time.
3. *Synchronized intermittent mandatory ventilation (SIMV)*: Ventilatory mode in which mechanical breaths are synchronized to the onset of patient breaths or delivered at a fixed rate if patient effort is inadequate. Spontaneous patient breaths in between mechanical pressure breaths are supported by PEEP only. Breathing time is divided into assist windows based on set rate, if patient attempts to breathe during the window the ventilator supports the breath to the set pressure (pressure mode) or volume (volume mode). Further attempts to breathe during the window result only in spontaneous breaths. If there is insufficient patient effort or apnea during the window a mechanical breath is delivered. It can be used both as a weaning mode or as primary management mode. Low assist sensitivity should be used and SIMV rate should be set at a level to maintain adequate minute ventilation. Other parameters are set as for IMV. Primary weaning parameters include SIMV rate, PIP (pressure mode) and tidal volume (volume mode). Problems include autocycling and failure to trigger if the assist sensitivity is too high or from patient fatigue.
4. *Pressure support ventilation (PSV)*: Spontaneous breaths are partially or fully supported by an inspiratory pressure assist above baseline pressure to decrease work of breathing. Can be used in conjunction with SIMV to provide a boost to non-SIMV breaths (as in weaning) or on its own in patient with reliable respiratory drive as there is no backup control rate in this mode.

### Potential Complications of Mechanical Ventilation and their Management

1. *Overdistension and baro/volutrauma*: Continuous bedside monitoring with weaning of pressures as lung compliance improves (increases). Risk of PIE and airleaks and subsequent chronic lung disease if this does not happen.
2. *Airway complication*: Traumatic intubation, malpositioned endotracheal tube (check position with X-ray), tube obstruction.
3. *Cardiovascular compromise*: At high mean airway pressures the venous return to the heart is impaired.
4. *Oxygen toxicity*: Leads to chronic lung disease and retinopathy of prematurity. Wean oxygen and aim for saturation's between 85-95 percent. Higher saturation's are associated with risk of PaO<sub>2</sub> above 10 kPa and oxygen toxicity. Direct pulmonary oxygen toxicity begins to occurs at FiO<sub>2</sub> greater than 0.6.
5. *Infection*: Prophylactic antibiotics are of no proven benefit and increase risk of resistant strains.

### MANAGEMENT OF SPECIFIC RESPIRATORY CONDITIONS

#### 1. Respiratory Distress Syndrome

It is the primary pulmonary disorder of preterm infants. Approximate incidence at 24 weeks is > 80 percent and at 36 weeks 5 percent. Surfactant deficiency is the main feature causing higher surface tension of alveolar surface and subsequent atelectasis. The number of functional alveoli also increases with gestational age and in extreme prematurity the distance of alveolus from nearest capillary is more thus increasing the diffusion barrier for gases. Physiological abnormalities include decreased compliance of the lungs, increased resistance and ventilation perfusion mismatch secondary to atelectasis. This increases the work of breathing and leads to respiratory failure. Grunting is a cardinal feature and is due to attempt by the infant to produce PEEP against a closed glottis. Radiographic features have been described earlier. Blood gases show hypoxemia. CO<sub>2</sub> levels may be normal initially if the

infant is able to compensate by breathing fast but will eventually rise. Blood gas may show respiratory or mixed acidosis if tissue hypoxia occurs. It has to be distinguished from infection, which can produce similar radiographs, and transient tachypnea. Antenatal administration of corticosteroids has reduced the incidence and severity of RDS.

## Management Strategies

### *Continuous Positive Airway Pressure*

This has been available for use in newborn babies since Gregory demonstrated its efficacy in 1971. To be effective it requires the infant to have a good respiratory drive. CPAP can be provided using a conventional ventilator, underwater bubble CPAP or the infant flow driver system which has the theoretical advantage of using variable flow. The patient interface can be single prongs (cut endotracheal tube), short binasal prongs or face mask. Binasal prongs are more effective than single prongs. Face masks can increase leaks but cause less trauma to the nose.

Early prophylactic CPAP is more effective than rescue CPAP in preventing the need for intubation in preterm babies with RDS. Recently there has been resurgence in the interest in the use of CPAP as it is perceived to be 'gentler' than conventional ventilation and in observational studies shown to reduce the incidence of BPD in preterm infants. The COIN trial compared the efficacy of using CPAP in babies of 25-28 weeks gestation from delivery and compared this to intubation and ventilation since birth.<sup>8</sup> There was no difference in the two groups in the combined outcome of death or BPD. Half of the babies in the CPAP group needed ventilation and there was a 3 fold rise in the incidence of pneumothorax in the CPAP group.

Another approach tried has been intubation and early extubation onto CPAP after surfactant administration (INSURE). Again there is no evidence that this approach reduces the incidence of BPD.

Use of CPAP improves the rate of successful extubation after mechanical ventilation.

### *Mechanical Ventilation*

It has traditionally been the mainstay of treatment of RDS. It is needed for more severe disease when surfactant replacement therapy is also given. Surfactant therapy has revolutionized the management of RDS and improves survival and complications like pneumothorax. Prophylactic therapy and early administration

is better than rescue treatment. Up to 3 doses can be given 12 hours apart. Indications for doses after the first include continuing oxygen requirements and high ventilatory support. Animal derived and synthetic surfactants are available. Animal surfactants have a quicker mode of action as compared to synthetic preparations due to presence of the carrier proteins and at present are the preferred surfactants but are more expensive than synthetic surfactants. Research is ongoing looking at newer novel artificial surfactants with added peptides and initial trials in humans are encouraging.<sup>9</sup>

Conventional or high frequency ventilation (HFV) are both used in the primary management of RDS. Despite several trials there has been no demonstrable benefit of HFV over conventional ventilation and most units use it as a rescue therapy in infants failing conventional ventilation.

In recent years newer modes of ventilation have become available. These include synchronized modes of ventilation and volume targeted modes of ventilation such as volume control ventilation and volume guarantee. Initial trials on the volume targeted modes have shown encouraging results and these therapies have the potential for improving the care delivered to babies with RDS.<sup>10-12</sup> A large randomized study comparing volume targeted modes with traditional ventilation is needed.

Blood pressure should be maintained with judicious use of volume expanders and inotropes and a close eye needs to be kept for complications like infections, airleaks, oxygen toxicity and patent ductus.

## 2. Neonatal Pneumonia<sup>13,14</sup>

Congenital pneumonia is present at birth and is acquired through hematogenous transplacental infection or ascending transamniotic infection and aspiration of infected amniotic fluid. Causes include Group B *Streptococcus*, *E. coli*, *Listeria*, *Ureaplasma*, Cytomegalovirus, etc. Features in history suggestive of infection are maternal pyrexia, prolonged rupture of membranes (> 18 hours), foul smelling liquor, premature onset of labor.

Postnatal pneumonia arises as a result of mucosal colonization, aspiration of gastric contents, and as a nosocomial infection. Causes include Gram-negative rods, *Staphylococcus species*, *Serratia*, etc. Clinical manifestations are non-specific with features of respiratory distress and failure. The infant may show features of sepsis like temperature instability and hypotension. Pneumonia may be associated in many

cases with a more disseminated infection. Radiological manifestations are non-specific and may mimic RDS or transient tachypnea. Blood cultures should be obtained and CSF examination may be indicated if more generalized infection is suspected. Endotracheal aspirates are useful if done soon after birth. Subsequently commensals and pathogens are difficult to differentiate although pure growth of one pathogen may be useful. Selected tests like PCR, latex agglutination may be available for specific organisms. Antibiotics are chosen to provide cover based on sensitivity patterns of the likely microorganisms. Aminoglycosides reach the bronchial lumen poorly although they achieve good concentration in the alveoli. Duration of therapy varies from 5-10 days. Hemodynamic and respiratory support along the lines discussed may be needed.

### 3. Neonatal Pulmonary Hemorrhage<sup>15</sup>

There is bleeding into the lungs and airways leading to acute deterioration. Prematurity and small for gestational age are risk factors. Other risk factors include RDS, surfactant treatment, air leaks, PDA, disseminated intravascular coagulation, hypothermia and pulmonary infection. Clinical features are due to mechanical blockage of airways, inhibition of endogenous surfactant, decreased pulmonary compliance, chemical irritation of the lungs by the blood, and volume depletion. Typically a stable infant suddenly deteriorates with or without loss of blood from the endotracheal tube. There is loss of tidal volume delivery as compliance decreases, hypotension and desaturations occur. Reduction of hematocrit occurs several hours later. Coagulation may be deranged due to consumption coagulopathy. Smaller hemorrhages may have a more insidious onset. Chest radiographs show diffuse haziness. Echocardiogram is recommended to look for PDA in all such infants even in the absence of clinical features. Treatment is mainly supportive. High ventilatory pressures (both PIP and PEEP) will be needed to deliver adequate tidal volume and move baby's chest. Circulatory support will be needed for hypotension. Clotting defects need to be corrected. Surfactant has been shown to improve lung compliance in these patients and this is probably due to replacement of the surfactant destroyed by the blood. PDA should be treated. Mortality averages 50 percent and the incidence of chronic lung disease in survivors is high.

### 4. Meconium Aspiration Syndrome<sup>16-19</sup>

Meconium passage *in utero* may be a marker of stress. It is not likely to happen before 36 weeks gestational age. To aspirate meconium the baby must have gasped *in utero* as a result of hypoxemic stress. About 5 percent

of babies born through meconium stained fluid develop meconium aspiration syndrome. This is more likely if the consistency of meconium is thick and the baby is depressed at birth. Pathophysiological mechanisms include air trapping, airway inflammation and edema, surfactant inactivation, cytokine mediated injury leading to respiratory failure and persistent pulmonary hypertension of the newborn. In chronic fetal hypoxia pulmonary vascular remodelling may cause PPHN.

At delivery of infant's shoulder and trunk gentle oropharyngeal suctioning was traditionally performed. This has however been shown to be of no benefit in a large randomized study. Maneuvers like compression of baby's chest to stop it from breathing before the larynx is suctioned are potentially dangerous and have no scientific evidence of benefit. Intubation and suctioning under direct vision using a laryngoscope should be performed only if the infant is depressed at birth with poor respiratory effort and bradycardia and never in a vigorous crying infant no matter how thick the meconium. Radiographic findings include diffuse patchy infiltrates, air trapping, air leaks and atelectasis. Management includes oxygen therapy to maintain high oxygen saturations as oxygen is a potent pulmonary vasodilator. CPAP may be used although some people prefer to move directly to mechanical ventilation due to worries about air trapping. Ventilation strategies including hyperventilation to achieve respiratory alkalosis and pulmonary vasodilatation have been proposed but this increases the likelihood of side effects associated with hypocarbia. More 'gentle' ventilation allows for higher PaCO<sub>2</sub> and lower pH and PO<sub>2</sub> in an attempt to lower barotrauma and air leaks. There are no large randomized controlled trials comparing various strategies of ventilating babies with MAS. Inotropes are used to keep the systemic pressures in high normal range. High frequency ventilation may be used but there are no trials documenting its superiority over conventional ventilation. Nitric oxide has been used for MAS complicated by PPHN ( see next section). Surfactant can be given to these babies although evidence for its efficacy is lacking. Steroid therapy has been suggested to reduce inflammation but cannot be recommended on current evidence. Other novel techniques tried include lung lavage but again its efficacy in terms of meaningful outcomes like improved survival has not been demonstrated.

### 5. Persistent Pulmonary Hypertension of Newborn (PPHN)<sup>20-24</sup>

There is a failure of the normal postnatal decrease in pulmonary vascular resistance (PVR). This causes right to left shunting at the level of the patent duct or

foramen ovale and severe hypoxia results. There may or may not be underlying parenchymal disease. The heart is structurally otherwise normal, i.e. cyanotic heart disease is not present.

### Pathogenesis

A number of factors contribute.

1. *Abnormal pulmonary vasculature*: This is seen in chronic intrauterine hypoxia which leads to abnormal muscularization of the pulmonary vascular tree as in some cases of MAS or idiopathic PPHN. It can also be seen in conditions with abnormal lung development like diaphragmatic hernia and pulmonary hypoplasia.
2. *Asphyxia*: Causes myocardial dysfunction, and hypoxia, hypercarbia and acidosis with associated vasoconstriction.
3. *MAS*: Gas trapping causes pulmonary distension and increased PVR. Associated hypoxia contributes to this.
4. *Sepsis*: Inflammatory mediators increase PVR and parenchymal disease produces hypoxia.

### Diagnosis

PPHN has to be distinguished from cyanotic congenital heart disease. The hyperoxia test and measuring pre and post ductal saturations is used to clinically distinguish cardiac and respiratory causes of hypoxia and diagnose PPHN. Low values from both sites do not however rule out PPHN as shunting may occur at patent foramen ovale (PFO) level. Echocardiography is used for definitive diagnosis. Shunting is seen, cyanotic heart disease excluded and pulmonary pressures can be measured.

### Management

Babies diagnosed to have high risk condition for PPHN for example diaphragmatic hernia should be delivered in centers capable of managing the infant. Hypothermia, acidosis and hypercarbia should be avoided. The initial approach should be to establish adequate ventilation and treat any treatable underlying disorder. Both conventional and high frequency ventilation have been used. Ventilation strategies include inducing alkalosis with hyperventilation and consequent hypocarbia. Sodium bicarbonate infusions have been given to augment this and keep pH above 7.5. This causes pulmonary vasodilatation. Some clinicians adopt a conservative approach accepting higher PaCO<sub>2</sub> and lower pH values to prevent barotrauma and decrease

lung over expansion, which contributes to, raised pulmonary pressures. It is important to maintain adequate cardiac output and blood pressure to reduce the right to left shunt. Tolazoline has been used but is a non specific vasodilator with unpredictable response and side effects include hypotension and renal failure. Inhaled nitric oxide has been shown to be effective in PPHN and works as a more specific pulmonary vasodilator and reduces the need for ECMO. Doses of 20 ppm are used although doses up to 80 ppm have been used in the iNO trials. ECMO is the rescue modality used when there is no response to iNO.

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**DEFINITION**

Shock is defined as a state of inadequate tissue perfusion characterized by a deficient supply of oxygen and nutrients and inadequate removal of toxic metabolic waste products at the cellular level. Failure of this function results in cellular death and organ dysfunction.

**TISSUE PERFUSION AND SHOCK**

Maintenance of adequate tissue perfusion is dependent upon 3 factors:

1. Cardiac output.
2. Local autoregulation.
3. Normal blood characteristics.

**Cardiac Output**

Cardiac output is the product of heart rate and stroke volume. Stroke volume is dependent on three factors: (a) Preload, (b) Contractility, and (c) Afterload. Hence, compensatory mechanisms for inadequate perfusion include:

1. Increasing heart rate.
2. Increasing preload (colloids and crystalloids)
3. Improving contractility (inotropes)
4. Decreasing afterload.

The resting heart rate in a neonate is high (140-160) and hence improvement in cardiac output by increasing heart rate is usually limited. Interventions for inadequate perfusion are usually limited to fluids and inotropes.

**Cardiac output** = Heart rate (HR) × Stroke volume (SV)  
= Heart rate × (preload/contractility/  
afterload)

**Blood pressure** = Cardiac output × systemic vascular  
resistance

**Blood pressure** = Heart rate × (preload/ contractility/  
afterload) × systemic vascular  
resistance

**Local Autoregulation**

Blood flow through the local arterial, capillary and venous bed to the tissues is maintained by a local autoregulatory mechanism, which maintains tissue perfusion over a wide range of blood pressure changes. Due to this control, changes in blood pressure are not directly reflected as changes in tissue perfusion. If this autoregulation is lost, blood flow becomes pressure dependent and results in ischemic and hemorrhagic manifestations. Factors controlling local vasomotor regulation are incompletely understood and interventions to modify this factor are not available.

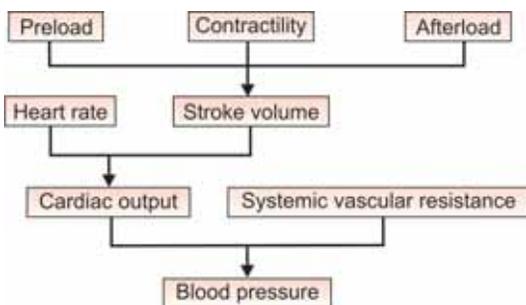
**Blood Characteristics**

The third factor responsible for tissue perfusion includes normal characteristics of blood components. Fetal hemoglobin binds oxygen more tightly as compared to adult hemoglobin and therefore supply of oxygen by fetal hemoglobin is less as compared to adult hemoglobin. Presence of anemia or methemoglobinemia would interfere with the oxygen carrying capacity of blood and maybe responsible for manifestations of tissue perfusion. Maintaining hemoglobin within a normal range, nursing in a thermoneutral zone and prompt treatment of hypocarbia and acidosis would help in oxygen delivery to the tissues.

**BLOOD PRESSURE AND SHOCK**

Blood pressure is an easily measurable parameter and usually considered to be a marker for systemic hypoperfusion and shock. Blood pressure is a product of cardiac output and systemic vascular resistance (Flow chart 53.1). Although changes in blood pressure often accompany clinical features of shock, a low blood pressure is not mandatory for a diagnosis of shock. **Early stages of shock may have normal blood pressure and a normal blood pressure does not exclude shock.** Hence, a low blood pressure should not be used as the only criteria for the diagnosis of shock.

**Flow chart 53.1:** Schematic presentation of regulation of blood pressure



### Normal Blood Pressure in Newborns

Various studies have attempted to document normative data for blood pressure (BP) in newborn babies.<sup>1-3</sup> Overall, there is a fairly good agreement between reports from various institutions. The British Association of Perinatal Medicine has adopted an operational definition for treatment purposes.<sup>4</sup> They have recommended that the mean arterial blood pressure (MAP) in mm Hg should be maintained at or above a numerical value equal to the gestational age of the infant in weeks. This would suggest that a neonate born at 30 weeks should maintain a MAP > 30 mm Hg and a term infant should have a MAP > 37-40 mm Hg. However, these values show an increase with postnatal age and most preterm infants, even with a lower gestation (24-26 weeks), have MAP values beyond 30 mm Hg by the third day of life.

### Measuring Blood Pressure in Neonates

Blood pressure monitoring in sick neonates may be done using invasive or non-invasive techniques. The gold standard of measuring blood pressure is an indwelling arterial line, which should be used for monitoring sick neonates. An indwelling arterial line for BP monitoring gives a continuous reading of the systolic, diastolic and mean arterial pressures. These arterial lines have a transducer which needs to be calibrated daily to prevent zero error in the readings. Non-invasive BP monitoring by automated instruments based on oscillometric technique (Dinamap, Critikare) is also available. These instruments have a fairly good reliability as compared to indwelling arterial lines and usually readings by the non-invasive technique are 3-5 mm Hg higher as compared to the invasive method.<sup>5-8</sup> One apparent reason for lack of agreement between the two methods may be due to the use of incorrect cuff sizes when performing oscillometric

measurements. The appropriate cuff width to arm circumference ratio should be between 0.45 to 0.70.<sup>9</sup>

### ETIOLOGY OF SHOCK

Various etiological factors associated with shock in the newborn have been listed in Table 53.1. Among them, common causes include sepsis, perinatal asphyxia and patent ductus arteriosus. Various clinical conditions that merit monitoring for shock include:

1. **Ventilation:** Neonates needing ventilation are sick neonates and should be monitored for poor perfusion. Use of high pressures in intermittent positive pressure ventilation may lead to increased intrathoracic pressures and reduced preload. Sudden increase and decrease in BP with suctioning may result in sudden changes in perfusion pressure and result in intraventricular hemorrhage (IVH).
2. **Very low birth weight babies (< 1500 grams):** VLBW babies, especially with respiratory distress should be monitored for shock. Common antecedent causes for shock in VLBW and preterm neonates include need for ventilation and sedation, increased risk for sepsis, opening of ductus arteriosus and lack of antenatal steroids. Use of antenatal steroids has been associated with a reduced need for blood pressure support in preterm neonates.
3. **Sepsis:** All neonates with a diagnosis of sepsis should be monitored for evidence of shock. Shock as a presentation is more common in late-onset, nosocomial sepsis as compared to early onset sepsis.

**Table 53.1: Etiology of shock in neonates**

#### Hypovolemic

Excessive insensible water loss  
Diarrhea, dehydration  
Perinatal blood loss  
Placental hemorrhage

#### Cardiogenic

Hypoplastic left heart  
Aortic stenosis, coarctation of aorta  
Severe birth asphyxia  
Cardiomyopathy (infant of diabetic mother)  
Arrhythmias

#### Distributive

Sepsis  
Third space losses, peritonitis

#### Obstructive

Cardiac tamponade  
Tension pneumothorax

#### Dissociative

Anemia  
Methemoglobinemia

4. **Perinatal asphyxia:** Shock may be related to acute volume loss (hemorrhage) or secondary to myocardial ischemia. All neonates with severe asphyxia should be monitored for 48-72 hours for evidence of poor perfusion.
5. **Blood loss:** Blood loss in neonates indicated by twin-to-twin transfusion, fetomaternal hemorrhage and subgaleal bleeds should be examined for evidence of shock.
6. **Pneumothorax, apnea**

## STAGES OF SHOCK

### Early/Compensated Stage

It is a stage characterized by normal blood pressure and normal perfusion to the vital organs including brain, heart and adrenal glands. Compensation occurs secondary to sympathetic reflexes and redistribution of fluid from the skin and GIT to vital organs. Sympathetic overactivity results in tachycardia and skin hypoperfusion results in pallor, cool extremities and prolonged capillary refill time. Pulse pressure becomes narrow in early stages of shock due to compensatory increase in systemic vascular resistance.

In ideal circumstances, all cases of shock should be diagnosed at this stage.

### Uncompensated/Late

This stage is diagnosed with the onset of hypotension. This stage heralds the failure of compensatory mechanisms and is characterized by hypoperfusion of the vital organs. The skin may be mottled or pale and the extremities are cold and clammy. Peripheral pulses are weak and thready. Capillary refill time becomes markedly delayed (> 5 seconds). Renal hypoperfusion results in oliguria and cerebral hypoperfusion results in altered sensorium, irritability and seizures.

### Irreversible Stage

When shock has progressed to cause significant, irreparable functional loss to vital organs, an irreversible stage is reached. There is no 'gold standard' parameter to diagnose when this stage has been reached. This stage is characterized by Multi Organ Dysfunction Syndrome (MODS) and eventually results in death.

## MONITORING FOR PHYSICAL SIGNS

### Compensated Shock

Common signs at this stage include tachycardia, tachypnea, pallor, prolonged capillary refill time and

peripheral cooling of extremities. Capillary refill time (CRT) should be assessed on the chest after pressing for 5 seconds. CRT >3 seconds is prolonged and needs intervention. Cold extremity is a reliable sign of poor peripheral perfusion and early shock. A difference of >2°C between core and peripheral temperature (great toe) is suggestive of hypoperfusion. Tachypnea may result as a compensatory mechanism for metabolic acidosis.

### Uncompensated/Late

This stage is characterized by hypotension, reduced urine output and evidence of cerebral hypoperfusion. Blood pressure is remarkably maintained till late in shock. It is thus a very insensitive sign of shock in infants. Blood pressure may be measured by either the invasive or non-invasive technique according to available resources. A strict urine output monitoring is essential at this stage.

### Irreversible Stage

This stage is characterized by signs of multi-organ failure. Acute renal failure (anuria), jaundice, disseminated intravascular coagulation, adult respiratory distress syndrome and GIT perforation and hemorrhage may be some manifestations of irreversible organ damage.

It must be emphasized that the most effective and sensitive physiological monitoring available is repeated and careful physical examination of the neonate by a vigilant clinician.

## INITIAL MANAGEMENT OF SHOCK

The principles of initial management include

1. Rapid recognition of shock state.
2. Initial resuscitation, supportive care.
3. Investigations.
4. Start treatment for the primary cause.

### Rapid Recognition of the Shock State

Prolonged capillary perfusion, peripheral cooling, tachycardia, tachypnea and metabolic acidosis are the earliest signs of poor tissue perfusion.

### Initial Resuscitation and Supportive Care

Prompt and aggressive supportive care should be provided to all neonates with shock. Care should be taken to maintain temperature, blood sugar and oxygen saturations within the normal range. Radiant warmers are preferred for thermoregulation due to ease of

monitoring and intervention. Hypoxia and respiratory acidosis should be managed aggressively using ventilation and head box oxygen as required. Two large lumen intravascular catheters should be secured as soon as possible. At least one of the catheters should be above the diaphragm. The umbilical vein is the best option when a rapid venous access is required in the first few days of life. An initial fluid bolus of 10-20 ml/kg should be administered over 30-60 minutes (see below).

### Investigations

During placement of catheters, blood should be collected for septic screen including hematocrit and blood counts, electrolytes, blood gas analysis, various cultures and renal function tests (blood urea and creatinine). A chest X-ray should be done to evaluate for cardiomegaly and chest expansion and stool occult blood should be checked to exclude GIT blood loss.

### Start Treatment for the Primary Cause

The specific primary cause should be identified and treated. Appropriate antibiotics for sepsis, correction for dyselectrolytemia, steroids for adrenal insufficiency and arrhythmias should be treated by specific drugs.

## ISSUES IN FLUID RESUSCITATION

### Volume of Fluid

An initial fluid bolus should be tried in all forms of shock. In hypovolemic and septic shock an initial volume of 20 ml/kg may be infused over 30-60 minutes. If inadequate or no response is seen after the first bolus, a repeat bolus of the same volume should be given. A total of two boluses may be tried in cases of septic and hypovolemic shock. In hypovolemic shock, compensated stage represents 25% loss of the intravascular volume, uncompensated stage represents up to 40% loss and irreversible stage represents >40% loss. If hypotension and shock is present, 40-50% of the estimated blood volume (2 boluses of 20 ml/kg) may be safely administered. Any further bolus should be given under central venous pressure (CVP) monitoring. Even in cases of suspected cardiogenic shock, a bolus of 10-20 ml/kg over 60 minutes may be tried if signs of pulmonary edema are absent.

### Special Situations

In preterm neonates, smaller volumes of 10 ml/kg over 30-60 minutes should be used for fluid resuscitation.

Preterm neonates have a higher circulating intravascular volume and higher volumes of 20 ml/kg may have adverse consequences.<sup>10-12</sup> Similarly, shock secondary to myocardial dysfunction in perinatal asphyxia may be treated with 1-2 fluid boluses of not more than 10 ml/kg.

### Choice of Fluid

The choice of the initial fluid should be crystalloid due to its easy availability. Both normal saline (NS) and Ringer Lactate (RL) are isotonic and are distributed to the extracellular space. Either of the two fluids may be used in the initial fluid management of shock. However only 25% of the crystalloid infused remains intravascular. Whole blood is best reserved for hemorrhagic shock and packed cells should be used in the presence of low hematocrit (< 40). Colloids are fluids with large molecules that are retained in the intravascular compartment, exerting an oncotic effect on distribution of water. Commonly used colloids in neonates include 5% albumin, fresh frozen plasma (FFP) and plasma. FFP should be preferred when shock is complicated by DIC in addition to volume depletion.

The major controversy lies in the type of fluid to be used in septic shock characterized by endothelial dysfunction and capillary leak. Crystalloid fluid boluses may leak into the interstitial spaces due to endothelial dysfunction and contribute to pulmonary edema. However, in the presence of capillary leak and endothelial damage, even colloids would leak into the interstitial compartment. Thus, it is currently advised that both crystalloid and colloid solutions should be used in combination during capillary leak syndromes. Crystalloid is cheap, universally available and therefore is the most frequently used initial fluid. In general, colloid should be used after every 2-3 boluses of crystalloid. It is important to emphasize that initial type of volume chosen is less important than its immediate and aggressive administration.

### Monitoring during Fluid Therapy

The infant should be monitored for adequate tissue perfusion as well as signs of overhydration. Heart rate, blood pressure, peripheral perfusion, sensorium and urine output should be strictly monitored. If shock persists after the initial bolus, a second infusion of 20 ml/kg should be given. If shock persists after 2 boluses, it is termed as refractory shock and more aggressive monitoring and therapy is required.

The infant should be monitored for signs of fluid overload including hepatomegaly, periorbital puffiness,

third and fourth heart sounds ( $S_3$ ,  $S_4$ ). Infants with fluid overload would show cardiomegaly, pulmonary edema, Kerley A and B lines, and prominent interlobar fissures on the chest X-ray. These infants should not receive any further fluid bolus and inotropes should be started if shock persists.

### REFRACTORY SHOCK

1. Supportive therapy including ventilation as required.
2. Central venous pressure (CVP) monitoring.
3. Inotropic support.
4. Reduction of afterload.
5. Management of complications.

### Supportive Therapy

Shock not responding to initial fluid therapy is termed as refractory shock. Management of this condition merits invasive monitoring of central venous pressure (CVP) and inotrope therapy. Arterial blood gases, hematocrit, serum electrolytes, glucose and ionic calcium should be re-evaluated. Correction of acidosis, hypoxemia and metabolic derangements is essential throughout management of shock. Positive pressure ventilation should be provided to all neonates presenting with shock.

### Central Venous Pressure (CVP) Monitoring

The first step in the management of refractory shock is the placement of a central venous catheter for measurement of CVP. Central venous pressure (CVP) monitoring is difficult in neonates as it may be difficult to put a central venous catheter. If the neonate is < 7 days old, the umbilical vein should be used for CVP monitoring. If CVP is less than 10 cm H<sub>2</sub>O and signs of fluid overload are absent, further fluid boluses should be administered till the CVP rises beyond 10 cm H<sub>2</sub>O. This CVP probably ensures the optimum preload. If CVP is more than 10 cm H<sub>2</sub>O (but <15) hypovolemia is unlikely. This implies adequate preload and inotropes should be started. Central venous pressure > 15 mm Hg should be treated by using diuretics (frusemide 1 mg/kg) and dobutamine. It is better to decide fluid therapy by looking at the trend of CVP after each fluid challenge rather than absolute value of CVP. In cases of septic shock large volumes (60-80 ml/kg) of fluid may be required to normalize the cardiac parameters.

### Inotropic Agents

These should be considered only if shock persists despite adequate fluid resuscitation. Inotropic agents

should be started after ensuring adequate preload under CVP monitoring. Among the various inotropes available, the commonly used ones include dopamine and dobutamine. Epinephrine and norepinephrine are generally reserved for use in septic shock refractory to dopamine and dobutamine.

### Dopamine

It is an endogenous catecholamine. Despite its limitations it is the most commonly used inotrope in neonates. It acts on dopamine receptors at 1-4 µg/kg/m, β-receptors at 4-10 µg/kg/m and α-receptors at > 10 µg/kg/m. It is the inotrope of choice if shock is associated with hypotension. Supplementation with dobutamine should be considered if there is no response despite using 10 µg/kg/m or in the presence of tachycardia. Dopamine should preferably be infused via the central route. If infused via the peripheral route, the line should be monitored regularly as extravasation of this drug results in severe thrombophlebitis and local gangrene. "Tracking" (pallor) of peripheral vein used is common and reversible and is not an indication for changing the IV site. The dose varies from 5-20 µg/kg/m.

### Dobutamine

It is the synthetic analogue of dopamine but does not exert any action on the dopamine receptors. It stimulates both the β-receptors. Dobutamine probably achieves better tissue perfusion and oxygen transport to tissues as compared to dopamine because of its β<sub>2</sub> receptor mediated vasodilatation and a decrease in SVR. Dobutamine is the initial inotrope of choice in shock without hypotension, cardiogenic shock, shock with CVP>10, and shock with congestive heart failure. The dose varies from 5-20 µg/kg/min.

### Adrenaline

It stimulates both α and β receptors, effectively increasing all factors contributing to normal blood pressure (stimulates generalized adrenergic response). Its use is reserved for patients not responding to a combination of dopamine and dobutamine. However it is the initial inotrope of choice in anaphylactic shock, post-cardiac arrest and septic shock with severe hypotension. The dose used is 0.1-2.0 µg/kg/m. Higher doses result in tachycardia, increased myocardial oxygen consumption and arrhythmias.

### Noradrenaline

It stimulates α and β<sub>1</sub> receptors, resulting in unopposed vasoconstriction and an increase in SVR. It is almost

exclusively reserved for sepsis with severe refractory hypotension unresponsive to dopamine and dobutamine.

### Choice of Inotrope

Although there is some controversy regarding which inotrope should be the drug of choice in shock, some guidelines are available. According to meta-analysis by Subhedar et al<sup>13</sup> on four studies comparing dopamine and dobutamine, the authors concluded that dopamine was more effective than dobutamine in treating hypotension. They did not find any difference in the left ventricular output or tachycardia with use of either agent.

### Protocol for Starting Inotropes

Dopamine is the drug of first choice in shock associated with hypotension. It is the drug of first choice in septic shock. Dopamine may be started at a dose of 5 µg/kg/m and increased to 10 µg/kg/m under BP monitoring. If hypotension persists or myocardial dysfunction appears dobutamine should be added for further support. Dopamine and dobutamine have been found to have a complementary role to each other at 5-10 µg/kg/m each.<sup>14</sup> If hypotension persists, higher doses of dopamine and dobutamine till 15-20 µg/kg/m may be used. Shock resistant to high doses of dopamine and dobutamine (especially septic shock) should be treated with infusions of epinephrine or norepinephrine.

Dobutamine is the drug of first choice in shock NOT associated with hypotension. It may be considered as the first line of therapy in shock without hypotension and in cardiogenic shock secondary to perinatal asphyxia.

### Points to Remember while Using Inotropes

Inotropes should be diluted only in 5% or 10% dextrose and the infusion syringe should be kept horizontal to prevent precipitation. Dopamine gets oxidized in saline and both dopamine and dobutamine are incompatible with sodium bicarbonate. Both the drugs are compatible with each other and may be infused through the same line. The dose of the infusion should be calculated in µg/kg/min and should be titrated according to the response. The infusion should be weaned off slowly and should not be interrupted to give any other medication. Inotropes have a very short half-life (1-2 min) and interruptions in infusion should be avoided. A close watch should be kept on the venous line and the infusion pump. Dopamine and adrenaline are best given by the central route; dobutamine may

be infused peripherally. Overdose of these drugs can cause life-threatening hypertension. The inotrope line should never be flushed and infusions should be clearly labeled in bold. Invasive BP monitoring is preferable. All negative inotropic influences (hypoxia, acidosis) should be promptly treated as they blunt the response of inotropes.

### AFTERLOAD REDUCTION

This plays an important role in improving myocardial performance in neonates with cardiogenic shock or in late stages of septic shock. Afterload reduction is also beneficial to curtail α-adrenergic effects of using epinephrine and norepinephrine. This combination of afterload reduction with inotropic support may provide the optimal benefit for a profoundly impaired myocardium. Both nitroprusside (NTP) and nitroglycerine (NTG) lower the systemic vascular resistance (SVR) and are useful afterload reducing agents. These agents are not used routinely in the neonatal intensive care unit.

Flow chart 53.2 provides an algorithm for shock management.

### MANAGEMENT OF COMPLICATIONS

#### Acidosis

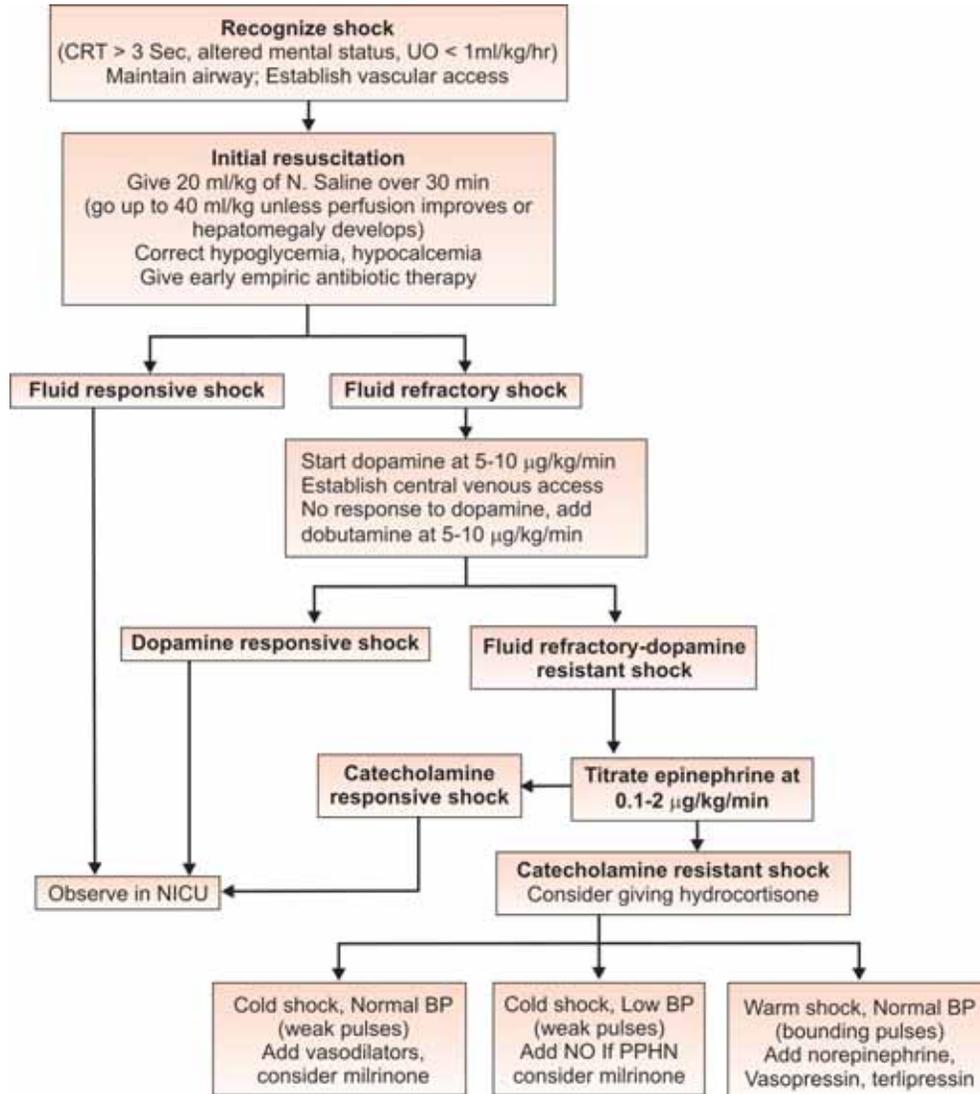
Metabolic acidosis should be treated by correction of hypovolemia, management of shock and treatment of underlying condition. Severe acidosis may compromise myocardial contractility, compromise cellular function and also blunt the effect of inotropes. Severe metabolic acidosis (pH < 7.15) should be treated with sodium bicarbonate, 1-2 meq/kg (diluted 1:1 in NS) and given slowly, only after ensuring adequate ventilation.

#### Hematological Support

Bleeding tendency should be treated with use of vitamin K, fresh frozen plasma and platelet transfusions. Hematocrit should be maintained above 40 with use of packed red cell transfusion.

#### Renal Support

Volume resuscitation should be used to maintain renal blood flow. Low dose dopamine (1-5 µg/kg/min) may not have a role in the prevention or treatment of acute renal failure, though it does increase the urine output. Dopamine does help in renal failure, by supporting the blood pressure and improving renal blood flow.<sup>15</sup> Doses of drugs excreted through kidneys should be altered as per creatinine clearance.

**Flow chart 53.2:** Algorithm for shock management (Adapted from ACCCM<sup>9</sup>)

### Adult Respiratory Distress Syndrome (ARDS)

Pulmonary failure may complicate septic shock. This is associated with very high mortality. Positive pressure ventilation with high positive end expiratory pressure (PEEP) should be used in the treatment of ARDS.

### Nutritional Support

Nutrition is an extremely important aspect of care. Enteral nutrition should be started after signs of peripheral hypoperfusion have subsided and hemodynamic stability has been ensured for 24 hours. Total parenteral nutrition should be started if enteral nutrition not possible for more than 72 hours.

### Corticosteroids in Shock

Helbock et al<sup>16</sup> have shown that the adrenal gland response to stress is inadequate in extremely low birth weight infants and many of them may present with features of adrenal insufficiency. Bouchier et al<sup>17</sup> compared the effect of hydrocortisone versus dopamine and found that hydrocortisone resulted in increased BP in 81% of babies. Gaissmaier et al<sup>18</sup> have shown that a single dose of dexamethasone, given to neonates with shock refractory to dopamine and fluid infusions, resulted in a better BP response. However, these are small studies and steroids should preferably be avoided in the management of shock until more evidence in its favor is available.

## CONCLUSION

In conclusion, shock in the newborn is a medical emergency. It is the final common pathway for varied insults. Early recognition, prompt resuscitation and watchful monitoring is the key to successful management of this condition in the neonate.

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Convulsions or seizures in the neonatal period is the most commonly seen sign of neurologic dysfunction. They are often difficult to recognize as they can mimic normal movements and are frequently transient.<sup>1-3</sup> Unlike in older children where etiology may not be evident, most seizures in the neonatal period have an underlying etiology either in the form of a neurologic or a metabolic abnormality. Early recognition of seizures and prompt treatment based on etiology is important to prevent long-term sequelae. Despite prompt treatment long-term prognosis can be poor in certain conditions such as severe perinatal asphyxia or inborn errors of metabolism.

### INCIDENCE

The incidence of neonatal seizures varies from 0.23 to 0.5 percent in full-term neonates. The incidence in preterm neonates may be as high as 20-25 percent.<sup>2</sup> Data from India suggests an incidence of 1.3 percent of all live births.<sup>4</sup> In our center the incidence is 0.63 percent of all live births and increases to 6 percent in preterm neonates.

### ETIOLOGY OF NEONATAL CONVULSIONS

The etiology of neonatal convulsions is listed in Table 54.1 and etiology based on age of onset in Table 54.2. The most frequent cause of neonatal convulsions in term neonates is birth asphyxia, followed by vascular causes (hemorrhage and infarcts) and CNS infections.<sup>1-3</sup> Though acute metabolic abnormalities used to be a common cause, its incidence is decreasing because of improved care of high risk neonates.<sup>1-3</sup>

In India the most frequent cause of neonatal convulsions is asphyxia followed by acute metabolic abnormalities and meningitis.

### CLASSIFICATION OF NEONATAL CONVULSIONS<sup>1-3</sup>

Neonatal convulsions may be classified as subtle, tonic, clonic and myoclonic seizures.

**Table 54.1: Neonatal seizures etiology**

#### *Acute metabolic events*

- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Hyponatremia

#### *Hypoxic ischemic encephalopathy*

#### *CNS infection*

#### *Vascular causes*

- Bleeds
- Infarcts

#### *CNS Malformations*

- Agenesis of corpus callosum
- Lissencephaly
- Hydranencephaly
- Porencephaly

#### *Inborn errors of metabolism*

#### *Neurocutaneous disorders*

#### *Peroxisomal disorders*

- Zellweger's syndrome
- Neonatal adrenoleukodystrophy

#### *Miscellaneous*

- Drug withdrawal (maternal narcotics)
- Local anesthetic injection
- Pyridoxine dependency
- Neonatal epilepsy syndrome

*Subtle seizures* are difficult to recognize and include movements such as sucking, chewing, tonic eye deviation and cycling movements, apneic episodes and autonomic phenomenon. These may or may not be accompanied by EEG seizure activity.

*Tonic seizures* may be focal or generalized. Generalized tonic seizures are more likely to occur in preterm babies and are usually not accompanied by EEG abnormalities. In contrast focal tonic seizures are often associated with EEG changes.

**Table 54.2: Etiology according to age of onset***0-24 hours*

- Perinatal asphyxia
- Hypoglycemia
- Local anesthetic
- Pyridoxine dependency

*24-72 hours*

- Perinatal asphyxia
- Hypoglycemia
- Hypocalcemia
- Intracranial bleed
- Drug withdrawal

*3-7 days*

- Meningitis
- Intracranial bleed
- CNS malformation
- Inborn errors of metabolism
- Neonatal epilepsy syndrome
- Late hypocalcemia

*> 7 days*

- Meningitis
- Late hemorrhagic disease of newborn
- Neonatal epilepsy syndrome
- CNS malformations
- Hypocalcemia

*Clonic seizures* may be focal or multifocal. These occur more frequently in term babies and are often associated with EEG abnormalities.

*Myoclonic seizures* can be focal, multifocal or generalized and usually have a poor prognosis. These need to be differentiated from "Sleep myoclonus" which typically resolves by 6 months of age.

## CLINICAL APPROACH

The important issues in the clinical approach to a neonate with convulsions are recognition of convulsions and determining etiology.

### Recognition of Neonatal Convulsions

The following aspects need to be borne in mind for this purpose:

- As mentioned earlier, neonatal seizures are often missed because of its transient nature and the fact that it can mimic normal activity (subtle seizures).
- A high index of suspicion and close observation will help in recognizing neonatal seizures.
- Subtle phenomenon such as blinking, sucking, eye deviation can be normal if transient, but if persistent or recurrent, will indicate seizure activity.

- Change in heart rate or respiratory rate during these episodes will favor a diagnosis of seizures.
- Seizures presenting as apneic episodes are more common in term neonates and are usually associated with an increase in heart rate thereby differentiating it from apnea of prematurity.
- Jitteriness needs to be differentiated from seizures. Jitteriness is repetitive rhythmic movements of any limb which stops when the limb is flexed. Clonic seizure activity will continue even if the limb is flexed.

### Determining Etiology

The following factors will help in determining etiology:

- A sick neonate is more likely to have seizures because of asphyxia or meningitis. Neonates with metabolic causes such as hypoglycemia and hypocalcemia, are likely to appear normal and alert inbetween episodes.
- The most common etiology in a preterm neonate is intraventricular hemorrhage (IVH).
- A large baby born to a diabetic mother may have seizures because of hypoglycemia or hypocalcemia.
- Age of onset of convulsions (Table 54.2): Day 1 convulsions are most likely to be due to birth asphyxia while in a sick neonate having seizures on day 5 it is most likely to be due to meningitis.
- Sibling history of neonatal seizures will possibly indicate an inborn error of metabolism or familial neonatal epilepsy syndrome.
- Need for resuscitation or evidence of intrapartum asphyxia will point to asphyxia as a possible etiology.
- Dysmorphic features and neurocutaneous markers will indicate an underlying CNS malformation.
- Presence of fever, poor feeding and lethargy will indicate meningitis as a possible etiology.
- Pallor and bulging fontanelle will indicate intracranial bleed.
- Refractory seizures usually suggest an inborn error of metabolism or structural abnormality of the brain.

Keeping this in mind one should look for the following factors in the history and examination of a neonate with seizures.

**History:** Birth details, asphyxia or birth trauma, setting or history suggestive of sepsis, maternal diabetes, family and sibling history of convulsions, age of onset of convulsion, and fever/poor feeding/lethargy.

**Examination:** Weight and gestation, sick looking child, bulging anterior fontanelle, features of sepsis, hypoxic

encephalopathy, neurocutaneous markers, malformation/dysmorphic features and blood pressure.

**Investigations:** Basic investigations that should be done in all neonates with convulsions are shown in Table 54.3. Special investigations include EEG, CT and MRI and metabolic work up for etiology.

### Role of EEG<sup>1-3,5-13</sup>

Continuous video EEG recording would be ideal and is the gold standard to diagnose neonatal seizures and to assess response to treatment. Studies have shown that there is dissociation between clinical and electrical seizure activity. Neonates may exhibit abnormal movements without electrical seizure activity and electrical seizure discharge may be present without clinical manifestation. The proportion of neonates with electrical seizures not having clinical seizures varies from 12 to 79% in various studies.<sup>1</sup>

There is a controversy regarding need to control electrical seizures. Most neonatologists are satisfied with clinical seizure control but there is some evidence now that the treatment goal should be control of electrical seizures. Though ideal, Video EEG recording may not be feasible in the routine management of neonatal convulsions. It would certainly be indicated in two situations: (a) To monitor pharmacologically paralyzed neonates with high risk of seizures; (b) To predict outcome in neurologically compromised neonates.<sup>8</sup>

Interictal EEG should ideally be done in all neonates with seizures but should definitely be done in those neonates where etiology has not been determined or seizures are not controlled with routine management. Abnormal interictal EEG recording has a prognostic implication. Background low voltage and burst suppression pattern indicates poor prognosis.

### Amplitude Integrated EEG (aEEG)

In aEEG a single channel recording is obtained from a pair of biparietal electrodes and this signal is amplified. It is a relatively simple way of continuous EEG monitoring and is particularly useful in assessing cerebral function in an asphyxiated neonate and has also been used to detect electrical seizures. However short episodes of seizures and focal seizures will not be picked up.<sup>9-12</sup>

Prolonged video-EEG remains the current gold standard in seizure monitoring but has limited availability in most centers. Although aEEG may be a useful screening tool that is more readily available for prolonged monitoring in many centers, it does not

replace conventional EEG. Given the lower sensitivity and specificity of aEEG for seizure detection, some authors suggest that neonates who are at risk of seizures or who exhibit possible clinical seizures also have a formal EEG recording of at least 1-hour duration.

### Imaging<sup>1,2,15,16</sup>

**Neurosonogram** should be done in all neonates and is useful in diagnosing cerebral edema, intraventricular hemorrhage and hydrocephalus. CT scan and MRI are more expensive investigations and should definitely be done if convulsions are refractory to first line anticonvulsant therapy or if etiology is not determined with routine investigations.

### CT Scan

CT scan is a better investigative tool than neurosonogram in diagnosing congenital malformations, intracranial hemorrhage, especially parenchymal, subdural and subarachnoid bleed, posterior fossa lesions and calcification. In hypoxic ischemic encephalopathy, CT scan findings include cerebral edema, hemorrhages and hypodense lesions. Presence of these findings are associated with poor long-term prognosis. CT scan should be done in HIE for prognosis and if etiology of seizures has not been determined by baseline investigations.

### MRI

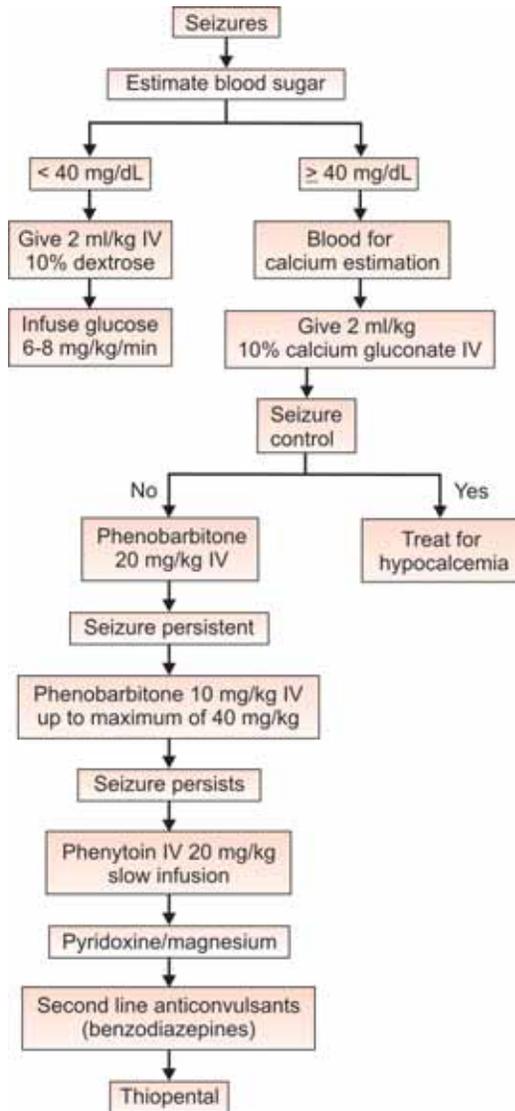
MRI is not an ideal investigation in the acute management of neonatal convulsions as it is not suitable for a critically ill neonate. However, it would be a useful diagnostic tool in those neonates who have persistent neonatal convulsions and are not critically ill. It is more useful than CT in diagnosing disorders of myelination and neuronal migration disorders. MRI is better than CT in diagnosing infarct, thrombosis and hemorrhages but is not good to detect calcification. Like CT scan it can help in predicting prognosis in neonates with hypoxic ischemic encephalopathy.

## MANAGEMENT OF NEONATAL CONVULSIONS<sup>1-3,5,8,17-25</sup>

Management of neonatal convulsions include (Flow chart 54.1):

- a. Immediate management of airway, breathing and circulation. This can be done by suctioning the neonate, providing oxygen and starting IV fluids if circulation is compromised. Many times a neonate

Flow chart 54.1: Therapeutic approach to neonatal seizures



may have a respiratory arrest during or post convulsion, in which case resuscitation with bag and mask ventilation or endotracheal intubation should be done immediately.

- After stabilizing the neonate, a heel stick glucometer blood sugar (GRBS) is done. If GRBS is < 50 mg/dL, 2 ml/kg of 10 percent dextrose is given IV, followed by 6-8 mg/kg/min of dextrose infusion.
- If seizures persist blood samples are collected for calcium, electrolytes, etc. (Table 54.3) and 1-2 ml/kg of 10 percent calcium gluconate is given IV slowly under continuous heart rate monitoring.
- If seizures persist anticonvulsant medications will have to be used.

Table 54.3: Investigations

*Baseline investigations*

- Blood sugar
- Serum calcium (phosphorus, alkaline phosphatase)
- Serum electrolytes
- Serum magnesium
- Septic screen, including CSF
- Neurosonogram
- EEG
- CT scan
- MRI

*Investigations for etiology*

- Work up for IEM
- Work up for intrauterine infection

**WHY SHOULD SEIZURES BE TREATED?**

Treatment of seizures is required to prevent immediate adverse outcome such as respiratory or circulatory failure and also to prevent subsequent adverse outcome on the developing brain. Although there has been debate as to whether seizures, per se, cause further brain injury, there is now some compelling evidence, predominantly from animal studies, that they do.

**WHEN TO TREAT SEIZURES?**

Most authors agree that seizures need to be treated with anticonvulsants if they last for greater than 1 minute and recur at a frequency of greater than 2 episodes per hour.<sup>14</sup>

**ADEQUACY OF TREATMENT**

There is a controversy regarding defining what is seizure control, should the goal of treatment be clinical seizure control or electrical seizure control. Many believe that the goal should be total or near total elimination electrical seizures. Although no study has definitely proven that aggressive therapy of seizures improves outcome, preliminary work has shown that seizures may exacerbate underlying brain injury in hypoxic-ischemic encephalopathy or brain inflammation. As such, the therapeutic goal should probably be elimination or marked reduction of both electroclinical and electrographic-only seizures in these infants.<sup>21</sup>

**CHOICE OF ANTI CONVULSANT**

Clinical management of seizures in the newborn has remained unchanged for more than a generation in spite of almost 10 years of evidence that medications

commonly used in the newborn are ineffective. A more recent study showed that clinically relevant levels of antiepileptic drugs including phenobarbital, phenytoin, and diazepam led to apoptotic neurodegeneration in the developing rat brain. The impact of therapeutic doses of these agents to neurodevelopmental outcome in newborns with seizures is not known. Despite this most neonatologists and neurologists still use phenobarbital as the first line anticonvulsant.

### Phenobarbitone

The drug of choice for neonatal convulsions continues to be phenobarbitone despite controversies surrounding its long-term use. Though other drugs have been tried, the most effective first line drug is phenobarbitone, 20 mg/kg IV slow infusion over 10 to 15 min and is found to achieve seizure control in 40 percent of neonates. Higher doses up to 40 mg/kg achieving serum levels of 40 µg/ml can control 70 percent of neonatal seizures. After the initial dose of phenobarbitone, if seizures continue, 10 mg/kg may be repeated every 15 minutes up to two times to reach a maximum dose of 40 mg/kg but this should be used only if ventilatory support is available as higher doses of phenobarbitone is known to cause respiratory depression. Dose of phenobarbitone should be adjusted to achieve serum levels of 20-40 mcg/ml. The maintenance dose of phenobarbitone is 3-5 mg/kg/day.

### Phenytoin

If the initial dose of phenobarbitone is not effective in controlling seizures, the next drug is phenytoin in a dose of 20 mg/kg IV slow infusion at the rate of 1 mg/kg/min. In view of the known cardiotoxicity of the drug this should be used as an infusion and not as IV bolus. Studies have shown that phenobarbitone and phenytoin are equally effective in control of seizures. The main disadvantage of phenytoin is that it is difficult to maintain serum levels as the drug is rapidly redistributed in body tissues and its oral absorption is poor. Phenytoin dose should achieve a serum concentration of 15 to 20 µg/ml. The maintenance dose of phenytoin is 3-5 mg/kg. But continuing oral phenytoin is not recommended because of its variable oral absorption. Phenytoin can be used as the first drug for control of convulsions if the baby has respiratory depression and facilities for ventilation is not available.

### Fosphenytoin

Fosphenytoin is a phosphate ester prodrug of phenytoin. Advantages of fosphenytoin include high water

solubility, ease of preparation in IV fluids, absence of tissue injury if extravasation occurs and a faster allowable rate of administration. It takes 8 minutes for fosphenytoin to be converted to phenytoin and 1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin.

### REFRACTORY SEIZURES<sup>1-3,5,8,21-30</sup>

Nearly, 60 percent of neonatal seizures are controlled with either or both of phenobarbitone and phenytoin. If seizures persist it is called refractory seizures. The causes of refractory seizures include severe birth asphyxia, intracranial bleeds, inborn errors of metabolism and CNS malformations.

If seizures are not controlled with the first line drugs, before using other antiepileptic drugs, it is useful to look for and correct hypomagnesemia and give a therapeutic trial of pyridoxine.

For hypomagnesemia (serum level < 1.0 mEq/L), 2-3 percent magnesium sulphate should be given IV in a dose of 2 mg/kg.

For pyridoxine dependent seizures, intravenous pyridoxine should be given at a dose of 50 to 100 mg. If isolated IV pyridoxine preparation is not available an injectable multivitamin containing the required amount of pyridoxine should be given. Oral maintenance therapy of 100 mg should be continued daily for atleast 6-12 months.

### SECOND LINE ANTICONVULSANTS

These are depicted in Table 54.4.

**Table 54.4: Medications that can be used in refractory neonatal seizures**

Drug	Bolus dose (IV)	Infusion
Diazepam	0.1-0.2 mg/kg	0.3 mg/kg/h
Lorazepam	0.05-0.2 mg/kg	
Midazolam	0.15 mg/kg	0.1-0.4 mg/kg/h
Clonazepam	0.1-0.2 mg/kg	
Paraldehyde	200-400 mg/kg (IV) 0.1-0.3 ml/kg (rectal)	16 mg/kg/h
Lidocaine	2 mg/kg	4-6 mg/kg/h

**Diazepam:** This is a short acting benzodiazepine. The recommended dose is 0.2 mg/kg IV followed by a maintenance dose of 0.3 mg/kg/h IV infusion. The disadvantage of diazepam is that it contains sodium benzoate as a preservative and this can displace bilirubin, increasing the risk of hyperbilirubinemia and kernicterus.

**Lorazepam:** It is also a short acting benzodiazepine having a longer duration of action and less cardio-respiratory depression. The dose is 0.05 mg/kg IV and can be repeated every 10-15 min to a maximum of 0.2 mg/kg. Onset of action is 2 to 3 minutes and duration of action varies from 6 to 24 hrs. Lorazepam has been used as the third line anticonvulsant or by some as the second line after phenobarbitone.

**Clonazepam:** The dose of clonazepam is 0.1 mg/kg IV. This has been used as the second line drug in many centers.

**Midazolam:** The dose of midazolam is 0.15 mg/kg IV followed by an infusion of 0.1 to 0.4 mg/kg/h. Midazolam has a shorter half-life and avoids problems of increased oropharyngeal secretions. There are recent studies which have demonstrated the use of midazolam in refractory seizures. Doses as high as 1.1 mg/kg/hr has been used. Adverse effects include hypotension, respiratory depression.

**Paraldehyde** can be given through the rectal or intravenous route. The per rectal dose is 0.1-0.3 ml/kg diluted 1:10 in mineral oil. The IV dose is 200-400 mg/kg IV over 1 hour followed by an infusion of 16 mg/kg/h to achieve a serum concentration of 10 mg/dL.

**Lidocaine** has been tried in refractory seizures at a dose of 2 mg/kg IV followed by an infusion of 4 to 6 mg/kg/h. Valproate and carbamazepine have also been used in refractory seizures. With availability of IV preparation of valproate this has been of some use in refractory seizures.

### NEWER ANTI-EPILEPTIC DRUGS<sup>21-23,30</sup>

**Vigabatrin** at a dose of 50 mg/kg/day oral and **lamotrigine** have been used in refractory neonates seizures. Other newer anti-epileptic medication which has been used in neonatal seizures are topiramate, zonisamide, bumetanide and levetiracetam.

### NEONATAL STATUS EPILEPTICUS<sup>26,31,32</sup>

Status epilepticus is defined as seizures persisting for longer than 30 minutes.

Hypoxic ischemic encephalopathy, CNS infection, uncorrected metabolic abnormalities, unrecognized pyridoxine dependency, inborn errors of metabolism and structural abnormalities of the CNS could all present as status epilepticus.

### Principles of Management

These include the following:

- Stabilizing the neonate.
- Monitoring for and treating metabolic abnormalities.
- Ensuring normal hydration status and adequate renal perfusion.
- Use of antiepileptic drugs.

The treatment protocol will include baseline anticonvulsants followed by any of the second line drugs such as an infusion of lorazepam or midazolam. If IV sodium valproate is available, a dose of 20-40 mg/kg IV followed by infusion of 5 mg/kg/h IV can be tried. If seizures persist the neonate will have to be ventilated and the following medications can be used.

- Thiopental:** 2-8 mg/kg IV followed by infusion of 1-10 mg/kg/h.
- Propofol:** 1-3 mg/kg IV followed by infusion of 2-10 mg/kg/h.

### SPECIAL SITUATIONS

#### Pyridoxine Dependency Seizures<sup>1-3,5,6,33</sup>

This is an autosomal recessive disorder. Seizures usually present in the first few days of life and can occasionally present *in utero*. Seizures occur due to decrease in gamma-aminobutyric acid (GABA) which is an inhibitory neurotransmitter. Pyridoxine is needed for production of GABA from glutamate. EEG is abnormal and has continuous diffuse, high voltage delta slow waves. Therapeutic and EEG response to intravenous pyridoxine is dramatic. The dose is 100 mg IV followed by 100 mg oral daily which should be given life long.

**Hypocalcemia:** This is defined as total serum calcium < 7 mg/dL or ionized calcium < 4.4 mg/dL. Early hypocalcemia occurs within 2 days of birth and late hypocalcemia any time after this. Hypocalcemia could be a transient phenomenon as in prematurity, asphyxia or if persistent could indicate an underlying disorder such as hypoparathyroidism. Initial treatment is 1-2 ml/kg of 10 percent IV calcium gluconate (10% solutions contains 9.4 mg of elemental calcium/ml). A dose of 45-75 mg/kg/day of elemental calcium is required to correct hypocalcemia. If hypocalcemia persists or recurs, investigations should be done to look for etiology and long-term calcium supplements may be needed.

### SEIZURE CONTROL—CLINICAL OR EEG CONTROL

Most neonatologists would be satisfied with clinical control of seizures. However, since persistent neonatal

seizures can cause harm by increasing cerebral blood flow and by glutamate release which causes cell death—many suggest it would be ideal to control EEG seizures. Long-term use of anticonvulsants especially phenobarbitone is known to cause problems to the developing brain. Therefore one has to weigh the risk and benefit of anticonvulsant therapy and it has to be individualized.

### DURATION OF ANTI CONVULSANT THERAPY<sup>1-3,21,34,36</sup>

Prolonged use of anticonvulsant especially phenobarbitone, is known to have adverse effect on the developing brain. Hence the policy is to withdraw anticonvulsants as early as possible. In neonates with known metabolic cause such as hypoglycemia and hypocalcemia, anticonvulsants can be stopped prior to discharge. In neonates with HIE, medications should be withdrawn prior to discharge if neurological examination and EEG is normal. If EEG is abnormal and neurological examination is not normal, anticonvulsant, usually phenobarbitone at 3-5 mg/kg/day, is continued for a month and the child is re-evaluated. If neurological examination remains abnormal, phenobarbitone can be continued for a maximum period of 3-6 months. Guillet et al evaluated 146 children with neonatal seizures and found that recurrence was independent of phenobarbital prophylaxis (30% in the group with phenobarbital prophylaxis and 22% in the group without prophylaxis).<sup>36</sup>

### PROGNOSIS<sup>1-3,35</sup>

While discussing prognosis three issues have to be addressed. Immediate outcome, long-term neurologic sequelae and recurrence of seizures.

**Immediate outcome** depends on etiology and is worse in neonates with stage 3 HIE, inborn errors of metabolism and serious CNS infection.

**Recurrence of seizures:** Risk of recurrence can be as high as 8-10 percent and is related to the underlying etiology.

**Long-term sequelae:** The long-term prognosis is dependent on the etiology, type of seizures and response to therapy.

- Neonates with stage 3 HIE, meningitis and hypoglycemia have a 50 percent risk of developing long-term neurologic sequelae. In HIE stage 2, the risk is 25 percent.
- Low birth weight and preterm neonates with seizures have a significantly worse prognosis than those without seizures.

- Subarachnoid hemorrhage and early hypocalcemia have the best prognosis.
- Presence of EEG abnormalities or abnormalities in CT/MRI will indicate a poor long-term prognosis.
- Myoclonic seizures, refractory seizures and those who have an abnormal neurologic examination at discharge will have poor long-term outcome.

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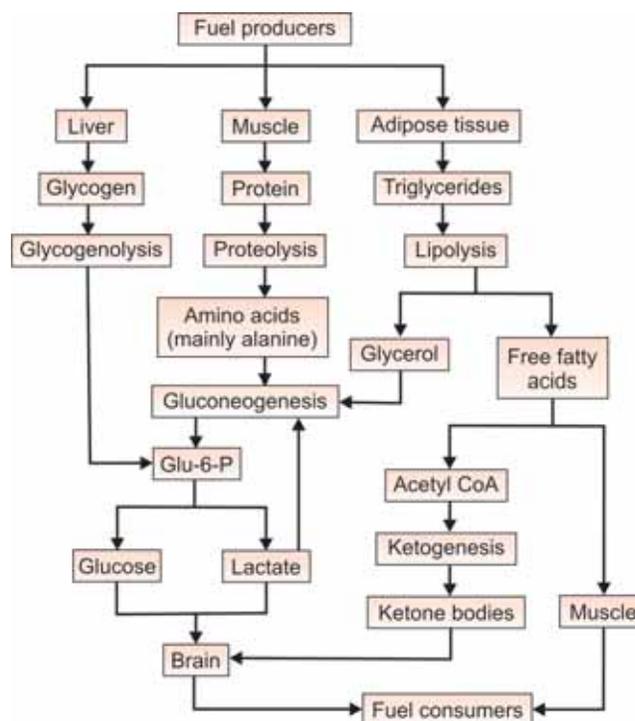
It seems strange that neonatal hypoglycemia, a condition that was recognized way back in 1937 by Hartmann and Jaudon, should continue to defy definition and abound in controversies even at the beginning of the twenty-first century.<sup>1</sup> Fortunately, within this maze of controversies many areas of consensus exist, and these areas of consensus shall be highlighted throughout this chapter.

In 1959 Cornblath described, for the first time, the adverse neurological consequences of symptomatic neonatal hypoglycemia among 2 out of the 8 babies he had followed up.<sup>2</sup> This study drew attention to the need to effectively treat hypoglycemia. It also drew the attention of researchers to the fact that the process of glucose homeostasis in newborns has several unique features.

#### GLUCOSE HOMEOSTASIS AND METABOLIC ADAPTATION AT BIRTH

The brain utilizes glucose as its primary fuel. Hence, the supply of glucose to the fetal and neonatal brain is a critically important activity. During fetal life the brain receives a constant and adequate supply of glucose. Glucose crosses the placenta by facilitated diffusion. Fetal glucose levels are approximately two-thirds of maternal levels. This happy state of affairs continues till the umbilical cord is clamped, after which the newborn blood glucose levels plummet to a nadir at 1 to 2 hours of life. The levels then increase and stabilize at mean levels of 65 to 71 mg/dL by 3 to 4 hours of life. It takes time for the newborn baby to establish effective feeding. The period between the cessation of glucose supply from the maternal circulation and the resumption of effective supply by enteral nutrition is akin to a period of fasting. The neonatal metabolic pathways quickly adapt to this period of fasting in order to preserve fuel supply to the brain. There are 5 key metabolic pathways and 5 key hormones that are involved in glucose homeostasis.<sup>3</sup> The metabolic pathways that adapt to fasting are outlined in Flow chart 55.1.

Flow chart 55.1: Metabolic adaptation to fasting



The five pathways are: (i) Hepatic glycogen stores undergo *glycogenolysis* to provide glucose for about 6 to 8 hours; (ii) Once hepatic glycogen stores get depleted, hepatic *gluconeogenesis* becomes the key source of glucose, using primarily amino acids from proteolysis, glycerol from lipolysis and recycled lactate from glycolysis. Lactate can also be directly used as a second alternate fuel by the brain after ketone bodies; (iii) Muscle *proteolysis* provides the major source of amino acids for gluconeogenesis. However, as there is no reserve of surplus protein, this source for gluconeogenesis does not last beyond 12 hours; (iv) Adipose tissue *lipolysis* releases free fatty and glycerol. The free fatty acids can be utilized by muscle as an alternative fuel, thus sparing glucose for the brain. The glycerol undergoes gluconeogenesis and this becomes the dominant source for gluconeogenesis.

**Table 55.1: Action of various hormones**

Hormone	Glycogenolysis	Gluconeogenesis	Proteolysis	Lipolysis	Ketogenesis
Insulin	–	–	–	–	–
Glucagon	+	+	0	0	0
Adrenaline	+	+	0	+	+
Cortisol	0	+	+	0	0
Growth hormone	0	0	0	+	0

+: stimulates; -: inhibits; 0: no effect

genesis after 12 hours of fasting. The free fatty acids undergo hepatic ketogenesis; (v) Hepatic *ketogenesis* converts fatty acids to ketone bodies. These ketone bodies can be utilized as an alternate fuel by the brain.

The five hormones that regulate glucose homeostasis are insulin, glucagon, adrenaline, cortisol and growth hormone. The effects of the latter four counter the effects of insulin, hence they are called counter-regulatory hormones. Insulin is an anabolic hormone, i.e. it tries to preserve the three major fuels—glycogen, protein and triglycerides in their respective storage organs. The other four are catabolic hormones and they try to break down the stored fuels to provide glucose, amino acids and fatty acids. The actions are summed up in Table 55.1.

The five metabolic pathways and the actions of the five hormones enable us to understand the various causes of neonatal hypoglycemia. They also illustrate why the levels of circulating ketone bodies and lactate can help to distinguish some of these conditions.

## CAUSES OF HYPOGLYCEMIA

The causes of neonatal hypoglycemia could be classified either on the basis of pathogenetic mechanisms or on the basis of clinical presentation. The classification based on the pathogenetic mechanisms shall be discussed first as this follows directly from the concept of the metabolic pathways and the regulatory hormones (Table 55.2). Small for gestational age (SGA) babies, preterm infants and sick infants with sepsis, hypothermia or shock can have multiple reasons for hypoglycemia. The causes can also be classified in a more clinically relevant system, according to whether the baby has transient, prolonged or persistent hypoglycemia. This system is enumerated below with a brief explanation, wherever applicable.

### A. Transient Neonatal Hypoglycemia

Transient neonatal hypoglycemia lasts up to 72 hours of life.

## Hyperinsulinemic States

### a. Maternal Causes

1. *Maternal diabetes mellitus or gestational diabetes*: The persistently raised maternal blood glucose levels reflected in an elevated fetal blood glucose level. This stimulates the fetal islets of Langerhans, which become hyperplastic and secrete increased amounts of insulin in an attempt to normalize the blood glucose level. After birth the maternal source of glucose is suddenly cut off, but it takes the hyperplastic islets several days to return back to normal insulin production. This period of mismatch between the insulin production and the glucose availability is characterized by severe hypoglycemia.
2. *Maternal tocolytic therapy* with beta-sympathomimetic agents (terbutaline, isoxsuprine, salbutamol).
3. Maternal usage of *oral hypoglycemic agents*, particularly chlorpropamide, which has a long half life. Metformin is a safe oral hypoglycemic agent in pregnancy.

### b. Neonatal Causes

1. *Erythroblastosis fetalis*: Causes hyperplasia of the islets of Langerhans.
2. *Malpositioned umbilical artery catheters*: If catheters that are used to infuse glucose in high concentration are misplaced in the origin of the celiac or superior mesenteric arteries (T11-12), they may stimulate insulin production.
3. Abrupt cessation of a high glucose infusion.
4. After exchange transfusion with blood containing a high glucose concentration.

## Decreased Stores

1. *Prematurity*: The incidence of hypoglycemia among premature small for gestational age babies is 67 percent and among premature large for gestational age babies is 38 percent.

**Table 55.2: Classification of hypoglycemia based on pathogenesis**

System affected	Condition	Mechanism	Lactate	Ketones
Glycogenolysis	SGA	Decreased stores	+/-	+
	Preterm	Decreased stores	+/-	+
	Most GSD's	Enzyme defect	-	+
Gluconeogenesis	Preterm	Immature enzyme	+	+
	Galactosemia	Inhibition by galactose	++	+
	Fructose intolerance	Inhibition by fructose	++	+
	GSD type 1	G-6 Phosphatase defect	++	+
	Glycolytic pathway defects	Enzyme defects	++	+
Proteolysis	SGA	Decreased stores	+/-	+
	Preterm	Decreased stores	+/-	+
	Amino acidopathies	Enzyme defects	+	+
Lipolysis	SGA	Decreased stores	+	+/-
	Preterm	Decreased stores, immature enzymes	+	+/-
	Beta-blockers	Inhibits adrenaline action	+	-
Ketogenesis	Non-ketotic hypoglycemia	Immature enzyme	+	-
	Fatty acid oxidation defects	Enzyme defects	+	-
Hormonal regulation	Infant of diabetic mother	Hyperinsulinism	-	-
	PHHI	Hyperinsulinism	-	-
	Beckwith-Wiedemann syndrome	Hyperinsulinism	-	-
	Islet cell tumors	Hyperinsulinism	-	-
	Malpositioned umbilical artery catheters	Hyperinsulinism	-	-
	Post-exchange transfusion	Hyperinsulinism	-	-
	Adrenal insufficiency	Cortisol deficiency	+	+
	Panhypopituitarism	GH, cortisol deficiency	+	+
Glucose consumption	Hypothermia	Increased consumption	++	+
	Sepsis	Increased consumption	++	+
	Polycythemia	Increased consumption	++	+
	Shock	Increased consumption	++	+

GH—Growth hormone; GSD—Glycogen storage disease; PHHI—Persistent hyperinsulinemic hypoglycemia of infancy; SGA—Small for gestational age.

Clinically, the causes are classified as transient, prolonged or persistent.

- Intrauterine growth retardation:** The incidence of hypoglycemia among term small for gestational age babies is 18 percent.
- Inadequate calorie intake:** This may occur in the setting of a late preterm baby born to a primigravida mother with poor milk flow or a mother who has undergone a cesarean section and who finds it difficult to feed.
- Shock:** The reasons for hypoglycemia are similar to that in sepsis.
- Asphyxia:** There is increased consumption of glucose to compensate for the inefficient ATP production during anaerobic glycolysis, resulting in hypoglycemia.
- Hypothermia:** Glucose is rapidly consumed to generate heat.
- Polycythemia:** Glucose is consumed rapidly by the increased mass of red blood cells.

### Increased Consumption and/or Decreased Production

- Sepsis:** The increased metabolic demands result in greater glucose consumption without commensurate glucose production.

### B. Prolonged Neonatal Hypoglycemia

Prolonged neonatal hypoglycemia is usually secondary to dysregulated insulin production lasting for 72 hours

to a few weeks. It has been recognized in recent years that SGA neonates, preterm neonates and asphyxiated neonates may have hyperinsulinemic hypoglycemia that resolves in a few weeks.

### C. Persistent Neonatal Hypoglycemia

#### Hyperinsulinemic States

1. *Congenital hyperinsulinism*: This entity has been variously called persistent hyperinsulinemic hypoglycemia of infancy (PHHI) or Nesidio-blastosis.<sup>4</sup> The revised nomenclature reflects the fact that non-hyperinsulinemic, euglycemic babies have also been found to have the so-called “nesidioblasts” which were earlier thought to be underdifferentiated beta cells with characteristic morphology. Congenital hyperinsulinism has now been recognized to be a disease of K<sup>+</sup> channels leading to abnormal beta cell function, with many cases having an autosomal recessive inheritance.
2. Insulin producing tumors.
3. *Beckwith-Wiedemann syndrome*: This entity is characterized by macrosomia, mild microcephaly, omphalocele, macroglossia, visceromegaly, a groove on the pinna of the ear, iris colobomas and hemangiomas.

#### Impaired Conversion of Glucose

1. *Fatty acid oxidation*
  - a. Carnitine palmitoyl transferase deficiency
  - b. Acyl CoA dehydrogenase deficiency
  - c. HMG CoA lyase deficiency
  - d. Beta-ketothiolase deficiency
2. *Amino acid metabolism defects*
  - a. Maple syrup urine disease
  - b. Propionic acidemia
  - c. Methylmalonic acidemia
  - d. Tyrosinemia
  - e. Glutaric acidemia type II
  - f. Ethylmalonic adipic acidemia
  - g. Glutaric acidemia

#### Decreased Production

1. *Defects in carbohydrate metabolism*
  - a. Glycogen storage disease
  - b. Galactosemia
  - c. Fructose intolerance
2. *Endocrine deficiency*
  - a. Adrenal insufficiency
  - b. Hypothalamic deficiency
  - c. Congenital hypopituitarism
  - d. Glucagon deficiency
  - e. Epinephrine deficiency
3. *Ketotic hypoglycemia*

### HYPOGLYCEMIA AND THE BRAIN

The newborn brain adapts to hypoglycemia by increasing cerebral blood flow and by using alternate metabolic substrates, particularly ketone bodies and lactate. The healthy term newborn has an enormous capacity to increase ketone body production in the face of hypoglycemia and is able to reach blood levels of ketone bodies in hours, which adults would take days to achieve.<sup>5</sup> Breastfed infants have lower blood glucose but higher concentrations of ketone bodies than formula-fed infants.<sup>6</sup> Ketone body concentrations appear to be directly proportionate to the degree of postnatal weight loss.

Experimentally induced severe hypoglycemia in animals has been shown to damage the dentate gyrus, the cerebral cortex, hippocampus and caudate nucleus, but it spares the brainstem and posterior fossa structures.<sup>7</sup> More recent MRI data from term neonates with symptomatic hypoglycemia shows that white matter abnormalities occurred in 94% cases, being severe in 43% and a predominantly posterior pattern in only 29% cases.<sup>8</sup> Cortical abnormalities occur in 51%, white matter hemorrhage in 30% and basal ganglia lesions in 30%. Neuronal injury attributable to hypoglycemia is not simply the result of lack of glucose but an active process because of excitatory neurotransmitters.<sup>9</sup> For a long time researchers have been trying to pin-point the level of blood glucose below which neural injury starts occurring in the human neonate and determining whether this injury is reversible or leads to long-term sequel. Since the brain is the major consumer of glucose, the majority of symptoms of hypoglycemia are related to neuronal dysfunction. These patients are said to have symptomatic hypoglycemia.

#### Symptomatic and Asymptomatic Hypoglycemia

Till 1960 the only responses to a low blood glucose level that were recognized in neonates were clinical manifestations. For a clinical manifestations to be attributable to hypoglycemia, Whipple's triad has to be satisfied namely, (i) The presence of characteristic clinical signs, (ii) Coincident with low blood glucose concentrations, and (iii) The reversal of the clinical signs within minutes to hour once normoglycemia is re-established. The clinical signs that are associated with hypoglycemia are listed in Table 55.3.

The definition of hypoglycemia on the basis of clinical signs excludes a large group of infants who

**Table 55.3: Clinical signs associated with hypoglycemia**

- Changes in levels of consciousness
  - Irritability
  - Lethargy
  - Stupor
- Apnea
- Cyanotic spells
- Feeding poorly
- Hypothermia
- Hypotonia
- Tremors
- Seizures

have no clinical manifestations despite very low blood glucose levels. The significance of this “asymptomatic hypoglycemia” group has been a matter of debate for a long-time. Two studies have shown that asymptomatic hypoglycemia is associated with greater neurodevelopmental sequelae than normal babies, although less than symptomatic hypoglycemia.<sup>10,11</sup> However, several other studies have failed to show any increased risk of sequelae.<sup>12,13</sup> The increased risk of adverse neurodevelopmental sequelae following symptomatic hypoglycemia is fairly well established, but in these studies the evidence for a direct causal link between glucose levels and outcome is weak.<sup>14</sup> The ability of the neonate to adapt to hypoglycemia and use alternate substrates has been discussed in the previous section. The ability to successfully adapt may explain the lack of symptoms in some babies and also explain why asymptomatic hypoglycemia does not show a consistent relationship with neurological outcome.

### DEFINITION OF HYPOGLYCEMIA

The following section highlights some of the problems related to the definition of hypoglycemia. Over the years the issue of definition has been addressed in four different ways: (i) Statistical definition, (ii) Metabolics definition, (iii) Neurophysiological definition, and (iv) Neurodevelopmental definition.

#### *Statistical Definition*

This is the most inappropriate way to define hypoglycemia because it completely ignores the clinical condition of the baby and it assumes that any value below, say 2 Standard Deviations from the mean or below the 5th percentile is abnormal. These definition had arrived at the value of 30 mg/dL in term babies and 20 mg/dL in preterm babies in the first 48 hours,

and 40 mg/dL after 48 hours of life.<sup>15</sup> Although these definitions have no role in modern day neonatology they dominated clinical decision making for many decades.

#### *Metabolic Definition*

If glucose is regarded as the primary metabolic fuel, does the glucose concentration below which the counterregulatory response becomes activated indicate a “safe” level. Unfortunately, few studies have looked at the levels of the counter-regulatory hormones and the alternate fuels simultaneously with blood glucose levels. Thus, this definition cannot boast of a definite numerical blood glucose level as yet. However, one fact has been unequivocally established—the ability of premature newborn to mount a counter-regulatory response or generate alternate fuels is less than term babies.<sup>15</sup> Thus, the “safe” value, if any, ought to be higher in preterms than in terms.

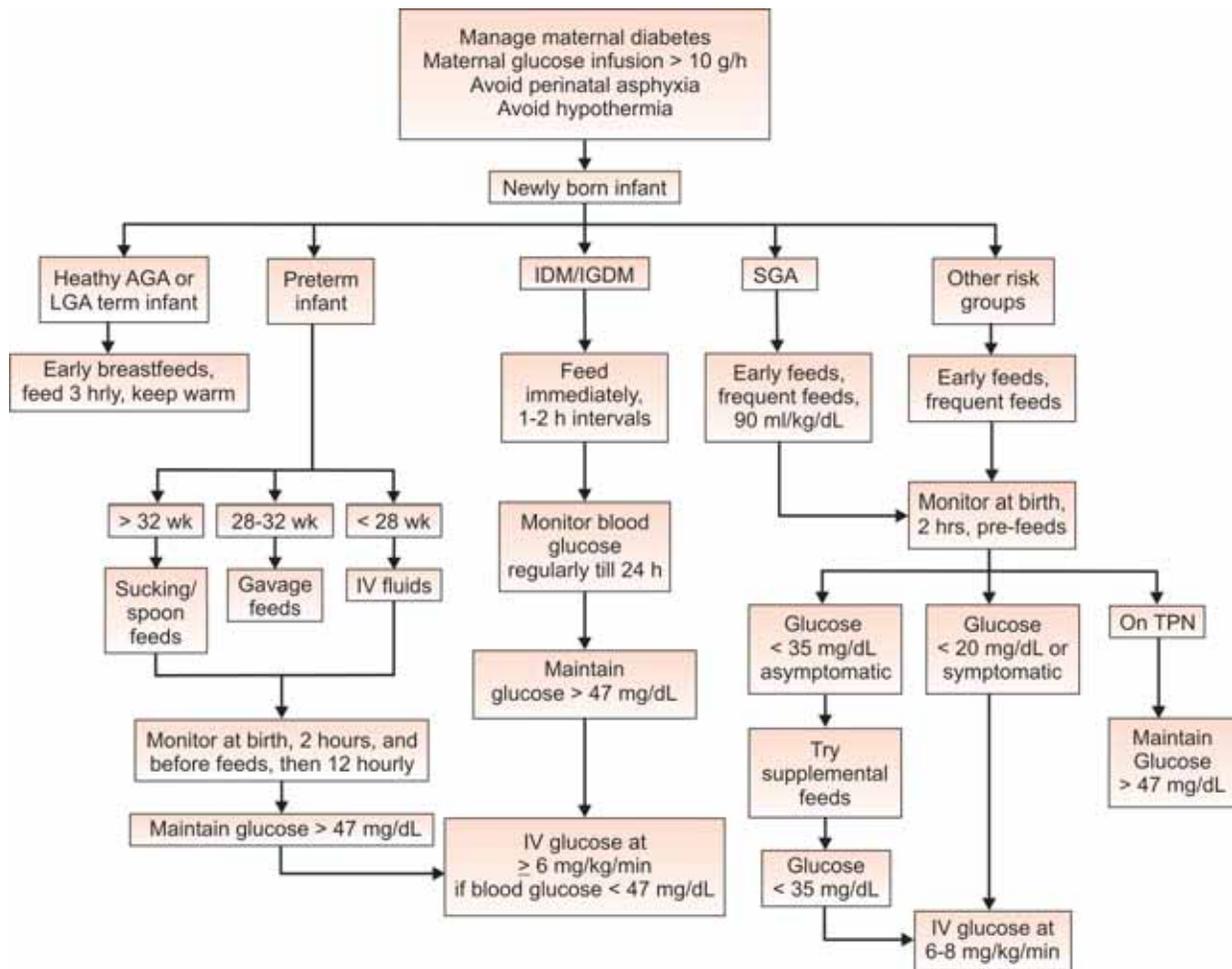
#### *Neurophysiological Definition*

If the ultimate goal of identifying and treating hypoglycemia is the maintenance of normal cerebral metabolism, a threshold blood glucose concentration associated with disturbed neurophysiology should give the definition. A study that evaluated infants with spontaneous and insulin-induced hypoglycemia concluded that brainstem auditory evoked potentials were deranged below a value of 47 mg/dL.<sup>16</sup> However, others have not been able to replicate these data.<sup>17</sup>

#### *Neurodevelopmental Definition*

In symptomatic hypoglycemia any value of less than 45 mg/dL is significant. Breastfed term babies with asymptomatic hypoglycemia are relatively protected because of their ability to generate alternate fuels. The real problem arises in the case of preterm babies with asymptomatic hypoglycemia. Since their metabolic pathways are immature, it is not clear how well they adapt to hypoglycemia. A systematic review on neurodevelopment after neonatal hypoglycemia concluded that of the 18 eligible cohort studies, 16 were of poor methodological quality and only 2 were of high quality.<sup>18-20</sup> In a study on the effect of transient hypoglycemia in healthy term LGA infants on neurodevelopmental outcomes at 4 years, no significant differences were found between normoglycemics and hypoglycemics in development, behavior and IQ.<sup>19</sup> A large retrospective study on preterm infants concluded that motor and mental development at 18 months follow-up was poor in those who had

Flow chart 55.2: Algorithm of prevention and management of hypoglycemia



blood glucose levels less than 47 mg/dL on at least 5 days during the neonatal period.<sup>20</sup> Interestingly, a longer follow-up showed only a decrease in arithmetic and motor test scores at 7½ to 8 years of age with a reversal of some of the findings observed at 18 months.<sup>21</sup>

These definitional dilemmas and debates are of little consolation to the clinician who has the unenviable task deciding which baby needs to be screened, which treated orally and which treated intravenously. Fortunately, a large measure of agreement does exist among experts working in the field of neonatal hypoglycemia regarding these issues.<sup>22,23</sup> The algorithm of an approach to screening, prevention and treatment of neonatal hypoglycemia is shown in Flow chart 55.2.

### Screening

Screening refers to the scheduled measurement of blood glucose in asymptomatic neonates.

*Healthy term neonates* with no risk factors should not be screened. This is because they can utilize substrates other than glucose; no safe cut-off has ever been defined in this group; and reagent strips tend to overdiagnose hypoglycemia in this group leading to overtreatment.<sup>24</sup> There is no evidence that transient asymptomatic hypoglycemia (value less than 36 mg/dL) is detrimental in this group.

The group of at-risk infants for whom monitoring of blood glucose is recommended is listed in Table 55.4.

The bulk of these cases comprise of one of the following three situations: Preterm infants, small for gestational age infants of diabetic mothers. Large for gestational age infants who are not hyperinsulinemic are not in this high risk group.

In *preterm* infants it is desirable to maintain a blood glucose level above 47 mg/dL. In achieving this aim, prevention by early enteral feeding (or provision of intravenous glucose in those unable to feed) is more

**Table 55.4: At risk babies for whom blood sugar monitoring is recommended**

- Prematurity
- Small for gestational age
- Infant of diabetic mother
- Hypothermia
- Perinatal asphyxia
- Sepsis
- Polycythemia
- Rh isoimmunization
- Administration of glucose to the mother intrapartum
- Administration of beta-blockers or oral hypoglycemia agents to the mother
- Congenital cardiac malformations
- Hyperinsulinism
- Suspected endocrine disorders
- Suspected inborn errors of metabolism

important than frequent blood glucose testing. Initially monitoring should be as soon as possible after birth, repeated at 2 hours and before feeds. Subsequently, daily or 12 hourly laboratory measurements are preferable to frequent but inaccurate reagent strip measurements.

*Small for gestational age infants* (weight less than 10th percentile) are very heterogeneous and not all are at risk for hypoglycemia. Those with a birth weight less than the 3rd percentile, those who have a disproportionate growth retardation and those who had abnormal umbilical artery Doppler flow velocity profiles in fetal life are probably most vulnerable.<sup>25</sup> Excessively frequent blood sampling with reagent strips is not necessary. Reliable laboratory measurements of cord blood glucose and at 4-6 hours (before the second feed) are preferable.

*Infants of diabetic mothers* often display transient hyperinsulinism, and hence they must be screened because they are at risk of hypoketonemic hypoglycemia. This must be done even if they are not large for gestational age. The blood glucose levels must be monitored for at least the first 24 hours of life and the levels should be maintained above 47 mg/dL. Monitoring can be discontinued after 24 hours if glucose levels are maintained without supplementary feeds or intravenous therapy.

*Large for gestational age infants* (weight more than 90th percentile) who are not infants of diabetic mothers need not be screened. The vast majority of them are simply large, normal healthy babies with (more than) adequate stores and intact metabolic pathways. As in the case of healthy term infants, there is no evidence that transient

asymptomatic hypoglycemia (value less than 36 mg/dL) occurs beyond 8 hours of life, or that it is detrimental in this group.<sup>26</sup> PPHI, insulinomas or Beckwith-Wiedemann syndrome are all very rare entities, they are phenotypically obvious, and it is unjustifiable to subject every large for gestational age infant to repeated sampling in the fear that it may turn out to be one of these three conditions.

For the rest of the conditions listed in Table 55.4, glucose monitoring should begin as soon as possible after birth, and repeated within two hours after birth and before feeding, or at any time there are abnormal signs. If glucose level is less than 36 mg/dL, a close surveillance should be maintained and intervention is recommended if (i) the level remains persistently below 36 mg/dL, or (ii) the level does not increase after a feed, or (iii) abnormal clinical signs develop.

### PREVENTION OF HYPOGLYCEMIA

Prevention consists of avoiding certain peripartur risk factors, instituting feeding or instituting intravenous fluids in those who cannot be fed.

Maternal glucose infusion during labor should be restricted. When the infusion rate is more than 10 g/h in the last 2 hours of labor it causes neonatal hyperinsulinemia, whereas an infusion rate greater than 25 g/h causes a significant increase in neonatal hypoglycemia.<sup>27</sup> Hypothermia should be prevented at birth, the baby must be effectively resuscitated at birth and skin-to-skin contact between the mother and the baby must be encouraged.

The most effective way of preventing hypoglycemia is feeding with milk as soon as possible after delivery. Here too, breast milk scores over formula milk. The inability to promote ketogenesis is yet another blot on the unsavoury reputation of formula milk. There is no justification to give 10 percent dextrose or any other form of pre-lactal feeds.

*Healthy preterm infants* between 32 to 36 weeks gestation should be allowed to suckle on the breast as soon as possible after birth and at 2 to 3 hourly intervals. If the baby is sleepy or unwilling to feed, he must be gavage fed. If the baby is awake but requirements are not met by direct breastfeeding the alternative is to offer cup and spoon feeds.<sup>28</sup> Expressed human milk is the milk of choice, and in the event of its non-availability formula milk is preferable to animal milk, which in turn is preferable to dextrose water. The volume of the gavage feed should be 60 ml/kg/day on day 1, but if the baby is alert and demanding there is no reason to believe that one cannot start with

volumes up to 100 ml/kg/day by spoon on day 1, provided it is expressed human milk.

*Healthy preterm babies* between 28 to 32 weeks of gestation can be started on 60 ml/kg/day of expressed human milk by oro-gastric gavage feeding from day 1. Infants less than 28 weeks gestation have immature bowel motility.<sup>29</sup> They can be started on minimal enteral nutrition with expressed human milk and an intravenous dextrose infusion.

*Small for gestational age infants* must be started on enteral feeds as soon as possible after birth. It has been found that the normal rate of endogenous glucose production in appropriate for gestational age term babies and in preterm babies is identical (about  $3.5 \pm 0.4$  mg/kg/min) whereas in small for gestational age infants it is  $4.3 \pm 1$  mg/kg/min.<sup>30</sup> To match this glucose production rate, a small for gestational age baby requires 90 ml/kg/day of milk feeds on day 1.

*Infants of diabetic mothers* should be breast-fed immediately after birth and frequently (at 1 to 2 hour intervals) thereafter: If a pre-feed blood glucose estimation at 3 hours is normal, it is unlikely that this baby will need supplementary feeds.

There are not enough well designed studies to endorse the practice of adding powdered sugar or glucose to milk to prevent hypoglycemia. However, there is some evidence that supplementing the milk feed with fat (in the form of medium chain triglycerides) can prevent hypoglycemia because fatty acids are the precursors of ketones and they can also be directly utilized by muscle.<sup>31</sup>

*Intravenous fluids* have to be started in the presence of cardiorespiratory distress, gastrointestinal malformations, ileus and gestational age less than 28 weeks. Glucose infusion should be started at the rate of 3 to 5 mg/kg/min in term babies, at 4 to 6 mg/kg/min in preterm babies and at 6 to 8 mg/kg/min in small for gestational age infants. There is no role of a “minibolus” of glucose for preventing hypoglycemia.

## TREATMENT OF HYPOGLYCEMIA

Concurrent with the treatment of hypoglycemia should be a prompt consideration of the cause. Term breastfed babies never develop symptomatic hypoglycemia as a result of simple underfeeding. An underlying illness must be looked for, such as sepsis.

Moderate, *asymptomatic hypoglycemia* (20 to 35 mg/dL) should be first treated by giving frequent and measured supplementary feeds. This should preferably be in the form of expressed human milk by cup and spoon. Supplementing with medium chain triglycerides has been shown to increase blood glucose and ketones.

There is not enough evidence to support the use of concentrated dextrose preparations or powdered sugar.

*Intravenous therapy* should be instituted if the “moderate; asymptomatic hypoglycemia” fails to improve on milk feeds, or if the blood glucose is less than 20 mg/dL or if it is symptomatic. The role of a routine “minibolus” of 2 ml/kg 10 percent dextrose prior to starting the dextrose infusion is still controversial. There is no role of a full bolus (2 ml/kg of 25% dextrose). Even with the “minibolus” there are fears that since the rate of administration exceeds the rate of cellular uptake it may cause a rebound hypoglycemia and the rapid administration may be detrimental to the brain of a preterm baby.<sup>32,33</sup> However, there is agreement that of the three indications for intravenous therapy, it is the symptomatic hypoglycemia group that merit the “minibolus” the most. In any case, the minibolus must be followed by a glucose infusion providing 6 to 8 mg/kg/min. Small for gestational age babies should be started on the higher end of this range. There is complete unanimity that there is no place for treatment with intermittent “miniboluses” alone.

*The objective of intravenous therapy* in the vast majority of cases is to maintain a blood glucose level higher than 45 mg/dL. It must be noted that the glucose level which is the objective of therapy is higher than the indications for starting therapy (i.e. single value less than 20 mg/dL or persistently less than 35 mg/dL). For a symptomatic infant with documented profound, recurrent or persistent hyperinsulinemic hypoglycemia the objective of therapy is to maintain blood glucose about 60 mg/dL.<sup>34</sup> For a preterm infant the objective is a level above 47 mg/dL at all times in the first 2 months of life. Babies on total parenteral nutrition should be maintained at a level above 47 mg/dL.

While on intravenous fluids, blood glucose should initially be monitored every hour (or earlier if symptoms persist) and the glucose infusion should be increased in increments of 2 mg/kg/min till a maximum of 10 to 12 mg/kg/min. A requirement of greater than 10 mg/kg/min or dependence on greater than 4 mg/kg/min for longer than 5 to 7 days should prompt investigations for the relatively unusual causes of hypoglycemia. A central venous line is required if glucose infusion rates cross 10.5 mg/kg/min. It is a good idea to continue breast milk feeds, especially if the anticipated fluid therapy will be brief and the combined volumes does not become unphysiological. This is because breast milk has beneficial effects on hormonal regulation and release of ketones and free fatty acids. Once glucose levels have stabilized, the rate of infusion should be gradually reduced at the rate of

1 ml/kg/h along with a concomitant increase in feed volume.

The place of glucagon in the treatment of hypoglycemia is controversial. A dose of 200 microgram/kg intravenous bolus can increase glycogenolysis, gluconeogenesis and ketogenesis for several hours. Surprisingly, glucagon seems to act even in situations where glycogen stores are expected to be depleted, such as preterms and small for gestational age infants.<sup>35</sup> What is not clear is the stage in the algorithm of therapy of hypoglycemia at which glucagon should be used. The side effects of glucagon include vomiting, diarrhea and hypokalemia.

Similarly, the exact indication of hydrocortisone in the treatment of hypoglycemia is ambiguous. Usually 5 mg/kg of hydrocortisone is administered 12 hourly if glucose infusion rates exceed 12 mg/kg/min. After normoglycemia is attained for 48 hours, first the intravenous fluids should be tapered and the baby should be kept on hydrocortisone for another 48 hours off intravenous fluids.<sup>36</sup>

Diazoxide, octreotide, nifedipine and somatostatin are required in conditions of persistent hyperinsulinism.

#### METHODS OF MEASURING BLOOD OR PLASMA GLUCOSE

The common laboratory methods for measuring glucose are the *glucose oxidase* method and the *hexokinase* method. In the former method hydrogen peroxide concentrations are measured following the oxidation of glucose, whereas in the latter NADPH levels are following the reduction of glucose-6-phosphate.

Arterial blood glucose value are generally higher than venous blood glucose, particularly under anaerobic conditions. Capillary blood glucose is unreliable if peripheral circulation is poor or if the heel has been squeezed. Contamination with alcohol used for preparing the skin can raise glucose values.<sup>37</sup> Hematocrit affects the measured glucose levels. This is because red blood cells have lower water content per unit volume compared to plasma, although they have the same glucose concentration per ml of water content. As a result plasma glucose concentration on an average is 18 percent higher than whole blood glucose, and the difference keeps widening with rising hematocrit. Hemolysis and hyperbilirubinemia also interfere with glucose estimation resulting in falsely low values.

*Reagent paper strips* are widely used for bedside glucose estimation. It must be remembered that these strips were developed for diabetics and were originally not meant to be used for the blood glucose ranges

encountered in neonatal hypoglycemia. Attempts have been made to improve the level of precision by shifting from the older colorimetric method to a reflectance metering system (e.g. Reflolux). Even when care is taken to avoid contamination by alcohol, to cover the test pad of the strip with a large drop of blood and to adhere to the stipulated time before wiping, there remains a margin of error. Reagent strips often overdiagnose hypoglycemia and that too in an unpredictable and erratic manner. Of the various reagent strips available in the world market, the most reliable appear to be Glucometer Elite XL and the Ames Glucometer Elite.<sup>38,39</sup> There are very few head-to-head comparisons between reagent strips. Hence it has been recommended that, although emergent treatment can be started on the basis of a reagent strip report, the final diagnosis must be based on a laboratory method.

#### CONCLUSION

There are five metabolic pathways and five hormones that maintain glucose homeostasis at all ages. They are particularly important during the transition period from the intrauterine to the extrauterine environment. Neonatal hypoglycemia has numerous causes, that can be divided into causes of transient or persistent hypoglycemia. The brain has various ways of adapting to hypoglycemia, the use of alternate fuels being an important mechanism. Hypoglycemia causes a characteristic brain pathology. Several symptoms have been attributed to hypoglycemia. Symptomatic hypoglycemia has been associated with an increased risk of adverse neurological outcome. The relationship of asymptomatic hypoglycemia with neurological outcome is still controversial, particularly if it occurs in otherwise healthy term infants. The definition of hypoglycemia is still uncertain, but there is a consensus on the levels at which action must be taken.

Transient asymptomatic hypoglycemia in healthy breastfed AGA or LGA term babies has not been linked to neurodevelopmental delay. In preterm babies the level must be kept above 47 mg/dL for the first 2 months. All symptomatic hypoglycemia must be treated. Babies with severe hyperinsulinemic hypoglycemia must be maintained at above 60 mg/dL, and those on TPN must be kept at above 45 mg/dL. Early and frequent milk feeds are the best way to prevent hypoglycemia. Breast milk is superior to formula milk. Moderate asymptomatic hypoglycemia (20 to 35 mg/dL) in high-risk groups can be managed first with aggressive supervised feeding. Intravenous fluids are recommended for those who do not respond to feeds, whose glucose levels is less than 20 mg/dL, who are

symptomatic and who are unable to tolerate feeds. Glucose infusions start at 6 to 8 mg/kg/min and may be preceded by a minibolus, particularly in symptomatic hypoglycemia. Glucagon and hydrocortisone are useful in the treatment of hypoglycemia. SGA babies should be started on higher glucose infusion rates.

Laboratory enzymatic methods are the gold standard for the measurement of hypoglycemia. Reagent strips may be used for starting treatment, but are too unreliable to be used for diagnosing a patient as having neonatal hypoglycemia.

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Jaundice in newborn is quite common affecting nearly 70% of term and 80% of preterm neonates during the first week of life. Adults appear jaundiced when serum bilirubin is  $> 2$  mg/dL and newborns appear jaundiced when it is  $> 5$  mg/dL. Jaundice in newborn might signal a serious potentially treatable illness and cause neurological damage, if bilirubin level is significantly elevated. National Neonatal Perinatal Database (NNPD-2003) reported an incidence of severe hyperbilirubinemia (requiring treatment) in 5.7% of inborn and 32.9% of outborns admitted to the network hospitals.<sup>1</sup> Nearly, 65 to 75% of very low birth weight infants develop severe jaundice necessitating treatment.<sup>2</sup>

### BILIRUBIN METABOLISM AND ETIOLOGY OF JAUNDICE

Bilirubin is produced in the reticuloendothelial system, transported in the blood by albumin, conjugated in the liver to mono or diglucuronide, enters the gastrointestinal tract as conjugate bilirubin and then excreted in the stool. In the absence of gut bacteria, beta-glucuronidase (intestinal enzyme) converts conjugate bilirubin back to unconjugate form and is reabsorbed into the blood (enterohepatic circulation).

**Bilirubin production:** Bilirubin is an end product of heme catabolism. Degradation of heme is the primary source of bilirubin. Lysis of red blood cells releases heme which in the presence of heme oxygenase is converted to biliverdin. This rate limiting step results in release of iron and carbon monoxide (CO) in equimolar amounts. Biliverdin is converted to bilirubin in the presence of biliverdin reductase. The degradation of 1 gram of heme forms 34 mg of bilirubin.

**Bilirubin transport:** Unconjugated bilirubin released into circulation is rapidly bound to albumin as it is insoluble in water at a pH of 7.4. Each gram of albumin binds to 8 mg of unconjugated bilirubin. Unconjugated bilirubin not bound to albumin is the free bilirubin. It is the free (unbound) bilirubin that crosses the blood-

brain barrier and causes neurological dysfunction or damage.

**Conjugation of bilirubin:** Excretion of bilirubin into the bile requires it to be converted to a water soluble compound. Bilirubin dissociates from albumin before entering the liver. Bilirubin enters the liver cell by a process of carrier mediated diffusion with  $\beta$ -ligandin being the major intracellular cytoplasmic protein. Conjugation of bilirubin with two molecules of glucuronic acid in the presence of UDPG-Glucuronyl transferase facilitates this process.

**Enterohepatic circulation:** Under the alkaline conditions of the duodenum and under the enzymatic activity of  $\beta$ -glucuronidase, conjugate bilirubin is hydrolyzed to unconjugate bilirubin. This unconjugate form is readily absorbed across the intestinal mucosa via the portal circulation. Intestinal bacteria prevent this enterohepatic circulation by converting conjugate bilirubin to urobilinoids, which are not substrates for  $\beta$ -glucuronidase.

The **increased risk of hyperbilirubinemia** in neonates is attributed to the following factors:

#### A. Increased bilirubin production caused by

- Increased red blood cell (RBC) volume per kilogram body weight.
- Decreased RBC survival (90 day versus 120 day) in newborn infants compared to adults.
- Increased ineffective erythropoiesis and increased turnover of non-hemoglobin heme proteins.

#### B. Defective uptake of bilirubin from plasma caused by

- Decreased ligandin.
- Binding of ligandin by other anions.

**C. Defective conjugation** due to decreased uridine diphosphoglucuronide transferase (UDPGT) activity. At birth the activity of UDPG-glucuronyl transferase is 5% of adult activity but increases significantly after 24 hours to handle the bilirubin load. In North Indian population, polymorphism (TA) 7 in the promoter sequence of UDP-Glucuronyl transferase is associated with increased risk of hyperbilirubinemia.<sup>3</sup>

**Table 56.1: Etiology of neonatal hyperbilirubinemia**

Increased production	Isoimmunization (Rh, ABO, minor blood group incompatibility), hemolytic anemia (G6PD deficiency, spherocytosis, elliptocytosis, pyruvate kinase deficiency, alpha thalassemia), acquired hemolysis (vitamin K, oxytocin, bipuvacaine, infection), Polycythemia, blood collection (cephalhematoma, subgaleal hemorrhage, intracranial hemorrhage)
Decreased conjugation	Prematurity, Infant of diabetic mother, hypothyroidism, hypopituitarism, Gilbert's syndrome, Crigler Najjar syndrome, mutations in UDPG gene (211G A, G71R).
Increased enterohepatic circulation	Breast feeding jaundice, poor feeding, meconium plug and ileus, Hirschsprungs disease

**D. Decreased hepatic excretion** of bilirubin and

**E. Increased enterohepatic circulation** caused by

- High levels of intestinal beta-glucuronidase.
- Preponderance of bilirubin monoglucuronide rather than diglucuronide.
- Decreased intestinal bacteria.
- Decreased gut motility with poor evacuation of bilirubin-laden meconium.

Increased bilirubin production due to RBC breakdown, deficiency of  $\beta$  ligandin, decreased or absent activity of UDPG-Glucuronyl transferase, obstruction in the pathway of bilirubin excretion after its conjugation and finally enhanced enterohepatic circulation all result in hyperbilirubinemia of the neonate (Table 56.1).

## CLINICAL EVALUATION OF A JAUNDICED NEONATE

Clinical evaluation would include an initial assessment of jaundice, differentiation from cholestasis and then the steps to answer the following questions

- Is the jaundice physiological or pathological?
- Is it possible to predict that jaundice will rise to a level needing treatment?
- If pathological jaundice is suspected what are the possible causes?
- Does the infant have clinical signs of bilirubin encephalopathy?
- Which infants require further investigations and what investigations are needed?
- When and how to treat jaundiced neonates?

Clinical judgment is widely used and utilizes the principle that jaundice first appears on the face and then progresses cephalocaudal from trunk to limbs as the intensity increases. Visual assessment is performed in a well lit room (day light or white fluorescent light) where there is no reflection of yellow or red colors from the surroundings. Skin is blanched by digital pressure, revealing underlying color of skin and subcutaneous tissue. Level of serum bilirubin is based on extent of

yellow discoloration and dermal zone of icterus. Once bilirubin levels are more than 15 mg/dL there is staining of palms and soles. Transcutaneous bilirubin estimation with bilichek offers an objective method of assessing the degree of hyperbilirubinemia. It may be used as screening tool in the initial assessment of jaundice and for expected bilirubin values < 14 mg/dL.<sup>4</sup> Total serum bilirubin may be estimated with spectrophotometer, diazo method and HPLC. Total serum bilirubin (TSB) by spectrophotometer is rapid, accurate and requires lesser blood sample. Jaundice associated with acholic stools, diaper staining, conjugated bilirubin > 2 mg/dL suggest cholestasis and its evaluation is discussed later in this chapter.

## Physiological vs. Pathological Jaundice

In term infants physiological jaundice usually has its onset by 36 to 48 hours of life, with the bilirubin peaking to 5 to 6 mg/dL by 72-96 hours of life in whites and 10 to 14 mg/dL by 72-120 hour in Asians. Between day 5 to day 10, the bilirubin begins to decline to reach normal adult levels (< 2 mg/dL). In preterms the onset is similar to term infants, but the peak is 10-12 mg/dL by day 5 of life, declines to adult value by day 14 of life. When the jaundice of newborn does not conform to the time of physiological jaundice or if the jaundice is severe enough to warrant therapy it is designated as pathological. *Occurrence of jaundice within first 24 hours of life, distinctly stained palms and soles, staining of diapers, acholic stools, persistence of jaundice beyond 10 days in term infants and beyond 2 weeks in preterm is definitely pathological and warrants specific workup and adequate therapy.* It must be remembered that exaggerated physiological jaundice may attain unconjugated bilirubin levels capable of transient and occasionally permanent neurological damage. It is dangerous fallacy to assume that the healthy, non-hemolyzing term infant is immune to bilirubin encephalopathy. In our own experience kernicterus was present in 9.8 % of babies with TSB 20-25 mg/dL.<sup>5</sup>

**Table 56.2: Risk factors for development of severe jaundice**

Major risk factors	Pre-discharge TSB in high risk zone, jaundice within 24 hours of life, DCT positive, G6PD deficiency, gestational age 35-36 wks, previous sibling received phototherapy, cephalhematoma or significant bruising, exclusive breastfeeding, weight loss >10%, East Asian race
Minor risk factors	Predischarge TSB in intermediate zone, gestation 37 to 38 weeks, jaundice before discharge, previous sibling with jaundice, infant of diabetic mother, maternal age > 25 years, male gender
Decreased risk	TSB in low risk zone, gestation > 40 weeks, black race, discharge after 72 hours.

## PREDICTION OF SEVERE JAUNDICE

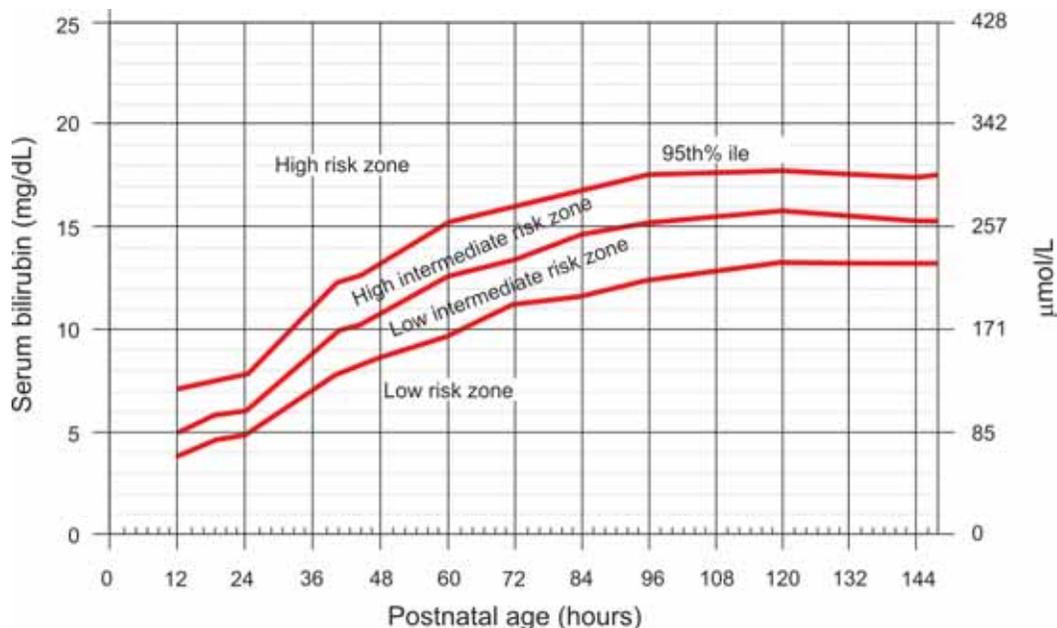
Risk factor based approach, pre-discharge bilirubin and cord bilirubin levels are often used to predict severe jaundice in neonates. Risk factor approach consists of assessing the perinatal factors associated with clinically significant hyperbilirubinemia. As the risk factors are common and the risk of severe jaundice is small, a combination of risk factors predict severe jaundice rather than individual ones<sup>6</sup> (Table 56.2).

In healthy term and late preterm infants (gestation of 34-36 weeks), hour specific serum bilirubin nomogram predicts the development of subsequent severe jaundice in the first week of life (Fig. 56.1). If the TSB value at any age is falling in the high risk zone (>95th centile) or in the intermediate risk zone (40th to 95th centile) the chance of subsequent hyper-bilirubinemia is 39.5% and 6.4% respectively. If the hour specific TSB is in the low risk zone (< 40th centile), there is no measurable

risk of subsequent severe jaundice.<sup>7</sup> In term healthy neonates if serum bilirubin at  $24 \pm 8$  hours is < 6 mg/dL the risk of subsequent hyperbilirubinemia is almost negligible.<sup>8</sup> A cord serum bilirubin of 2.5 mg/gl or more has 71% sensitivity and 96% specificity in the prediction of severe jaundice.<sup>9</sup>

## Cause of Jaundice

A detailed history, examination (Table 56.3), onset of jaundice (Table 56.4), baseline investigations give us a clue to most important causes of neonatal jaundice (Table 56.1). Rh negative or O blood group mother, onset within the first 24 hours of life, pallor, splenomegaly and rapid increase in jaundice suggests hemolytic jaundice. Affection of a previous sibling, parental origin from North West India, rapid rise of jaundice and absent clinical signs of hemolysis such as pallor or splenomegaly indicates G6PD deficiency. Difficult delivery,



**Fig. 56.1:** Prediction of severe hyperbilirubinemia and hour specific TSB

**Table 56.3: History and clinical examination and relevance in neonatal jaundice**

<i>History</i>	
Previous sibling with neonatal jaundice, family history of anemia, splenectomy	Blood group incompatibility (Rh, ABO), G6PD deficiency, hereditary spherocytosis, Crigler Najjar Syndrome
Maternal fever and rash during pregnancy	Intrauterine infections
Labor and delivery events	Asphyxia, trauma, oxytocin, delayed cord clamping
Maternal drugs	Sulphonamides, nitrofurantoin and antimalarials may cause hemolysis in G6PD deficient infant
Liver disease in the family	Galactosemia, Alpha 1 antitrypsin deficiency
Prolonged parenteral nutrition	Cholestatic jaundice
<i>Examination</i>	
Small for date	IU infections, polycythemia
Microcephaly	IU infections
Pallor	Hemolysis, extravasation of blood
Petechiae	IU infection, Rh immunization, sepsis
Hepatosplenomegaly	IU infections, hemolytic jaundice, liver disease
Chorioretinitis	IU infections
Urine diaper staining and acholic stools	Cholestatic Jaundice

**Table 56.4: Etiology based on the age at onset of jaundice**

<i>Less than 24 hrs of birth</i>	<i>24-72 hrs of age</i>	<i>After 72 hrs of age</i>
Rh isoimmunization	Physiological	Sepsis
ABO and minor blood group incompatibility	Sepsis	Neonatal hepatitis
Intrauterine-infections (TORCH, malaria, bacterial)	Polycythemia	Extrahepatic biliary atresia
G6PD deficiency	Extravasations	Breast milk jaundice
	Increased enterohepatic-circulation	Metabolic (galactosemia, tyrosinemia, fructosemia alpha 1 anti-trypsin deficiency organic acidemias, cystic fibrosis). Hypertropic pyloric stenosis, and intestinal obstruction.

instrumental delivery, pallor, and scalp swellings indicate cephalhematoma or subgaleal bleeds. Family history of gallstones, splenectomy, early onset of jaundice, pallor and splenomegaly suggests hereditary spherocytosis. History of maternal fever and rash, intrauterine growth restriction, microcephaly, petechiae, hepatosplenomegaly suggests intrauterine infections.

### **Bilirubin Encephalopathy (Bilirubin Induced Brain Damage: BIND)**

All neonates with jaundice should be screened for early signs of encephalopathy. Early signs of bilirubin encephalopathy include decreased activity, poor suck, head lag and high pitch cry. In neonates with jaundice,

staining of palms and soles, evidence of hemolysis, intrauterine growth restriction, high serum bilirubin, low serum albumin, acidosis, sepsis/meningitis, asphyxia, low birth weight /premature, Asians/Indian race are the added risk factors that make them prone for bilirubin encephalopathy. In a prospective study from North India asphyxia, small for gestational age, maximum serum bilirubin, high free bilirubin levels and high bilirubin/albumin ratio correlated with kernicterus.<sup>10</sup> When bilirubin enters the brain, it predominantly affects the reticular system, globus pallidus/subthalamus, brainstem, cranial nerve nuclei and hypothalamus. Depending on severity of damage to the above structures, acute bilirubin encephalopathy is divided into 3 progressive stages (Table 56.5).

**Table 56.5: Stages of bilirubin encephalopathy and kernicterus**

Brain injury	Stage I	Stage II	Stage III	Kernicterus
Reticular system Globus pallidus and subthalamus	Lethargic Hypotonia	Stupor Variable tone, Retrocollis, Opisthotonus	Coma Hypertonia, Retrocollis, Opisthotonus	Extrapyramidal movements, athetosis
Brainstem Cranial nerve	Poor suck High pitch cry	Minimal Feeding difficulty High pitch cry	No feeding Shrill cry	Gaze palsy Sensorineural deafness
Hypothalamus		Fever	Fever	

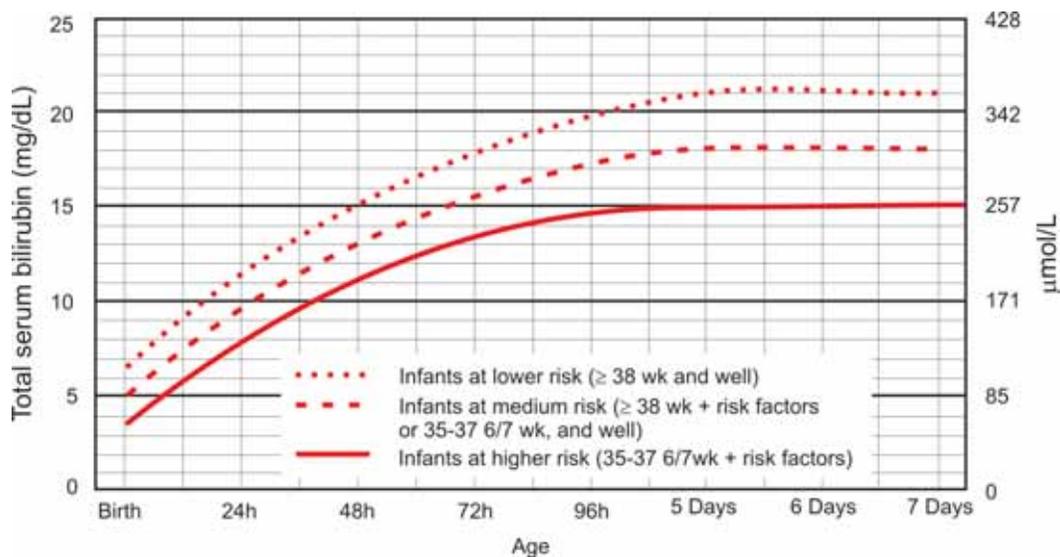
## INVESTIGATIONS

Investigations are required for assessing the severity of jaundice, to differentiate conjugated from unconjugated jaundice, to identify the etiology and to predict the risk of bilirubin encephalopathy. As a routine, in all babies with severe jaundice a total serum bilirubin with direct and indirect fraction, packed cell volume, reticulocyte count, direct Coomb's test, peripheral smear, serum albumin and G-6-PD screening are the baseline investigations. When sepsis is suspected a sepsis screen (C-reactive protein, blood counts), cultures of blood and urine are recommended. In Rh isoimmunized mothers, cord blood should be screened for total serum bilirubin, hematocrit, blood grouping and Direct Coombs Test (DCT). If the jaundice lasts for more than 2 weeks in term and 3 weeks in preterm infants, a thyroid profile, urine culture and galactosemia screen are the needed investigations. A packed cell volume < 40%, reticulocyte

> 5% after day 3, peripheral smear showing marked aniso-poikilocytosis, heterochromia and nucleated RBC's suggest hemolysis as the cause of jaundice. Plenty of microspherocytes on the peripheral smear is suggestive of ABO incompatibility. A positive indirect Coomb's test in the mother or positive direct comb test in the baby is indicative of immune hemolysis.

## TREATMENT OF SEVERE JAUNDICE

Traditionally Cockington's charts or Maisel's charts were used for deciding the need for treatment in jaundiced neonates. But with age based recommendations of starting phototherapy and exchange transfusion by American Academy of Pediatrics (AAP), a strong recommendation is now made to use AAP guidelines<sup>6</sup> (Fig. 56.2). For deciding the initiation of intervention, jaundiced neonates (gestation 35 weeks or more) are classified into three incremental risk groups based on



**Fig. 56.2:** Guidelines for phototherapy in hospitalized infants  $\geq$  35 weeks of gestation

gestation and presence of risk factors. The risk factors are isoimmune hemolysis, G6PD deficiency, asphyxia, sepsis, acidosis, temperature instability, significant lethargy, albumin < 3 g/dL. In our population an additional risk factor should be small for gestation.<sup>10</sup>

- Infants at low risk (dotted line): Gestation  $\geq$  38 weeks and well.
- Infants at moderate risk (interrupted line) : Gestation  $\geq$  38 weeks and with risk factors or Gestation 35 to 37 6/7 weeks and well.
- Infants at high risk (solid line) : Gestation 35 to 37 6/7 weeks.

AAP guidelines are recommended for total serum bilirubin (TSB). One should not deduct direct or conjugate fraction from TSB for the management. If TSB does not fall or continues to rise despite phototherapy, hemolysis is suspected. All babies requiring phototherapy should preferably be given intensive phototherapy. Intensive phototherapy implies irradiance in the blue green spectrum (wavelength of 430 to 490 nm) of at least 30  $\mu\text{w}/\text{cm}^2$  per nm and delivered to cover as much of the infant's surface as possible.

Phototherapy detoxifies bilirubin and facilitates its excretion from the body via routes other than conjugation in the liver. The photochemical reactions that promote bilirubin excretion are photo oxidation, configurational isomerization and structural isomerization. Photo oxidation plays only a minor role in bilirubin excretion. In configurational isomerization the ZZ isomer of bilirubin is converted to the ZE, EZ, EE, isoforms. The ZE isoforms maintains the polar groups at one end of bilirubin molecule and enables it to be excreted in the bile. Once in the bile rapid reversal of the ZE form occurs and bilirubin re-enters the circulation by enterohepatic route. The structural isomer, lumirubin, is currently considered to be the major excretory product of phototherapy. This structural change is irreversible and allows the more polar

bilirubin to be excreted in bile and urine. Phototherapy may be given with compact fluorescent lamps<sup>11</sup> or light emitting diodes<sup>12</sup> or conventional blue lights (TL 52 blue lights). However, fiber optic phototherapy should always be accompanied with any of the above three.<sup>13</sup> The practical aspects of phototherapy are given in Table 56.6.

### Monitoring Under Phototherapy

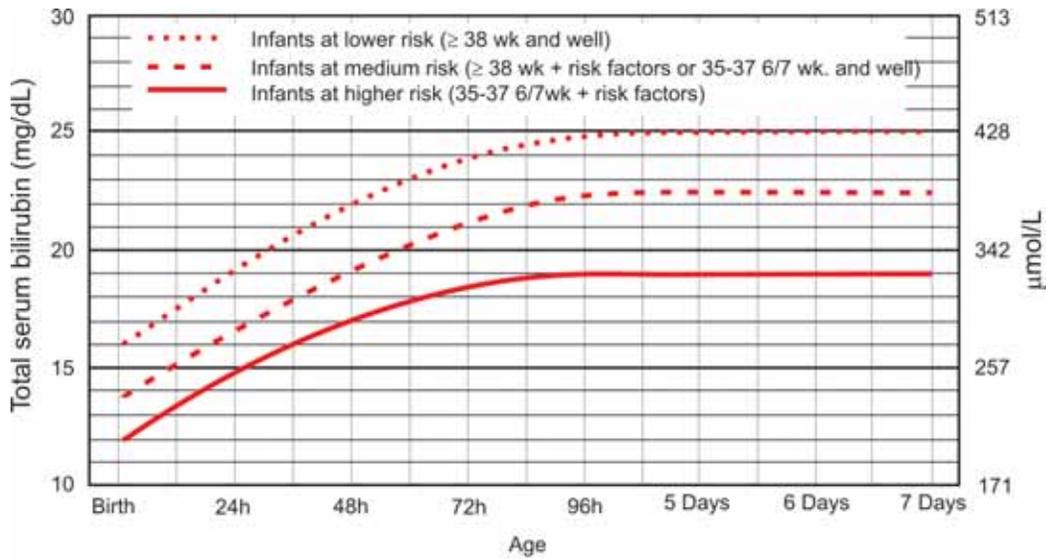
Clinical assessment of jaundice in babies under phototherapy may be fallacious. Hence, they need to be monitored by serum bilirubin estimation. If TSB > 25 mg/dL, repeat TSB within 2–3 hours, if TSB between 20–25 mg/dL, repeat within 3–4 hours. If TSB < 20 mg/dL repeat every 4–6 hours. If TSB is on a decreasing trend repeat at 8–12 hours intervals. Prior to omitting phototherapy, one should have consecutive TSB values below phototherapy zone for duration of 24 hours. After stopping phototherapy, one should check for rebound rise in TSB after 12 hours. Phototherapy is not recommended for conjugated hyperbilirubinemia. It may cause bronze discoloration of skin in these babies.

### Exchange Transfusion

Exchange transfusion removes much of the circulating bilirubin and sensitized red cells, replacing them with red cells compatible with mothers' antibody rich serum and providing fresh albumin with binding sites for bilirubin. After an exchange the low levels of serum bilirubin may increase rapidly for several hours as bilirubin in tissues migrate back into the circulation. For babies greater than 35 weeks of gestation AAP guidelines may be recommended (Fig. 56.3). For premature and low birth weight infants the need for exchange is based on the birth-weight or gestation and

**Table 56.6: Practical aspects of administering phototherapy**

1. Place baby naked under phototherapy.
2. Cover eyes and genitalia (in males) and lower abdomen (in female).
3. Mother should be encouraged to remove the baby from under the lights, uncover the eyes and breastfeed every 2-3 hours.
4. Whenever baby is put back under phototherapy, the posture should be changed every time from prone to supine and supine to prone.
5. Hydration, fluid and electrolyte (especially in preterm babies) status should be monitored.
6. Mother should be reassured about the transient and benign nature of greenish loose stools and rash that may be seen in some babies.
7. Check efficacy of blue lights with irradiance meter every 2 months (or change all tubes if some tubes begun to blacken).
8. Use of white/aluminium slings along with phototherapy increases irradiance and decreases the duration of phototherapy.<sup>14</sup>



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is  $\geq 5$  mg/dL ( $85\mu\text{mol/L}$ ) above these lines.
- Risk factors isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin, do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Fig. 56.3: Guidelines for exchange transfusion in hospitalized infants  $\geq 35$  weeks of gestation

Table 56.7: Management of jaundice in premature or low birth weight infants

Birth weight (g)	Phototherapy	Exchange transfusion
< 1500	5-8 mg/dL	13-16 mg/dL
1500-1999	8-12 mg/dL	16-18 mg/dL
2000-2499	11-14 mg/dL	18-20 mg/dL

Gestation (wk)	Phototherapy	Exchange Transfusion	
		Sick	well
36	14.6 mg/dL	17.5 mg/dL	20.5 mg/dL
32	8.8 mg/dL	14.6 mg/dL	17.5 mg/dL
28	5.8 mg/dL	11.7 mg/dL	14.6 mg/dL
24	4.7 mg/dL	8.8 mg/dL	11.7 mg/dL

sickness (Table 56.7). Exchange transfusion in Rh incompatibility is recommended for the following:

- Hydrops (initially only partial exchange may be done to increase hematocrit if baby cannot tolerate double volume exchange).

- History of previous sibs requiring exchange because of Rh isoimmunization in a baby born with pallor, hepatosplenomegaly and positive DCT.
- Cord Hb < 11 g/dL and cord TSB  $\geq 5$  mg/dL.
- Rate of rise of TSB > 1 mg/dL/hour despite phototherapy.
- Rate of rise of TSB  $\geq 0.5$  mg/dL despite phototherapy if Hb is between 11-13 g/dL.
- Any TSB > 12 mg/dL in first 24 hours and any TSB  $\geq 20$  mg/dL in the neonatal period are also indications for exchange transfusion.

Practical Aspects

A 'two-volume' exchange is performed, i.e. the volume of blood exchanged equals twice the infant's blood volume, that is,  $2 \times 80 \text{ ml/kg} = 160 \text{ ml/kg}$ . This replaces 87% of the infant's blood volume with new blood.

**Technique:** Fresh blood (Hepatitis, HIV and CMV negative and irradiated if facilities exist) should be used, less than 4 days old and should be cross-matched against mother's blood. In endemic areas one should

use G6PD normal<sup>15</sup> and malaria screened blood to avoid post-exchange hemolysis.

*The in-out method* is the commonest method but is being used less often now. Aliquots of 5 or 10 ml of infant blood (3% to 5% of birth weight in smaller infants) are withdrawn via an umbilical venous catheter and replaced by an equal volume of donor blood via a three-way tap. This method has higher incidence of complications.

*The continuous flow method* is being increasingly preferred. Peripheral arterial and venous lines are inserted. Donor blood is infused at a constant rate via the vein and the baby's blood is withdrawn at the same rate via the artery. It is essential to balance the rate of withdrawal with the infusion rate. Complications are lower with this method.

No matter which method is used, a two-volume exchange should take 45 minutes to 75 minutes to complete (in smaller and sick babies a slower rate should be used).

**Choice of blood group:** (a) In the case of Rh-isoimmunization, O negative blood or if there is no ABO incompatibility, baby's own ABO type-Rh-negative blood may be used; (b) In the case of ABO incompatibility, O blood group with the same Rh types as that of the baby; (c) In cases where hyperbilirubinemia is not due to isoimmunization, then the blood of the same ABO and Rh type as that of the baby or O Rh-negative blood may be used for exchange transfusion.

**Complications:** Exchange transfusions are associated with risks of apnea, bradycardia, arrhythmia, vasospasm, thrombosis, hypothermia, thrombocytopenia, necrotizing enterocolitis, infections and mortality risk of 0.5 percent. High concentration of glucose in the transfused blood may stimulate insulin production and increase risk of severe hypoglycemia. The citrate in the anticoagulant chelates calcium ions and there may be a need for calcium gluconate during the course of exchange especially in sick neonates. In case the calculations are not right, there is a chance of overloading or depleting the blood volume following exchange transfusion leading to cardiac failure or shock. In addition the complications of blood or blood products such as malaria, CMV, hepatitis and graft versus host disease may occur in a minority.

## INTRAVENOUS IMMUNOGLOBULIN

High dose IVIG in a single or dual dose of 500 mg/kg or 1 gm/kg early in the course of jaundice is effective

in decreasing the need for exchange transfusions and in preventing significant hyperbilirubinemia in babies with isoimmune hemolytic anemia.<sup>16</sup> Hyperbilirubinemia in both Rh and ABO-sensitized infants results from the destruction of neonatal red cells that have been coated by transplacentally acquired maternal isoantibodies causing extravascular erythrocyte destruction. Fc receptor bearing cells within the reticuloendothelial system probably mediate this red cell destruction. IVIG therapy may alter the course of immune hemolytic disease by blocking Fc receptors, resulting in inhibition of hemolysis and subsequent reduction of bilirubin formation. For maximum efficacy IVIG needs to be given as soon as possible after birth. Late anemia may be a problem in neonates treated with IVIG. In addition, IVIG is a pooled blood product, so the potential for transmission of blood borne infections.

## Metalloporphyrins

Synthetic metalloporphyrins limit the production of bilirubin by competitively inhibiting heme oxygenase, the rate-limiting enzyme in bilirubin synthesis. They have been used to treat hyperbilirubinemia in Coombs positive ABO incompatibility and in Crigler Najjar type I patients. In 517 preterm infants who weighed 1500 to 2500 grams, a single intramuscular dose (6 mol/kg) of tin-mesoporphyrin given within 24 hours after delivery reduced the requirement for phototherapy by 76 percent and lowered the peak bilirubin concentration by 41 percent.<sup>17</sup> Similar results have been reported in term healthy breastfed babies and in G6PD deficient babies.<sup>18</sup> The only untoward effect is a transient erythema due to phototherapy. Although the results are promising, metalloporphyrins are not currently approved for use in newborn infants.<sup>19</sup> Whether one metalloporphyrin is more effective and safer than others is not known, and none are available for oral administration.

## Phenobarbital

Phenobarbital in the dose of 5 to 8 mg/kg every 24 hours induces microsomal enzymes, increases bilirubin conjugation and excretion and increases bile flow. It is useful in treating hyperbilirubinemia of Crigler Najjar syndrome Type I and in the treatment of direct hyperbilirubinemia associated with hyperalbuminemia. Phenobarbital given antenatally to the mother is effective in lowering bilirubin levels in erythroblastic infants but concerns about toxicity limits its routine use. Phenobarbital is neither effective for prevention of severe jaundice in G6PD deficient neonates<sup>20</sup> nor for augmenting the efficacy of phototherapy.

### Fluid Supplementation

In neonates with severe jaundice when the TSB is approaching exchange levels or in whom there is clinical or lab evidence of dehydration, fluid supplementation (extra 50 to 100 ml/kg/day) with oral feeds or sometimes with intravenous fluids decreases the need for exchange transfusion and also the duration of phototherapy.<sup>21</sup>

### Albumin

In plasma, bilirubin binds to albumin and enters the tissues at a rate that is proportional to the amount of free bilirubin that is available. Hence giving albumin infusion of 0.5 to 1 g/kg prior to exchange transfusion may potentially allow it bind the free bilirubin and decrease the risk of neurotoxicity. However the evidence is not strong enough for routine recommendation.<sup>6</sup>

### Clofibrate

Clofibrate, an anti-lipidemic agent, is an activator of peroxisome proliferators activated receptors. It increases bilirubin conjugation and excretion. A single oral dose of 100 mg/kg is effective in decreasing the duration of phototherapy in some neonates.<sup>22</sup> However, gastrointestinal disturbances, muscle cramps, leukopenia, altered lipid and glucose metabolism are associated side effects.

### Agar

Agars, activated charcoal, cholestamine and polyvinyl pyrrolidone have been used to bind bilirubin in the gut and to prevent enterohepatic circulation. Minimal benefit has been demonstrated in association with phototherapy<sup>23</sup> but in the case of cholestamine the benefits are outweighed by potential side effects including hyperchloremic acidosis.

### Hemolytic Disease of Newborn

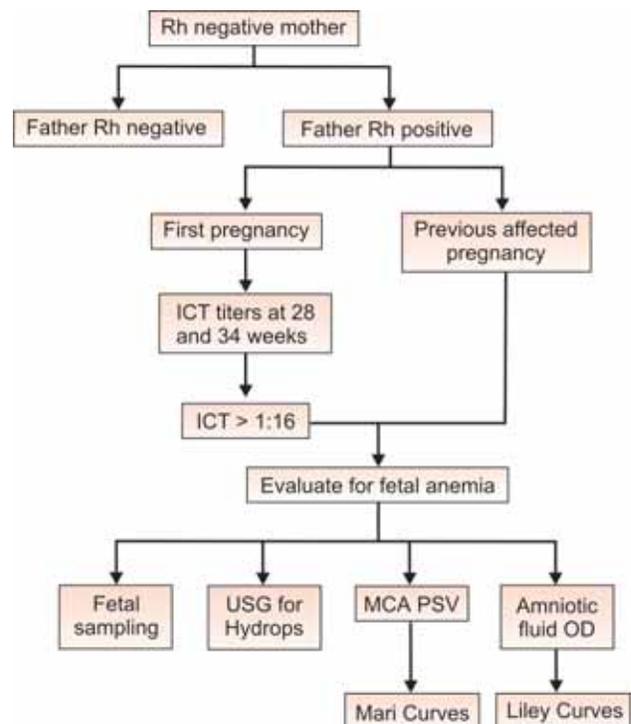
Hemolytic disease of newborn results from the blood group incompatibility between mother and fetus. Maternal IgG antibodies produced in response to the antigens derived from fetal red cells cross the placenta and are responsible for fetal hemolysis and anemia. The most important one in terms of severity is due to anti D antibodies of Rh-negative mothers. The others are ABO incompatibility, anti-kell group, anti-c, anti-E, anti-duffy and other rare group incompatibilities. The incidence of Rh hemolytic disease of newborn disease depends on the prevalence of Rh-negative mothers. Eight percent of Indian women are Rh-negative as

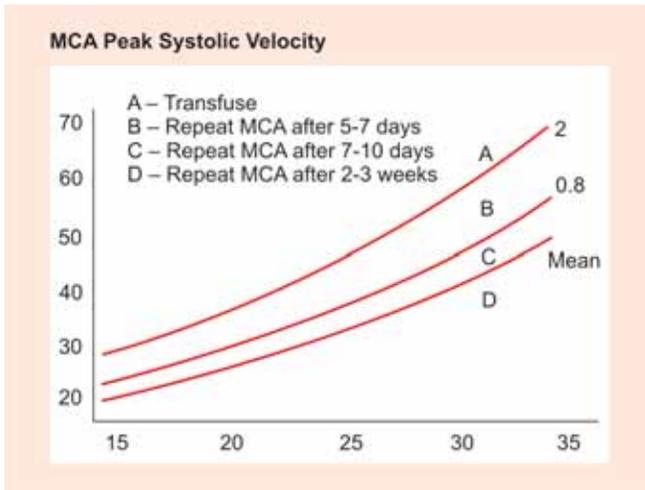
compared to 14.4 percent of Americans and 11-21 percent of Europeans whereas none of the Chinese and Japanese is Rh-negative. In Northern India<sup>24</sup> 6.4 percent women were found as Rh-negative as compared to 5.7 percent of the women in Mumbai. However amongst them only 6-8 percent is isoimmunized with varying degree of severity. This might be due to several reasons. The husband may also be Rh-negative or heterozygous positive, which offers a 25 percent chance of having Rh-negative fetus. The coexistent ABO incompatibility and inability on the part of the mother to mount response by producing antibodies also offers protection against Rh isoimmunization.

*The clinical manifestations* may vary from mild anemia to severe pallor with hepatosplenomegaly and generalized anasarca (hydrops fetalis). In severe cases the baby may die *in utero* or born with birth asphyxia and acidosis. Affected babies develop jaundice within first 24 hours. Hypoglycemia, respiratory distress, leukopenia, thrombocytopenia and late onset hyporegenerative anemia are other additional findings in these babies.

**The recent algorithm for the management of Rh-negative mother<sup>25</sup> is shown in the Flow chart 56.1 and 56.4.** If the fetus is isoimmunized, cord blood is taken for blood grouping, direct Coombs' test (DCT),

**Flow chart 56.1:** Algorithm for antenatal management of Rh negative pregnancy





**Fig. 56.4:** Mari curves for antenatal management of Rh isoimmunization based on MCA PSV

hemoglobin and bilirubin assessment. Severely hydropic babies require immediate resuscitation at birth, including thoracentesis and paracentesis to allow lungs to expand. A partial exchange with O negative red cells may be required to correct the severe anemia. Once the baby is stabilized double volume exchange transfusion may be performed. Less severe form may present with indications for exchange at birth (see later text) or may require phototherapy. In some neonates with severe hemolysis and very high bilirubin levels, biliary sludging may present as cholestasis jaundice. The treatment is mainly supportive and it includes correction of coagulation defects and adequate nutrition.

### ABO Hemolytic Disease of Newborn

It is the most common form of hemolytic disease of newborn though severe form is rare. ABO incompatibility is present in approximately 12 percent of pregnancies, although evidence of fetal sensitization is seen in only 3 percent and less than 1 percent of live births are associated with significant hemolysis.<sup>26</sup> ABO incompatibility is largely limited to type O mothers with type A and type B fetuses. In type A and type B mothers the isoantibodies are largely IgM and in type O mothers the alloantibodies are predominantly IgG molecules. IgG readily crosses the placenta causing fetal affection while the IgM molecules do not cross the placental barrier. Unlike Rh disease even the first pregnancy may be affected and the disease does not get worse with subsequent pregnancies. High IgM and IgG titers more than 1:1024 are followed by severe

disease in the baby requiring exchange transfusion. It is critical that infants with ABO incompatibility be monitored closely for evolving jaundice and hyperbilirubinemia in the first few days of life. In most cases jaundice is managed with phototherapy and if exchange transfusion is required group 'O' Rh compatible RBCs are used. Additional follow up at 2 to 3 weeks of age to check for anemia is essential in these infants.

### Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency is one of the commonest causes of jaundice in the term healthy neonate in India. The pathogenesis of jaundice in neonates with G6PD deficiency has not been definitely elucidated and is controversial. Some believe that decreased hepatic bilirubin elimination is a key factor whereas others maintain that increased hemolysis is the cause. Acute drug induced hemolysis, in the setting of G6PD deficiency, has been implicated frequently in the pathogenesis of hyperbilirubinemia in adults. A similar rationale, of acute intravascular hemolysis, was initially extended to the newborn period but it subsequently was shown that hyperbilirubinemia occurs in G6PD deficient jaundiced neonates even when there is no evidence of hemolysis. Since the hematocrit remains normal in most jaundiced neonates it appears that decreased liver conjugation of bilirubin does contribute significantly to the pathogenesis of jaundice. Serum bilirubin levels reflect a balance between bilirubin production on one hand and bilirubin conjugation and elimination on the other, hence the latter factor alone or in combination with the first might be operating in the genesis of hyperbilirubinemia in G6PD deficient neonates. There are a large number of variants of G6PD deficiency, and it may also be possible that the different forms of G6PD deficiency cause hyperbilirubinemia by different mechanisms. Among the common variants found in India are G6PD Mediterranean, G6PD Chatham, G6PD Kalyan and G6PD Orissa.

Jaundice in these babies most often resembles the pattern seen in babies with physiological jaundice. Sudden, dramatic and unexplained elevation of serum bilirubin is known to occur in these babies. Pre-discharge bilirubin levels and hour specific bilirubin levels are presently available to predict significant jaundice in these G6PD deficient neonates. Serum total bilirubin values were determined between 44 to 72 hours of life in a cohort of term healthy G6PD deficient neonates. Percentile based bilirubin nomograms were constructed in G6PD deficient and normal control infants according to age of sampling. In G6PD deficient neonates the

incidence of hyperbilirubinemia was 23 and 82 percent when the predischarge bilirubin was 50-74 percentile and more than 75 percentile, respectively.<sup>27</sup> The validity of these nomograms as applied to our population needs to be studied yet.

Methemoglobin reduction test and fluorescent spot test are useful screening tests and tetrazolium cytochemical method is diagnostic to quantify the defect. The fluorescent spot test is the simplest, most reliable and most sensitive screening test. This test is based on the fluorescence of NADPH, after glucose-6-phosphate and NADP are added to a hemolysate of test cells. The test requires just a few minutes and can be done on anticoagulated stored blood and on a blot of dried filter paper. This, however, requires a source for long UV light. In methemoglobin reduction test the NADPH generated from G6PD normal cells reduces the dye, methylene blue, changing its color. The test requires 1-2 ml of blood and a few hours for the dye reduction to occur. This test should be performed within one hour of sample collection.

In addition to the routine management of jaundice, all neonates with G6PD deficiency should be counseled on the need to avoid medications that induce hemolysis (Table 56.7).

### Jaundice in Premature

Hyperbilirubinemia in preterm infants is more prevalent, more severe, and its course is more protracted than in term neonates, as result of exaggerated neonatal red cell, hepatic and gastrointestinal immaturity.<sup>28</sup> The postnatal maturation of hepatic bilirubin uptake and conjugation may also be slower in premature infants. In addition a delay in the initiation of enteral feedings so common in the clinical management of sick premature newborns may limit intestinal flow and bacterial colonization resulting in further enhancement of bilirubin enterohepatic circulation. Phototherapy if used appropriately (Table 56.8) is capable of controlling the bilirubin levels in almost all low birth weight infants with the possible exception of the occasional infant with severe erythroblastosis fetalis or severe bruising.

Late preterm gestation (a special group of prematurity) is one of the most prevalent identified risk factor for the development of severe hyper-bilirubinemia and kernicterus. There is approximately eightfold increased risk of developing TSB > 20 mg/dL in infants born at 36 weeks as compared with those born at 41 or 42 weeks of gestation. Inadequate breastfeeding in exclusive breastfed preterm infants, male sex, large for gestational age, and G6PD deficient are the added risk factors which increase the risk of severe jaundice and

**Table 56.8: Medications to be avoided in G6PD deficient subjects**

Medication	Use
Dapsone	Leprosy
Mefenide cream	Topical antibiotic
Methylene blue	Antidote for methemoglobinemia
Nalidixic acid	Antibiotic for UTI
Nitrofurantion	Antibiotic for UTI
Phenazopyridine	Analgesic for dysuria
Primaquine	Antimalarial
Rasburicase	Adjunct to cancer chemotherapy
Sulfacetamide	Antibiotic (opthal and topical use)
Sulfamethoxazole	Antibiotic (Septran)
Sulfanilamide	Antifungal agent

kernicterus in these premature infants.<sup>29</sup> The management of jaundice in late preterm is as per AAP guidelines.

### Prolonged Jaundice

Clinical jaundice persisting for more than 2 weeks in term babies and for more than 3 weeks is termed as prolonged jaundice. Most common etiology in these babies is breast milk jaundice but one needs to rule out more sinister causes such as hypothyroidism and biliary atresia. Staining of diapers and pale stools suggest cholestasis. Relevant investigations are necessary to rule out hypothyroidism, urinary tract infection, galactosemia, sepsis, malaria, ongoing hemolysis, Criggler-Najjar syndrome, pyloric stenosis and neonatal cholestasis syndromes. The details of these conditions are outside the scope of this chapter.

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Neonatal units throughout the world encounter neonates with catastrophic hemorrhage. The causes for such bleeding are protean, and to an extent dependent on local factors, such as uptake of Vitamin K prophylaxis.

This chapter gives an overview of major causes for serious hemorrhage in neonates, bleeding at some specific sites which could potentially be life threatening and a general approach to the emergency management of bleeding in the neonate. The management of neonatal thrombosis is not discussed.

### MAJOR CAUSES OF BLEEDING

#### Hemorrhagic Disease of the Newborn (Vitamin K Deficiency Bleeding—VKDB)

This is a bleeding disorder resulting from a deficiency of vitamin K dependent coagulation factors II, VII, IX and X. Vitamin K is essential for  $\alpha$ -carboxylation of these proteins, which converts them to their active form.<sup>1</sup> Newborns are relatively vitamin K deficient for a variety of reasons including low vitamin K stores at birth, poor placental transfer of vitamin K, low levels of vitamin K in breast milk, and sterility of the gut. The daily requirement of vitamin K is 1  $\mu\text{g}/\text{kg}/\text{day}$ . VKDB is exceedingly rare in formula-fed infants for whom intakes are typically 50  $\mu\text{g}/\text{day}$  compared to 1  $\mu\text{g}/\text{day}$  in breast-fed infants.<sup>2</sup>

Before the routine use of prophylactic vitamin K, as many as 1% of neonates developed this condition. Typical clinical manifestations include bruising, cephalohematomas, gastrointestinal and umbilical hemorrhage, as well as oozing from mucous membranes, circumcisions and venepuncture sites. Intracranial bleeding remains the main cause of mortality and long-term morbidity.

Three forms are recognized:

- **Early onset**, at less than 24 hours after birth, is caused by vitamin K deficiency *in utero*, and is usually as a result of maternal medications that interfere with vitamin K, such as anticonvulsants (phenobarbitone,

phenytoin), anti-tuberculous therapy and oral anticoagulants.<sup>1</sup> This risk can be minimized by giving such mothers vitamin K during the last four weeks of pregnancy.

- **The classic onset**, 2-6 days after birth, occurs almost exclusively in breastfed infants who have not received vitamin K supplementation.
- **Late onset**, which occurs between 8 days and 6 months of life. In addition to breastfeeding, risk factors include diarrhea, hepatitis, cystic fibrosis, celiac disease, and alpha1-antitrypsin deficiency. Late onset VKDB tends to be more severe than early or classic onset and has a high incidence of intracranial hemorrhage. It has not been reported in infants receiving prophylactic intramuscular vitamin K at birth unless they also had liver dysfunction.

A coagulation screen will show prolongation of the prothrombin time (PT) and activated partial thromboplastin times (APTT). Factor VIII, factor V, platelet count and fibrinogen levels are within normal limits. Vitamin K direct assay is not useful because levels normally are low in newborns. Thrombocytopenia or an isolated prolongation of APTT should prompt workup for other causes of bleeding.

Treatment is with 1 mg of vitamin K given intravenously. Decreased hemorrhage and return of vitamin K dependent factor levels to normal usually occurs within 2-3 hours. If significant hemorrhage has occurred, an infusion of 10-15 ml/kg of fresh frozen plasma is also indicated to rapidly correct the coagulation defects.

Prophylaxis is the key to prevention of this disorder. The recommended policy is to offer intramuscular vitamin K to all infants at birth. The dose is 1 mg for term infants and 400 mcg/kg (maximum 1 mg) in preterm infants.<sup>3</sup> In the early 1990s, an association between parenteral vitamin K and the later occurrence of childhood cancer was reported.<sup>4</sup> This was explored later by others<sup>5</sup> who reported the lack of any convincing evidence based on the outcome of several other studies. As there is no known link between oral vitamin K and

malignancy, where parents decline intramuscular vitamin K, oral vitamin K can be offered. Two doses of 2 mg each are required, given at birth and one week with a further dose at one month of age for breastfed infants.<sup>3</sup> As there was concern regarding the possible role of the solubilizing agents, this was replaced with Konakion MM Paediatric<sup>®</sup> which is solubilized using natural components.<sup>2</sup> This can be given i.m., i.v. with dilution or orally.<sup>3</sup>

### Disseminated Intravascular Coagulation (DIC)

This is not an uncommon condition encountered in sick infants with risk factors such as sepsis, hypoxia, hypotension, acidosis or hypothermia. There is activation of the coagulation cascade with consumption of platelets and coagulation factors, and secondary activation of fibrinolysis. If the infant is able to restore consumed factors quickly and the trigger is speedily removed, the process will be arrested; otherwise a full-blown DIC will set in.

The clinical presentation typically comprises bleeding from multiple sites including heel pricks and venepuncture sites. Laboratory tests will reveal a low platelet count, prolonged prothrombin and partial thromboplastin times, and decreased fibrinogen levels, with schizocytes in a peripheral blood smear. D-dimers are elevated but not essential for diagnosis.

Localized DIC with severe bleeding can occur in Kasabach-Merritt syndrome characterized by consumption of platelets and coagulation factors within a giant hemangioma. Spontaneous resolution may occur; however, treatment by surgical removal, or with interferon<sup>6</sup> may be required.

Treatment comprises elimination of the trigger factor, with replacement of factors using fresh frozen plasma and platelet concentrate as required. Packed cells may be indicated if the infant is anemic. There have been no recent randomized trials that address optimum management of bleeding associated with neonatal DIC. The usual approach is to maintain the platelet count  $> 30-50 \times 10^9 /L$ , PT  $\leq 3$  seconds above the upper limit of normal and the fibrinogen  $> 1 \text{ g/L}$ .<sup>1,7</sup>

Although inhibiting the activation of the coagulation system with prophylactic dosing of heparin (5-10 U/kg/hr) has been considered, trials of anticoagulation in neonates have not been conclusive and the risk of bleeding may be increased.<sup>7</sup> Recombinant factor VIIa has been used successfully to treat life-threatening bleeding in babies with DIC but its use is still anecdotal.<sup>8</sup>

### THROMBOCYTOPENIA

The normal platelet count in neonates is the same as in adults –  $150$  to  $400 \times 10^9 /L$ .

Infants with significant thrombocytopenia will develop petechiae but in addition could bleed from any site including into the cranium.

In term infants, thrombocytopenia is extremely uncommon affecting only 2% at birth.<sup>9</sup> The most common clinically important cause in term infants is alloimmune thrombocytopenia.<sup>9</sup> This is discussed later in this section.

It is not uncommon, however, for low birth weight infants to have a lower count secondary to placental insufficiency or fetal hypoxia due to conditions such as maternal pre-eclampsia. This is secondary to impaired platelet production.<sup>10</sup> An estimated 22-35% of infants admitted to neonatal intensive care units have thrombocytopenia, rising to 50% in those receiving intensive care.<sup>10</sup> The reasons for this include bacterial and fungal sepsis, disseminated intravascular coagulation, necrotizing enterocolitis and perinatal asphyxia. The mechanism is through platelet consumption and sequestration and usually develops within 72 hours of admission to neonatal units.

Other causes such as those associated with congenital malformations and genetic conditions are relatively rare, as are thrombasthenias.

15-20% of neonatal thrombocytopenias occur secondary to transplacental passage of maternal platelet allo- and autoantibodies.

#### *Alloimmune Thrombocytopenia*

In this condition, fetal and neonatal thrombocytopenia results from transplacental passage of maternal platelet specific antibodies. Severe thrombocytopenia occurs in the fetus or in the early neonatal period with a 10% risk of intracranial hemorrhage.

In Caucasian populations, 80% result from antibodies to HPA -1a and most of the rest to HPA -5b platelet antigens. Diagnosis is based on demonstration of maternal antibodies, which in some may not be detected until 2-6 weeks after delivery.<sup>11</sup>

Therapy during pregnancy is controversial comprising close monitoring and using fetal platelet transfusions and maternal intravenous immunoglobulin. A combined approach has been advocated by some comprising fetal platelet count monitoring and intrauterine platelet transfusion combined with maternal IVIG for cases with a previously affected sibling who suffered an intracranial hemorrhage; if not, they are managed with maternal IVIG only with no monitoring of the fetal platelet count.<sup>12,13</sup>

Following delivery, if the platelet count is less than  $30 \times 10^9/l$ , or if there is evidence of bleeding, the infant will need transfusing with HPA compatible platelets (usually HPA 1a and HPA 5b negative ABO and RhD compatible) until the platelet counts stabilize. If this is not available, maternal platelets can be considered. HPA incompatible platelets can be used but survival will be poor in most cases. High dose immunoglobulin (1 g/kg) for two days is effective in most cases but will not work immediately. The aim is to keep platelet counts above  $30 \times 10^9/L$  for the first week of life or for as long as there is evidence of continuing bleeding.<sup>12,14</sup>

#### *Neonatal Autoimmune Thrombocytopenia*

Maternal autoantibodies in women with idiopathic thrombocytopenic purpura and SLE can similarly cross thrombocytopenia but it is quite infrequent, occurring in only 10% of cases. Major morbidity is rare. Routine delivery by cesarean section is therefore not justified. Platelet transfusions of any antigen type are usually ineffective.

All neonates of mothers with autoimmune disease should have a cord blood platelet count determined at birth and again at 24 hours. If low, the platelet count should be checked daily as the nadir is usually reached after the next three to four days, before rising spontaneously by day 7 in most cases. As most babies found to have an intracranial hemorrhage secondary to maternal autoimmune disorders have had platelet counts of  $< 30 \times 10^9/l$ , it is common practice to treat any neonates with platelets  $< 30 \times 10^9/l$  with intravenous immunoglobulin regardless of whether or not there is evidence of bleeding, at a dose of 1 g/kg/day on two consecutive days or 0.5 g/kg/day for four days.<sup>12,15</sup>

#### *Treatment of Thrombocytopenias*

This is dependent on the underlying mechanism and conditions. There are no evidence-based guidelines for platelet transfusion but consensus-based guidelines exist.<sup>12</sup> These recommend transfusions when counts fall below  $30 \times 10^9/l$  or in the case of very sick or preterm infants, below  $50 \times 10^9/l$ . Attention to the underlying cause is of course necessary.

### **Coagulation Disorders**

These are relatively uncommon but can cause significant hemorrhage. Hemophilia A and B are the most frequently encountered conditions. Other disorders such as afibrinogenemia and deficiencies of

other factors are rare but need to be considered in the differential diagnosis. Von Willebrand disease only unusually presents in the neonatal period because of their higher VWF factor levels.

#### *Hemophilia*

Hemophilia A and B are X-linked bleeding disorders characterized by deficiency of coagulation factors VIII and IX respectively. Though they can present with hemorrhage in the neonatal period, the diagnosis may be delayed by several months. The availability of prenatal diagnosis is now allowing an increasing number to be diagnosed in the neonatal period.<sup>16</sup>

An analysis of reported bleeding episodes in neonates between 1966 and 1999 showed that intracranial bleeding accounted for 27% of episodes, while 13% were sub-galeal bleeds or cephalhematomas. Bleeding from puncture sites were reported in 16%; 30% were from circumcisions; and 6% were from the umbilical stump.<sup>16</sup> Intracranial hemorrhage can occur irrespective of severity of hemophilia.

Management of these infants can be aided by antenatal diagnosis especially where there is a family history of this condition. Delivery by cesarean section does not seem to help prevent intracranial hemorrhage, but application of forceps and Ventouse extraction is best avoided. On delivery, a sample of cord blood or peripheral venous blood should be processed as soon as possible for coagulation screen and coagulation factor assay. Mild hemophiliacs may have a normal prothrombin and activated partial thromboplastin time. If the initial presentation is with an intracranial hemorrhage, assay of coagulation factors should always be performed as other processes such as DIC and thrombocytopenia may affect the coagulation profile.

These infants should not have any arterial stabs, and heel pricks should be kept at a minimum. Intramuscular injections should be avoided and vitamin K can be given orally. Circumcision should be discouraged or performed with adequate preparation. Once the diagnosis is established, the role of prophylactic factor VIII administration to hemophiliac newborns is controversial but may be considered where a previous sibling has had a major intracranial bleed.<sup>1</sup>

In case of life threatening hemorrhage, recombinant factor VIII or IX as applicable should be administered as soon as possible. The usual treatment dose of factor VIII for neonates is 50-100 units/kg intravenously twice daily.<sup>1</sup> The goal is to increase plasma levels of factor VIII or IX to 100% for at least 24 hours and above 50%

from the second day onwards.<sup>17</sup> Another recommended dosage for hemophilia A is recombinant factor VIII concentrate, 50 IU/kg is given as a bolus, followed by a continuous infusion of 2-3 U/kg/hr for 7 to 14 days. The dose for factor IX is 80 U/kg as a bolus, followed by 20-40 U/kg every 12-24 hours to maintain factor IX levels above 40% for the first five days and above 30% for 5-10 days.<sup>18</sup> Further dosing will depend on clinical circumstances.

If recombinant factor concentrate is not available, highly purified virally inactivated plasma derived factor VIII or IX products can be administered. Cryoprecipitate can be used if factor concentrates are not available. If the diagnosis is not known, fresh frozen plasma, 10-15 ml/kg can be administered.<sup>19</sup> Those with intracranial bleeding will usually need a CT or MRI scan of the head to establish the diagnosis.

## HEMORRHAGE IN THE PERINATAL PERIOD

### *From the Placenta*

Massive fetal bleeding may result following placenta previa, placental abruption or incision of the placenta at cesarean section.

Another potential problem is vasa previa. Here, fetal blood vessels, unsupported by either the umbilical cord or placental tissue, traverse the fetal membranes of the lower segment of the uterus below the presenting part. The condition has a high fetal mortality due to exsanguination resulting from fetal vessels tearing when the membranes rupture. They can however be diagnosed antenatally using trans-vaginal ultrasound and color Doppler in those at risk - with bilobed, succenturiate lobed, and low lying placentas, placentas resulting from *in vitro* fertilization, and in multiple pregnancies.<sup>20</sup> The perinatal mortality rate is very high, and there is high early neonatal mortality as well from unrecognized neonatal anemia.

### *From Umbilical Vessels*

Accidental hemorrhage can occur following slippage of a cord clamp. Rupture of the umbilical cord and hematomas into the cord can occasionally lead to severe neonatal anemia with a high perinatal mortality rate.

### *Fetomaternal Hemorrhage*

This can occur spontaneously and may be increased by invasive procedures such as fetal blood sampling and cesarean section. Most episodes involve very small quantities of blood but acute loss of > 20% of the blood

volume may cause intrauterine death, circulatory shock or hydrops.<sup>1</sup>

## IATROGENIC

The invasive nature of intensive care coupled with the small blood volume of infants could lead to disastrous consequences in the event of accidental hemorrhage. Examples include bleeding from arterial lines and intra-abdominal bleeding after insertion of umbilical lines.<sup>21</sup>

Drugs such as steroids, tolazoline and indometacin carry an attendant risk of serious hemorrhage especially from the gut. Heparin therapy can lead to thrombocytopenia.<sup>22</sup> A report and review on the use of recombinant tissue plasminogen activator for thrombolysis in neonates have reported an associated risk of mild to severe bleeding.<sup>23</sup>

ECMO therapy carries a reported 16% risk of intracranial hemorrhage.<sup>24</sup> There is likewise a significant risk of hemorrhagic complications after cardiopulmonary bypass in neonates undergoing corrective heart surgery. These risks are secondary to activation of the coagulation and fibrinolytic systems with consumption of coagulation factors, together with dilutional thrombocytopenia. Management includes careful monitoring of heparinization, replacement therapy with hemostatic factors and platelets, use of aminocaproic acid,<sup>25</sup> and more recently, recombinant factor VIIa.<sup>26</sup>

## SITES OF MAJOR HEMORRHAGE

### Pulmonary Hemorrhage

Historically associated with term infants as a terminal event, the spectrum has now changed to involve mainly sick preterm and growth retarded infants. A mortality rate of 46% has been reported in very low birth neonates with moderate to severe pulmonary hemorrhage, with pre-existing respiratory distress syndrome and surfactant treatment.<sup>27</sup>

The etiology is hemorrhagic pulmonary edema from multiple causes. The principal risk factors include sepsis, left heart failure, congenital heart disease, patent ductus arteriosus, hypothermia, fluid overload, oxygen toxicity and hemostatic failure. Other risk factors include the need for positive pressure ventilation for resuscitation, meconium aspiration, thrombocytopenia and hypotension.<sup>28</sup> The use of synthetic surfactants has been associated with an increased risk for pulmonary hemorrhage, with only a marginal increase with natural surfactants.<sup>29</sup>

These infants present with profuse bleeding from the endotracheal tube, associated with desaturation,

bradycardia and hypotension. They often become pale and unresponsive. Management consists of more effective ventilation usually with a high PEEP of 6-7 cm H<sub>2</sub>O, fluid restriction, diuretics, packed cell transfusion, correction of acid base balance and treatment of underlying factors such as sepsis and patent ductus arteriosus. Fresh frozen plasma may be required to correct secondary DIC. There is evidence of a beneficial effect of treating these infants with surfactant.<sup>29</sup>

### GASTROINTESTINAL HEMORRHAGE

Minor amounts of gastric bleeding are common in infants receiving intensive care and are attributed to stress.<sup>30</sup> It is common practice to treat such infants with ranitidine to prevent the possibility of bleeding becoming severe and life threatening. It is also often given to infants under treatment with steroids and indomethacin although of unproven benefit.

If major hemorrhage is encountered, immediate treatment with fluids, blood transfusion and intravenous ranitidine is instituted. There is no published work evaluating proton pump inhibitors such as omeprazole in these situations although it has been used anecdotally in neonates.<sup>31,32</sup> If bleeding persists, gastroscopy may be required to establish a diagnosis.

Other causes of significant upper gastrointestinal bleeding include necrotizing enterocolitis and bleeding diathesis. Rare causes include esophageal varices, gastric or intestinal volvulus, duplications, hemangiomas and teratomas. Appropriate treatment as indicated is necessary.

Lower gastrointestinal bleeding is uncommon but can be encountered with necrotizing enterocolitis, anal fissures, and infective enteritis. Proctocolitis secondary to cow's milk allergy is well known as a cause of rectal bleeding.<sup>33</sup> and has been known to produce bloody stools within 28 hours of life.<sup>34</sup> Colonoscopy and biopsy will reveal an eosinophilic colitis. It will respond to withdrawal of cow's milk from diet.

### INTRA-ABDOMINAL BLEEDING

Infants are known to sustain tears and ruptures of internal organs such as liver and spleen both after normal and traumatic deliveries.<sup>35,36</sup> Perforation of gastric and duodenal ulcers with bleeding is also known.<sup>37</sup> These infants will present with hypovolemic shock, pallor and a tense abdomen within hours of delivery. After resuscitation, immediate surgical exploration and repair is required.

Bleeding into the adrenal glands is also not uncommon but usually presents as a silent abdominal

mass. Rarely, it may be associated with severe hemorrhage and hypovolemic shock.<sup>38</sup>

### SUBGALEAL HEMORRHAGE

The sub-aponeurotic layer of the scalp encloses a large potential space traversed by large emissary veins unrestricted by periosteum at the skull sutures. Bleeding into this space can occur following traumatic deliveries especially with application of metal suction cups for Ventouse extraction. Inappropriate application of these cups over the parietal regions, which are highly vascular, rather than over the vertex; and their application from a high station with an unprepared cervix allowing application of angular shearing traction forces further increase the risk of bleeding.<sup>39</sup> The advent of silicon cups has led to a decline in its prevalence.<sup>40</sup> The bleeding can initially be concealed and the affected infants will present a few hours after birth with an extensive boggy swelling under the scalp together with evidence of hypovolemic shock.<sup>41</sup> A mortality rate of 17% was quoted in a large series from Hong Kong.<sup>42</sup> The diagnosis requires alert monitoring of infants born under these circumstances. Appropriate resuscitation with packed cell transfusion is life saving and an underlying coagulopathy needs to be excluded.

### INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage in term neonates can occur at various planes – subarachnoid, subdural, convexity, intra-parenchymal, or intraventricular. They are of serious concern with all major bleeding diathesis.<sup>43</sup> They are also associated with traumatic deliveries, ventouse extractions, ECMO therapy, arteriovenous aneurysms and thrombophilias. Spontaneous hemorrhage with no explicable cause is also known to occur in term infants.<sup>44</sup>

These infants could present with a bulging fontanelle, signs of neurological irritability or depression, and seizures. Sometimes, they are well to begin with and gradually lapse into an encephalopathic illness. Cranial ultrasound scan can pick up intra-parenchymal hemorrhages to an extent but of little value in diagnosing other forms of hemorrhage. Cranial CT or MRI scanning is diagnostic. Infants require screening for coagulopathy as well as thrombophilia. In addition to supportive care and transfusion, if indicated, neurosurgical attention may be necessary.

Intraventricular bleeding in preterm infants is a sign of brain injury rather than a bleeding diathesis and beyond the scope of this chapter.

### BLEEDING FROM THE UMBILICAL CORD

This can occur following a slipped cord clamp, and in vitamin K deficiency bleeding, congenital afibrinogenemia and hemophilia.

Delayed hemorrhage is associated in over 90% of infants with Factor XIII deficiency. Up to a third of these infants could have intracranial hemorrhage at some point. The condition is diagnosed by an overnight clot solubility test or by factor XIII assay. Treatment is with monthly infusions of factor XIII concentrate or cryoprecipitate.<sup>1</sup>

### APPROACH TO A CHILD WITH BLEEDING

#### Is it Bleeding?

There are some common pitfalls:

- Babies born to mothers with significant hemorrhage in the perinatal period can vomit previously swallowed maternal blood. The infant is well and usually presents within 24 hours of birth. A careful history usually clarifies the picture. The Apt test can help to differentiate maternal from fetal blood but it is not infallible. The condition is self-limiting but persistent bleeding requires further investigation.
- Infants often excrete urate crystals with urine, which produce yellow-pink deposits on nappies. This could be misinterpreted as bleeding but is benign and needs no treatment.

#### Is it Significant?

Bruising over presenting parts of a newborn is self-limiting. Further, hemorrhages at some sites are common and inconsequential. These include subconjunctival bleeds, small cephalhematomas, and withdrawal bleeding in female infants. Large bleeds in these areas, or bleeding elsewhere, however mild, could potentially become life threatening and needs immediate evaluation for possible causes.

#### Salient Features in History

1. **Family history:** Enquire about hemorrhagic diathesis in other members. Note that 30% of hemophiliacs are likely to have a negative family history.<sup>45</sup> as will coagulation disorders with an autosomal recessive inheritance.
2. **Maternal drugs:** Traditional anticonvulsants such as phenytoin, phenobarbitone and carbamazepine can prolong cord blood prothrombin time by inducing vitamin K deficiency but this is quite uncommon as a clinical problem.<sup>46</sup>

3. **Maternal illness:** Inquire for any history suggestive of autoimmune disorders such as systemic lupus erythematosus and idiopathic thrombocytopenic purpura in the mother. Check for a history of genital herpes as neonatal herpes simplex infection can present with severe coagulopathy secondary to hepatitis and this should always be kept in mind in an ill infant.
4. **Vitamin K:** Whether or not administered to the infant.

### Physical Examination

Look for evidence of respiratory and hemodynamic compromise. The presence of pallor, thready pulses, tachycardia, cool extremities, increased capillary refill time and a low blood pressure would suggest hypovolemia. Blood pressure, however, can be maintained within normal range through vasoconstriction and is unreliable as a marker for hypovolemia.

A well baby with petechiae or bleeding episode is more likely to have immune mediated thrombocytopenia or a coagulation disorder. A sick infant could have a serious systemic illness such as sepsis and necrotizing enterocolitis.

### Investigations

Collect blood samples for a full blood count, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen assay, group and cross match and blood culture, if appropriate. D-dimers are elevated in DIC but may be elevated in healthy neonates with no evidence of coagulopathy thus limiting its usefulness.

Sampling for coagulation studies should ideally be obtained by venepuncture. Sampling from arterial lines is likely to be affected by heparin contamination. If there is no alternative, it is worthwhile to first withdraw at least 2-5 ml of blood in a separate syringe before collecting the sample for analysis. The laboratory can help by doing a Reptilase time to detect heparin contamination.<sup>1</sup>

The results of coagulation studies should be interpreted in relation to gestational age. As a general principle, higher values are accepted in newborns when compared with adults. Detailed charts listing the normal range for various coagulation tests and individual coagulation factors at various ages and gestations are available for reference.<sup>47,48</sup> A brief summary of normal ranges for commonly performed tests is listed in Table 57.1.

Commonly encountered abnormalities are depicted in Table 57.2.

**Table 57.1: Results of hemostasis screening tests in bleeding disorders**

PT	APTT	TT	Fibrinogen	Platelets	FDP	Diagnosis
↑	↑	↑	↓	↓	↑	Disseminated intravascular coagulation
↑	↑	N	N	N	Negative	Vitamin K deficiency bleeding
N	↑	N	N	N	Negative	Hemophilia A, B, C
↑	N	N	N	N	Negative	Factor VII deficiency
N	N	N	N	↓	Negative	Thrombocytopenia
↑	↑	N	N	N	Negative	Factor V, X deficiency
↑	↑	↑	N/↓	N/↓	Negative	Liver disease
N	N	N	N	N	Negative	Factor XIII deficiency*
↑	↑	↑	Absent	N	Negative	Qualitative platelet disorder
N/↑	↑	↑	N	N	Negative	Afibrinogenemia
						Heparin contamination**

\*Diagnosis requires clot solubility test

\*\* Reptilase time is prolonged in DIC but not with heparin contamination

PT: Prothrombin time

APTT: Activated partial thromboplastin time

TT: Thrombin time

FDP: Fibrinogen degradation products

N: Normal

**Table 57.2: Normal values for hemostasis screening tests in the newborn\***

Test	30–36 weeks gestation	30–36 weeks gestation	Term infant	Term infant
	Day 1	Day 30	Day 1	Day 30
Prothrombin time (sec)	Mean: 13.0 Range: 10.6–16.2	Mean: 11.8 Range: 10.0–13.6	13.0 ± 1.43	11.8 ± 1.25
Activated partial Thromboplastin time (sec)	Mean: 53.6 Range: 27.5–79.4	Mean: 44.7 Range: 26.9–62.5	42.9 ± 5.8	40.4 ± 7.42
Thrombin clotting time (sec)	Mean: 24.8 Range: 19.2–30.4	Mean: 24.4 Range: 18.8–29.9	23.5 ± 2.38	24.3 ± 2.44
Fibrinogen (g/l)	Mean: 2.43 Range: 1.50–3.73	Mean: 2.54 Range: 1.50–4.14	2.83 ± 0.58	2.70 ± 0.54
Platelet count ( x 10 <sup>9</sup> /l)	Range: 150–400	Range: 150–400	Range: 150–400	Range: 150–400

\*Data from Andrew M et al.<sup>47,48</sup> All infants received vitamin K at birth.

Once the results of coagulation screening is available, further testing such as coagulation factor assays may be required to establish a precise diagnosis. If a coagulopathy is suspected, check the coagulation profile in the parents. When platelet counts are significantly low, further testing especially on the mother are required to establish immune thrombocytopenia. Other investigations would be directed at etiological factors such as infection if applicable.

## EMERGENCY MANAGEMENT

If the infant is obviously sick, assess for hemodynamic stability. Resuscitation, if required, should commence in the recommended order – attention to airway, breathing and circulation should always come first. If clinical signs suggest hypovolemia, establish an

intravenous line quickly and administer an intravenous bolus of 0.9% saline, 10 ml/kg of body weight and repeat if necessary. If intravenous access proves difficult, vascular access can be established rapidly especially in the delivery suite with an umbilical venous catheter. The intra-osseous route is an alternative in other settings.

If there is in addition clear evidence of overt bleeding, packed cell transfusion, 10–20 ml/kg over 5–10 minutes may be given if readily available. Most units keep an emergency supply of O rhesus negative blood, usually on the delivery suite, for use without cross matching in these situations.

Collect blood samples for full blood count, coagulation studies and other tests as relevant to the clinical setting, e.g. blood culture. These should ideally be collected before a blood transfusion is given.

## SUBSEQUENT MANAGEMENT

Initiate supportive treatment as indicated by the infant's condition. Once results of initial tests become available, appropriate therapy for the bleeding diathesis can be given. These could include:

- Vitamin K1**, 1 mg intravenously. Intramuscular injections should be avoided in any bleeding diathesis.
- Packed cell transfusion:** Usually, 10-15 ml/kg body weight is infused at a time over 4 hours. This is not applicable where there is profuse hemorrhage and proportionately larger volumes may then be required more quickly. Blood for transfusion needs to be cross-matched with mothers' serum for compatibility. In addition to screening for hepatitis B, syphilis and HIV, blood for neonatal transfusions should be obtained from cytomegalovirus negative donors and should also be leukodepleted to minimize risk of transmission of this infection. Blood from related donors especially parents should preferably be avoided as it could pose potential immunological risks and a greater likelihood of graft versus host disease.<sup>49</sup> Irradiated blood is indicated especially when the infants have received intrauterine transfusions and when they are known to be immunocompromised.
- Fresh frozen plasma**, obtained from screened donors, is used where rapid correction of coagulation defects is desired as in bleeding associated with vitamin K deficiency and DIC. It is useful in many coagulation factor deficiencies including V, VII, IX, X, XI, XIII, AT-III and alpha 2-antiplasmin. One infusion of 10-15 ml/kg increases the level of these coagulation factors by 10-15% and may need to be repeated 8-12 hourly in DIC depending on response.
- Platelet concentrates** are indicated if the platelet count is less than  $30 \times 10^9/l$ . In unwell neonates, infuse if the count is below  $50 \times 10^9/l$ . A platelet concentrate obtained from one donor is suspended in 50 ml of plasma. The dose is 10-15 ml/kg, which would be expected to increase the platelet count by  $100 \times 10^9/L$ . In sick neonates, however, such increases in platelet numbers are seldom seen due to rapid consumption or sequestration. It should be given as soon as possible usually at a rate of 10-20 ml/kg/hour.<sup>50</sup>
- Factor VIII or IX concentrates** are indicated in hemophilia. Cryoprecipitate is an alternative and can also be used in factor XIII deficiency and in afibrinogenemia if specific factor concentrates are unavailable. The dose is one unit per 5-10 kg of body weight.

**6. Exchange transfusion** can be performed in disseminated intravascular coagulation especially if associated with sepsis.

**7. Whole blood** is used principally for exchange transfusions and could be used for resuscitation in hypovolemic states. However, crystalloids are effective in initial management, with packed cell transfusions given later. Further, coagulation factors deteriorate rapidly in stored blood. For these reasons, most centers preparing blood components provide little or no whole blood.<sup>17</sup>

**8. Recombinant activated factor VII** is being used in neonates for life threatening hemorrhage in a variety of clinical settings.<sup>8</sup> Recombinant FVIIa is unique because it does not have enzymatic activity without its cofactor, the tissue factor (TF).

The hemostatic active complex VIIa/TF can only be formed in the presence of a tissue trauma. Thus, the effect of activated factor seven is mainly localized to the site of trauma – and general activation of coagulation does not usually occur. A dose range of 90-200 mg/kg has been used.

## PREVENTION

Universal use of vitamin K at birth would go a long way in preventing serious hemorrhage. In many conditions including hemophilia and alloimmune thrombocytopenia, antenatal diagnosis allows optimal management of the fetus, including preparation for safe methods of delivery and immediate attention to the neonate after birth. Genetic counseling should be arranged for couples of infants affected with inheritable coagulation disorders.

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The last two decades have witnessed tremendous advances in refinements of surgical and catheter interventions in newborns with congenital heart defects with steadily improving outcomes (91-95% discharge survivals – survival after operation for dtransposition of great arteries being 95-100% in the current era).<sup>1</sup> During the last decade there has been a meteoric growth in neonatal cardiac services in our country too with excellent and comparable outcomes for catheter interventions and surgery despite the problems of late presentation, presentation in circulatory collapse, pre-existing sepsis and associated growth reduction.<sup>2</sup>

This chapter aims to provide a simple and pragmatic diagnostic approach to a baby with suspected congenital heart disease as well as current prognostic implications for the short term. The second part of the chapter discusses guidelines for initial stabilization and transport of a newborn with suspected congenital heart disease, since such a baby would need care in a specialized unit for optimal outcome.

### MAGNITUDE OF THE PROBLEM

Congenital malformations of the heart occur in about 8 out of every 1000 live births. Of these, cardiac infants who are sick constitute 2.7/1000 livebirths. These babies are likely to die in the absence of a catheter or surgical intervention. Nearly 50 percent of these infants (roughly 1.2/1000 livebirths) present in the first two weeks of life. The current practice of readier recourse to catheter interventions or corrective surgery even in the early neonatal period has substantially reduced the morbidity and mortality of cardiac neonates to less than 0.8/1000 livebirths.<sup>3</sup>

It is estimated that approximately 100,000 newborns with congenital heart disease are born in our country each year who need some form of intervention during infancy.<sup>4</sup> Prompt recognition by the primary caregiver who is usually a pediatrician or a neonatologist, early stabilization and timely referral, however, are crucial to an optimal outcome. Heart disease in the newborn,

can for ease of management be classified into those who need urgent or immediate intervention and those who have nonurgent heart disease, i.e. those who can wait.

### CLINICAL PRESENTATION

It is useful to have a diagnostic approach based on the clinical presentation. Neonates who have “urgent heart disease” usually present with major problems,<sup>3,5-8</sup> including cyanosis, cardiovascular collapse, congestive heart failure and arrhythmia.

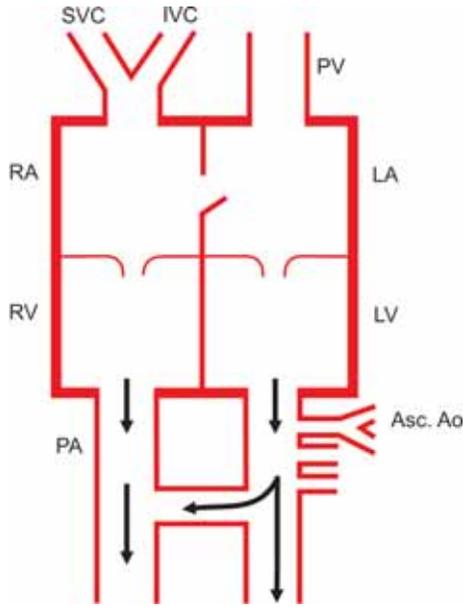
On the other hand newborns without urgent heart disease, usually have been detected to have a murmur on routine examination. These categories are not always comprehensive, often there being an overlap in presentation, i.e. a newborn may present with both cyanosis and heart failure. Thus, it is essential for the primary caregiver or neonatal pediatrician to have a knowledge base to approach a newborn with suspected heart disease.

### Transitional Circulation

Most neonates with urgent heart disease have **duct dependent** circulation either:<sup>3,5-8</sup>

1. To **ensure adequate mixing** as in conditions with parallel non-mixing circulations like dTGA (d transposition of the great vessels), or
2. To maintain **adequate pulmonary blood flow** in lesions causing right ventricular outflow obstruction (RVOTO), or
3. To maintain **adequate systemic perfusion** as in left sided obstructive (LVOTO) or hypoplastic lesions.

In the first few days of life, the ductus arteriosus tends to close and ductal constriction or closure may be associated with profound circulatory changes in newborns with cardiac defects who depend on an adequate blood flow through the ductus to ensure hemodynamic stability. *The pediatrician/neonatologist if familiar with the clinical manifestation of these circulatory changes is in a better position to organize prompt stabilization and early referral so that a speedy catheter or surgical solution can be instituted whenever possible (Fig. 58.1).*



**Fig. 58.1:** Transitional circulation (Modified from Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book Medical Publishers, Inc, 1974)

**Cyanosis as Presentation**

In neonates who present predominantly with cyanosis, the changes associated with transitional circulation are least tolerated. These babies are usually symptomatic in the first few days to weeks of life and become desperately unwell very quickly. Pulse oximetry is useful in confirming the presence of cyanosis, the saturation in these babies being not greater than 80-85%, often in the 50s. Flow chart 58.1, published nearly 40 years ago provides a useful diagnostic algorithm for a cyanotic neonate.

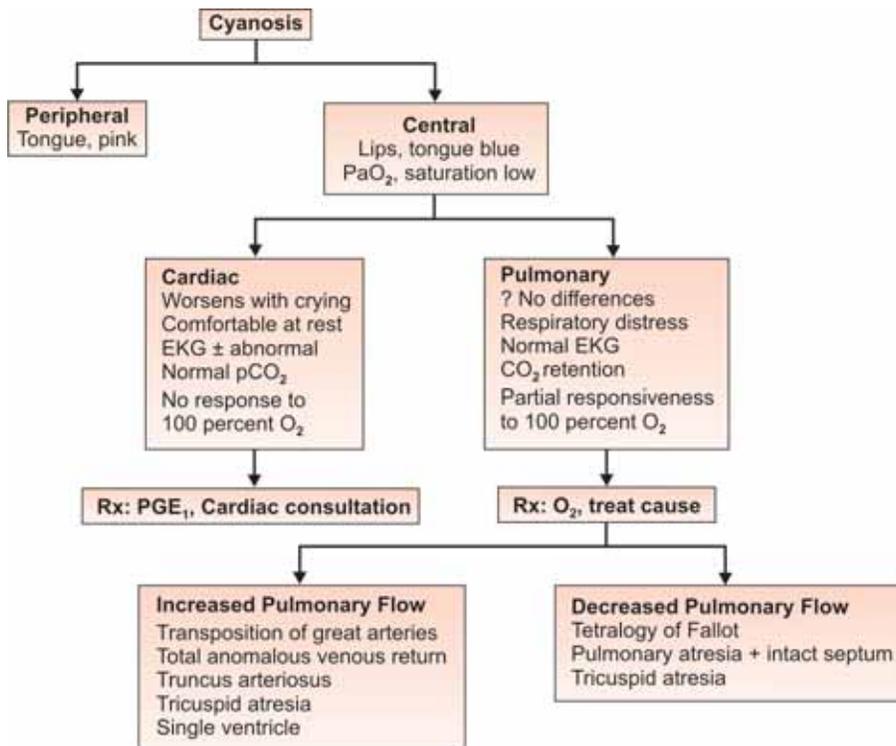
The usual congenital heart diseases causing cyanosis are enumerated in Table 58.1

These congenital heart defects produce cyanosis because of *right-to-left intracardiac shunting*. Many of these lesions are dependent on the *ductus arteriosus (PDA) to remain patent* and maintain blood flow to the lungs. When the PDA finally closes, the baby may suddenly become *visibly and noticeably cyanotic*.

**dTGA (Fig. 58.2)**

dTGA is the commonest of congenital cyanotic heart disease presenting in the newborn period. About

**Flow chart 58.1:** Algorithm for evaluation of a cyanotic newborn (Modified from Rudolph AM: Congenital Diseases of the Heart, Chicago, Year Book Medical Publishers Inc. 1974)



**Table 58.1: Congenital heart disease causing cyanosis<sup>5-7</sup>**

- Transposition of great arteries (dTGA)
- Right sided obstruction (RVOTO)
  - Tetralogy of Fallot (often overlooked in NICU)*
  - Tricuspid atresia*
  - Pulmonary atresia or stenosis*
- Total anomalous pulmonary venous return (TAPVR)
- Truncus arteriosus (may be overlooked in NICU)
- Less common stenotic lesions

50 percent of all infants with dTGA present in the first hour of life with *cyanosis and some tachypnea*, and 90 percent are symptomatic by the first 24 hours of life. These babies can rapidly deteriorate due to hypoxia and develop profound metabolic acidosis and severe capillary leak syndromes if the parallel circulations are allowed to continue without ensuring adequate mixing.

Clinically, the baby is relatively comfortable in the presence of cyanosis, i.e. has *peaceful cyanosis* in the early stages, the second heart sound is split, a murmur may or not be present, the chest skiagram reveals cardiomegaly and increased pulmonary artery markings with a narrow mediastinum or classically an “egg on string” appearance. Occasionally, cardiomegaly may not be present especially in babies with dTGA and an intact septum and classical features may be missing. In the presence of *cyanosis and nonligemic lung fields the probability is very high that the baby has a dTGA.*<sup>3,5-8</sup>

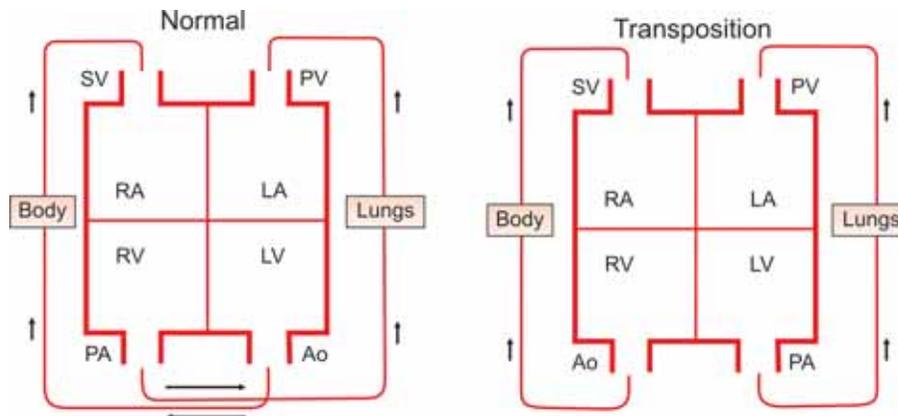
*An important differential includes PPHN or persistent pulmonary hypertension of the newborn. These babies often have a setting for PPHN-like aspiration syndromes, or are an infant of a diabetic mother; they are usually sicker and have a greater degree of respiratory*

distress for the degree of cyanosis. These are however, only relative guidelines and sometimes it can be extremely difficult to differentiate between a baby with PPHN and dTGA. Hyperoxia test may be useful in that babies with a cyanotic heart disease in an  $\text{FiO}_2$  of 1.0 are unlikely to have a  $\text{PO}_2$  exceeding 150 torr. Once again a baby with severe PPHN may not show a good response to hyperoxia and again occasionally PPHN and dTGA may coexist, making *definitive diagnosis extremely difficult in an individual baby.*

Finally, the ideal management of these babies depend on a prompt and definitive evaluation by color flow guided two dimensional Doppler echocardiography. The diagnosis can be established rapidly and accurately, and today most often surgical decisions in more than 90 percent of newborns with heart disease are based on 2D echocardiography. It is only in an occasional instance that invasive diagnostic modalities like cardiac catheterization is required.

*Once the diagnosis of dTGA is suspected, prompt and speedy referral to a pediatric cardiac unit is essential.* There is no good reason to retain a baby with suspected dTGA in a neonatal unit as such a baby will decompensate sooner or later and then it may be very difficult if not impossible to reverse the adverse hemodynamic consequence discussed later.

The current most physiologic surgical solution is an arterial switch operation. The morphologic left ventricle begins to regress rapidly after birth. It is uncertain when the regression becomes irreversible. Once the left ventricle regresses then it is not in a position to support the systemic circulation and such babies develop severe refractory unrelenting low output states postoperatively. Thus, *in most instances the arterial switch operation should be done in the first month of life and preferably in*



**Fig. 58.2:** Parallel nonmixing circulation in dTGA (Modified from Rudolph AM: Congenital Diseases of the Heart, Chicago Year Book Medical Publishers Inc 1974)

the first two weeks of life. It is thus, of great importance that these babies with dTGA and intact septum are diagnosed, stabilized and referred to an appropriate unit before this window period of one month, preferably within the first two weeks so that the optimal surgical option can be offered to these babies. If an arterial switch is performed at the ideal age and under stable conditions, the current mortality is between 0-5 %.<sup>1,8,9</sup>

To share our current unit experience, the average baby with dTGA presents to us between 3-5 weeks of age. Today, these babies usually undergo a primary arterial switch operation—an operation which has been associated with progressive improvement in outcomes—current hospital survival approaching ~95%.<sup>10</sup> In summary, it is useful to remember that a newborn with cyanosis and nonligemic chest X-ray is very likely to have an underlying dTGA.

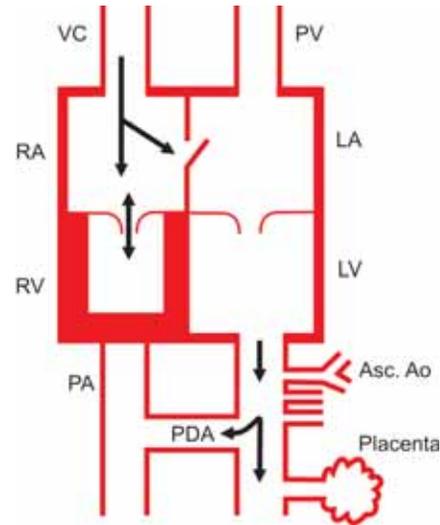
#### The Sicker dTGA

There is a small subset of babies who have a tiny ductus and a very small PFO, who very rapidly deteriorate due to inadequate mixing between the two parallel circulations, develop profound metabolic and lactic acidosis and a severe uncontrolled capillary leak leading to significant hypotension and impaired systemic perfusion which leads to an overwhelming cascade of metabolic and hemodynamic events viciating the capillary leak and the metabolic and lactic acidosis. It is of paramount importance that little babies do not develop this problem since the capillary leak can very rapidly become irreversible. Such a situation often precludes safe surgery, particularly since, even well neonates undergoing open heart surgery have a propensity to develop capillary leak following cardiopulmonary bypass.

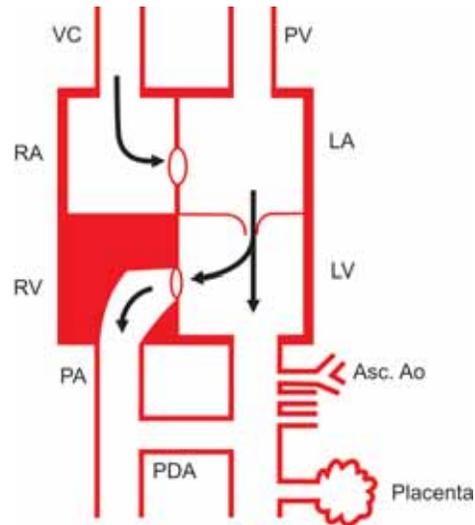
Such babies, however, can be managed quite satisfactorily if detected early. These babies present very early—often within a few hours of age, with marked cyanosis which increases very dramatically and rapidly over a very short period of time. Since they tend to decompensate very easily, it is at this time that they should be referred for a balloon atrial septostomy, so that early mixing between the two parallel circulations is initiated.<sup>9</sup>

#### Right Sided Obstructions (Figs 58.3A and B)

The second group of babies who present with cyanosis are those with right sided obstructions. Of these the commonest is critical pulmonary stenosis, which is often a part of tetralogy of Fallot. Tetralogy of Fallot is the commonest of the congenital cyanotic heart defects and constitutes nearly 10 percent of all congenital cardiac



**Fig. 58.3A:** Duct dependent circulation in pulmonary atresia, intact ventricular septum (Modified from Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book Medical Publisher Inc. 1974)



**Fig. 58.3B:** Duct dependent circulation in tricuspid atresia (Modified from Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book Medical Publisher Inc. 1974)

defects. Sometimes, the pulmonary stenosis is so severe that the pulmonary artery is virtually atretic. These babies are cyanosed, their cyanosis increasing with ductal closure since their pulmonary blood flow is virtually duct dependent.<sup>5-7</sup>

Clinically, they are not in failure, their second heart sound is single, and the chest skiagram reveals a normal sized or small cardiac shadow with oligemic

lung fields. If there is associated tricuspid atresia, the EKG shows left axis deviation. *In summary, if a neonate has cyanosis and has oligemic lung fields on chest skiagram with a normal or small cardiac size, the newborn is likely to have a significant right sided obstruction, i.e. pulmonary artresia or stenosis*<sup>7,8,11-13</sup>

The diagnosis is readily established by 2D echocardiography and color flow guided Doppler. These babies whatever the underlying anatomy, if there is significant right sided obstruction, i.e., RVOTO urgently need an alternate source of pulmonary blood flow in the form of a surgically placed communication between the systemic and pulmonary circulation—most often a modification of the Blalock-Taussig shunt. In the event of isolated pulmonary valve stenosis a balloon valvotomy (catheter intervention) is often enough and is usually lifesaving. Again, if a suspicion of RVOTO is raised, then the baby should be referred immediately to a specialized cardiac unit.<sup>3,7,8,11-13</sup>

### Presentation as Cardiovascular Collapse

Neonates who present with cardiovascular collapse constitute a medical emergency and usually do so in the first two weeks of life. These babies need aggressive resuscitation and prompt intervention for optimal outcome. Stabilization in these highly sick infants must be speedily accomplished even before definitive diagnostic evaluation to prevent ongoing decompensation which may rapidly lead to multi-organ failure and become irreversible.<sup>3,5,6,8,14,15</sup>

Table 58.2 enumerates the congenital heart diseases resulting in cardiovascular collapse.

- Patent ductus had allowed adequate right to left blood flow to the systemic circulation prior to its closure
- After PDA closure, greatly diminished systemic blood flow results (Figs 58.4A and B)
- Can also result in congestive heart failure with pulmonary edema.

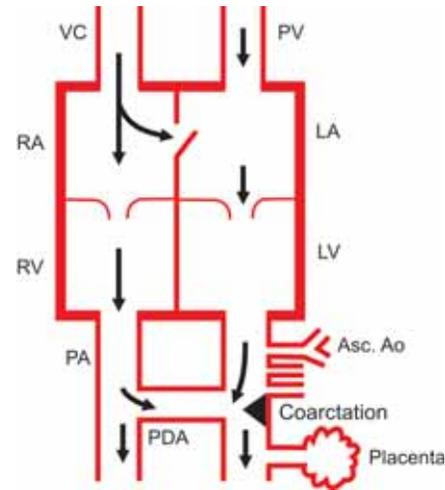
### Clinical Features

These babies clinically are lethargic, tachypneic, feed poorly, have a poor mottled color with evidence of impaired peripheral perfusion. The femoral pulses are feeble or impalpable and often all pulses are poorly felt. **The underlying structural defect is usually a critical left sided obstruction** the cause of which is one of the following: (i) Hypoplastic left heart syndrome; (ii) Critical aortic stenosis; and (iii) Significant coarctation of the aorta or aortic interruption.

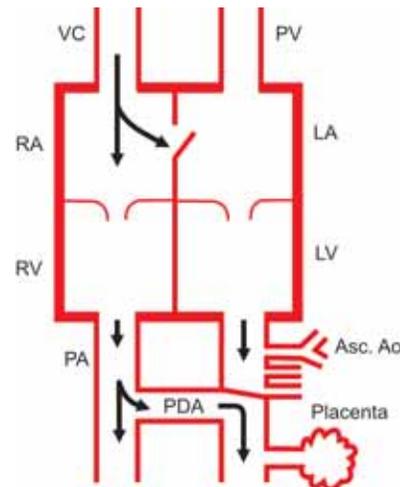
Hypoplastic left heart syndrome is the commonest cause of cardiac death in the first week of life. These

**Table 58.2: Congenital heart disease causing cardiovascular collapse**

- Coarctation of the aorta
- Interrupted aortic arch
- Hypoplastic left heart
- Critical aortic stenosis



**Fig. 58.4A:** Duct dependent systemic circulation in coarctation of aorta (Modified from Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book Medical Publisher Inc. 1974)



**Fig. 58.4B:** Duct dependent systemic circulation in aortic interruption (Modified from Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book Medical Publisher Inc. 1974)

babies have a diminutive left ventricle, often a critical aortic stenosis or aortic atresia, and sometimes mitral stenosis or mitral atresia. In severe cases, there is extensive aortic atresia or hypoplasia and an associated

coarctation. These babies present with cardiovascular collapse after ductal closure and are often critically ill. The chest skiagram reveals cardiomegaly and increased pulmonary artery markings, and the EKG shows diminished left ventricular forces. Prior to ductal closure, many of these babies have subtle problems which can be detected by the discerning. These signs constitute tachycardia, tachypnea, cyanosis and sometimes peripheral pulses which steadily become less vigorous.

Likewise, babies with *critical aortic stenosis* have severe compromise of the systemic circulation after ductal closure and present in much the same manner as babies with hypoplastic left ventricle. In addition clinically, the second heart sound is single there is often a well audible ejection systolic murmur and a third heart sound. *The chest skiagram shows cardiomegaly, occasionally pulmonary edema and the EKG has left ventricular hypertrophy.*

Babies with coarctation of the descending thoracic aorta constitute 5-8 percent of all cases of congenital heart disease, and associated interruption is seen in <1 percent. Children with severe coarctation, with associated aortic interruption, and complex coarctations, i.e. those with other associated cardiac defects like a large ventricular septal defect present in the newborn period. These babies again tend to decompensate with ductal closure and very rapidly progress into heart failure and a shock like state due to cardiogenic shock and multiorgan failure syndrome (MOFS). Recognition of pulse discrepancy is crucial to clinical diagnosis and upper and lower limb blood pressure recording is also helpful.<sup>14</sup>

*Critical aortic stenosis in the newborn* can be adequately managed today with balloon dilatation—a catheter intervention.<sup>3,6,8,15</sup> Similarly, various surgical options are available for aortic interruption and both catheter interventions and surgical solutions are feasible in aortic coarctation if these sick babies present before irreversible multiorgan damage has set in.

Again to share our experience, 90 percent (9/10) of neonates in the last year, with LVOTO presented late to us with either impaired left ventricular function and very low ejection fraction or in a state of extremis with bradycardia and profound circulatory collapse. Two were diagnosed at the time of referral, to have coarctation, the others were referred as cardiomyopathy or VSD. *It is thus useful to palpate the femorals in a newborn, as a weakened femoral or impalpable pulse leads to a strong suspicion of a significant left sided obstruction.*

So, in summary, all babies with congenital heart disease who are symptomatic in the early neonatal period, essentially constitute urgent heart disease or

duct dependent heart disease. All these neonates, whether with transposition of the great vessels, right sided obstructions or left sided obstructions need prompt recognition, immediate stabilization with prostaglandin E1 infusion, appropriate colloid and inotrope therapy, and correction of associated metabolic acidosis and speedy planned referral to a pediatric cardiac center.

### Mixed Presentation

There is a small group of newborns who present with mild cyanosis and rapidly worsening heart failure. Some of these babies have total anomalous pulmonary venous connection (TAPVC), i.e. all the pulmonary veins are draining into right side of the heart, usually the right atrium. *If the pulmonary venous drainage is obstructed, these babies can deteriorate very rapidly unless the pulmonary veins are surgically re-routed.* Some babies who do not destabilize very quickly go on to develop severe pulmonary hypertension and pulmonary vascular disease—hence the need to establish the diagnosis quickly and organize timely surgery before they become inoperable.

*There are few specific diagnostic signs clinically* except for a fixed split of the second heart sound, the chest skiagram shows a normal heart size and pulmonary congestion often pulmonary edema. Presence of these two features on chest X-ray should prompt an echocardiographic study. The diagnosis is essentially made on 2D echocardiography based on a high degree of clinical suspicion.

Often the diagnosis is delayed and current literature reports a very high mortality if babies with obstructed TAPVC present after two weeks of age. Hence the need for early diagnosis since neonates with obstructed TAPVC constitute a surgical emergency.<sup>5,6,8</sup>

The second group of babies with mild cyanosis and cardiac failure are babies with a truncus arteriosus who again present with tachypnea and in addition a prominent systolic murmur and a systolic ejection click. The pulses are usually bounding due to a run off into the pulmonary artery. These babies usually are symptomatic by three weeks or later, i.e. by the time the pulmonary vascular resistance drops so that the pulmonary overcirculation increases. Again, such a baby should be referred in time, since today the best early and long-term surgical outcome is related to surgery performed in early infancy.

A very unusual cause of structural heart defect in the newborn period is Ebstein's anomaly of the tricuspid valve. These babies present with cyanosis, right heart failure, a systolic murmur of tricuspid valve

regurgitation, loud third and fourth sounds, massive cardiomegaly on chest X-ray and right ventricular hypertrophy on EKG. In fact this cluster of findings in the presence of massive cardiomegaly makes clinical diagnosis almost certain.

### Late Onset Congestive Cardiac Failure

Table 58.3 enumerates the causes of late onset congestive cardiac failure. Some neonates develop cardiac failure more gradually and their presentation is more insidious. *These babies present usually between two to eight weeks of age* and are symptomatic due to pulmonary overcirculation secondary to a left to right shunt following a steady decline in the pulmonary vascular resistance with increasing age.

**Table 58.3: Causes of neonatal heart failure<sup>3,8,16</sup>**

- Congenital heart disease
- Myocarditis
- Arrhythmia
- Arteriovenous malformations
- Asphyxia
- Hypoglycemia, hypocalcemia
- Anemia
- Sepsis

The underlying defect is *most commonly a ventricular septal defect, an AVSD, i.e. atrioventricular septal defect or a large ductus arteriosus or rarely all three together*. It is unusual for ostium secundum atrial septal defects to present in the neonatal period with cardiac failure. However, large atrial septal defects as well as those associated with partial anomalous pulmonary venous connections can present with severe cardiac failure even in the neonatal period. Other less common causes include myocarditis, cardiomyopathy, anomalous origin of the coronary artery from the pulmonary artery and systemic arteriovenous malformations.

Table 58.4 enumerates the usual cardiac conditions causing heart failure. Normal transitional circulation

**Table 58.4: Congenital heart disease causing heart failure**

- Large L-R shunts (Pulmonary overcirculation)*
- Large ventricular septal defect
  - Complete AV canal
  - Large patent ductus arteriosus
  - Arteriovenous malformations
- Diminished left ventricular function (Less common)*
- Myocarditis
  - Dilated cardiomyopathy
  - Anomalous origin of left coronary from the pulmonary artery

after birth progresses to a situation with a gradual decline in pulmonary vascular resistance; this allows a pre-existing left-to-right shunt to progressively increase its flow. This may happen in neonates usually after 2 weeks of age, sometimes as late as several months. The symptoms present more gradually, often insidiously; a murmur may not present until the baby is 2 weeks-2 months old.

All these babies tire easily during feeds, nurse more frequently, are tachypneic at rest, have a diastolic apical flow rumble and frequently a gallop rhythm due to left ventricular failure. Babies with more florid failure have clinical signs of poor peripheral perfusion like decreased toe temperature and poor capillary refill. In addition, babies with a VSD have a heaving precordium, a harsh holosystolic murmur while those with an AVSD have similar clinical findings but a fixed split of the second sound. Babies with an ASD have a soft systolic ejection murmur, and again a fixed split of the second sound with or without a diastolic rumble depending on the degree of shunting. Babies with a systemic AV malformation can present with very severe heart failure and shock like state, and may be symptomatic even in the first few hours of life if the systemic run off is very large. Careful examination in these babies usually reveals a cerebral bruit, or a bruit over the liver and sometimes bouncy pulses. The chest skiagram in all instances shows cardiomegaly, plethora and sometimes patchy atelectasis. *Differentiation on the basis of chest X-ray and EKG is seldom possible and once a left to right shunt is suspected it is best to confirm the exact nature of the defects by early echocardiography*. Likewise cardiomyopathy/myocarditis can also be diagnosed by a 2D echo study.<sup>3,5,6</sup>

### Arrhythmias<sup>(3,8)</sup>

Some babies present predominantly with an arrhythmia, i.e. tachyarrhythmia (heart rate persistently >200/min) or a bradyarrhythmia (heart rate <70/min). *Both conditions if allowed to persist can rapidly evolve into cardiac failure and secondary low output state and cardiogenic shock*. Most of these arrhythmias are potentially treatable. Narrow QRS tachyarrhythmias can be managed with vagal maneuvers like ice application on the forehead, use of an anal probe or intravenous adenosine or metoprolol infusion. Wide QRS tachyarrhythmias are managed by synchronized cardioversion or amiodarone infusion. Bradyarrhythmias may need an artificial pacemaker. Thus, it is best to refer these babies in time to a pediatric cardiac unit so that they can be managed appropriately and in time.

### Nonurgent Heart Disease

Babies noted to have a murmur on routine examination constitute a fairly large group. The commonest cause is an innocent murmur due to peripheral stenosis. This is typically, a low intensity short systolic murmur best heard at the left sternal border. The commonest cause of a significant murmur is a small ventricular septal defect. The real challenge lies in identifying the infant with a pathologic murmur due to a congenital heart defect. If a murmur is heard in the first three months of life, the potential for a congenital heart defect is greatest—the chance of a murmur being due to a congenital heart defect being 1 in 12 if heard in the first 24 hours of life. *Such babies with an isolated murmur can be observed for some time, watched for development of symptoms and growth pattern.* If the murmur persists and appears related to a structural heart defect, then the baby should be referred for a two dimensional color flow guided Doppler echocardiography, so that a timely diagnosis is established and a timely catheter or surgical solution is offered.

### EMERGENCY MANAGEMENT AND INITIAL STABILIZATION

The preliminary management of a neonate with suspected heart disease has a tremendous bearing on eventual surgical outcome. A baby who reaches a specialized unit in a stable condition has much better chances of early intact survival than a baby who arrives in a moribund, preterminal state. This is particularly relevant in the group of babies considered to have “urgent heart disease”. Multi-institutional studies from across the world have shown that presentation in a sick state with circulatory collapse, severe metabolic acidosis, multi-organ failure syndrome (MOFS) or capillary leak adversely impacted survival following surgery.<sup>17</sup>

The successful treatment of a neonate born with a critical congenital cardiac disorder involves a carefully conducted sequence of events.<sup>3,5,6,8</sup>

1. A high index of suspicion on the part of the pediatrician is essential for the chain of events to be initiated. This aspect has already been discussed.
2. Prompt referral and safe transport to tertiary care center is necessary. When close to the city, road transport is feasible, but from distant places rail or air transport has to be resorted to. The safety of transportation would depend on the nature of the cardiac defect, the clinical status of the neonate and the distance to be travelled. Ideally transportation is best organized as in most centers across the world in close consultation with the receiving cardiac team, so

- that optimal stabilization, within the resources of the referring doctor or team, is done prior to transfer.<sup>18</sup>
3. Of paramount importance to optimal surgical outcome is an accurate diagnosis. Cross-sectional echocardiography with color Doppler is the single most important diagnostic modality as it provides a quick and accurate diagnosis of not only the structural defect but the alterations of flow dynamics as well. With the accuracy of the current generation of echocardiography machines, cardiac catheterization is required only in a very small percentage of cases.<sup>3,8</sup> Thus, apart from prompt recognition by the primary caregiver who is usually a pediatrician or a neonatologist, early and appropriate stabilization and timely referral, are crucial to an optimal outcome.

The initial management of the common neonatal cardiac problems will be considered individually. *Essential broad principles of stabilization include maintaining appropriate cardiac output by a combination of modalities.*<sup>3,6,8</sup>

1. Stabilization involves timely restoration of ductal circulation to maintain systemic or pulmonary blood flow as the case may be.
2. Advanced life support including appropriate ventilatory strategies.
3. Volume repletion.
4. Myocardial support by inotropes.
5. Correction of metabolic derangements like hypoglycemia and hypocalcemia.

The negative inotropic effect of hypoglycemia, acidosis and hypocalcemia are often underestimated, and if uncorrected these metabolic derangements may lead to rapidly progressive negative cascade of events which are often difficult to reverse.

1. **Restoration of ductal circulation:** Ductal patency is maintained by initiation of prostaglandin E1 (PGE1) in doses of 0.025-0.1microgram/min.<sup>3,6,8,19</sup> PGE1 is commenced on clinical suspicion, in a neonate in shock during the first week of life or in a neonate who fails the hyperoxia test. A neonate should ideally be watched for 30-60 minutes prior to transport after commencing PGE1. Side effects noted are apnea (12%), vasodilatation (10%), fever (14%), bradycardia (7%), and seizures (4%).

Occasionally, clinical deterioration is noted following commencement of PGE1.<sup>6,8</sup> This may occur in the absence of a ductus, an unresponsive ductus or in the presence of obstruction at the PFO or pulmonary veins. Structural conditions associated with clinical deterioration with PGE1 include obstructed total anomalous pulmonary veins, restrictive patent foramen ovale with d-transposition of great

arteries and intact ventricular septum, hypoplastic left heart syndrome or mitral atresia with restrictive patent foramen ovale. In the event of deterioration, PGE1 should be immediately ceased and the baby re-evaluated by ECHO.

2. Advanced life support include supplemental oxygen to maintain saturations of 80-85%. Intubation may be needed if the baby is deeply cyanosed or has respiratory distress.
3. **Volume repletion:** Normal or reduced maintenance fluids is needed in these neonates. Additional volume augmentation may be required in many of these neonates due to the non compliant neonatal myocardium or PGE1 induced hypotension. Volume repletion may be with normal saline, Ringer's solution or albumin.
4. **Myocardial support by inotropes:** Myocardial support by inotropes<sup>3,6,8</sup> is often needed to improve myocardial contractility and improve tissue perfusion once intravascular volume status is replete. Dobutamine is the usual preferred inotrope. Occasionally, epinephrine or isoprenaline is used in the presence of a slow heart rate.
5. **Correction of metabolic derangements like hypoglycemia and hypocalcemia:** Associated hypoglycemia and hypocalcemia need to be speedily addressed. There is published evidence that hypocalcemia adversely impacts the neonatal myocardial systolic and diastolic function worsening low cardiac output states.<sup>20</sup>

All these measures usually help in improving perfusion and secondary tissue and metabolic acidosis. Sodium bicarbonate correction is usually not required—in fact sodium bicarbonate administration has been associated with poor outcomes.<sup>6,8</sup> In the event of refractory acidosis half correction may be administered.

### dTGA.IVS

The management of a baby with dTGA with intact ventricular septum involves three phases:<sup>1,3,5-9,18,19</sup> (a) initial stabilization and management of metabolic derangements as above (b) palliation, and (c) subsequent surgical correction.

A balloon atrial septostomy is performed as a palliative measure, at the earliest only in some of these babies, to ensure maximal mixing at the atrial level between the two parallel circulations to avoid protracted hypoxemia and its attendant complications. Occasionally, in about 5-10 percent a balloon atrial septostomy might fail, necessitating an emergency

arterial switch operation—the current physiologically ideal operation.<sup>1,3,5-9</sup>

There is an increasing trend towards a primary definitive arterial switch surgery without a prior balloon atrial septostomy. The current survival following an arterial switch operation in India is greater than 95%.<sup>2,10</sup>

### Initial Stabilization and Transport

This includes the basics of advanced life support as detailed above. These babies also need fairly large amounts of colloid (fresh frozen plasma, or 5 percent albumin) to maintain plasma oncotic pressures, since minimal degrees of capillary leak is almost invariable. *It is also customary to underestimate the degree of metabolic acidosis; these babies often have a base deficit of 15 to 25 mmol/L at presentation.* The sicker babies also need dobutamine for adequate stabilization. *The really ill babies may also need assisted ventilation prior to palliative balloon atrial septostomy.*

### Case Study

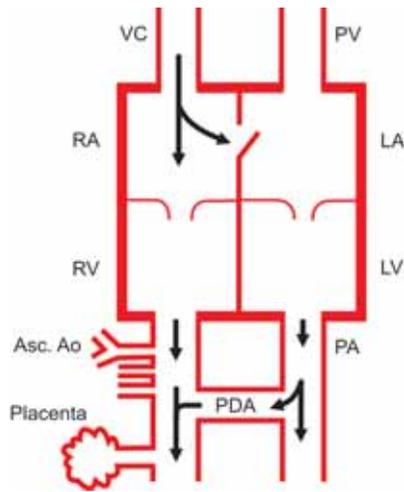
A neonate presented with cyanosis, minimal respiratory distress and severe acidosis (BE -15 mmol/L) at 21 days of age. Chest X-ray revealed mild cardiomegaly and nonoligemic lungs. He was intubated, ventilated, PGE1 commenced to maintain ductal patency. Bedside Echo revealed dTGA, small PFO and a tiny ductus. Balloon atrial septostomy was planned after stabilization. After initial improvement, there was rapidly worsening metabolic acidosis (Base excess - 25 mmol/L) unresponsive to volume replacement and inotropes. Emergency balloon atrial septostomy was done. Metabolic derangement rapidly normalized and the baby was extubated 8 hours later. He subsequently underwent an arterial switch operation and was discharged 7 days after surgery (Fig. 58.5).

### Right Sided Obstructions (RVOTO)

#### Stabilization and Transport

Sometimes, if the right sided obstruction is very severe, or if ductal closure has already occurred prior to diagnosis, these babies need stabilization prior to surgery. Prostaglandin E1 infusion is used to maintain pulmonary blood flow, oxygen therapy withdrawn to prevent ductal closure, the associated metabolic derangements treated and sometimes inotropes are required to maintain adequate cardiac output.

Occasionally, these babies also may need ventilation if there is apnea following PGE1 infusion or in the



**Fig. 58.5:** Stabilization involves restoration of “transitional circulation” to ensure adequate mixing

presence of severe hypoxemia and secondary metabolic acidosis.<sup>3,6,8,11-13,19</sup>

### Critical Left Sided Obstruction

As discussed before this is usually due to one of following:

1. Hypoplastic left heart syndrome.
2. Critical aortic stenosis.
3. Significant coarctation of the aorta or aortic interruption.

#### Preoperative Stabilization and Transport<sup>3,5,6,8,14,15</sup>

In all three instances, adequate stabilization prior to intervention or surgery is crucial. Stabilization is accomplished by assisted ventilation if required, since a number of these babies present in extremis. Early commencement of prostaglandin E1 infusion is also recommended to open the ductus to ensure reasonable systemic perfusion. Most of these babies at presentation are severely acidotic and hypoglycemic due to impaired peripheral perfusion. *Aggressive correction of hypoglycemia, intravascular hypovolemia and inotropic support may also be warranted. Appropriate stabilization often leads to correction or improvement of severe metabolic and lactic acidosis.*

#### Case Study 2

A term neonate presented on day 5 in a shock like state with MOFS (SGOT 6000 IU, SGPT 5200 IU, BUN 120 mg/dl, creatinine 3.5 mg/dl). Echo revealed critical coarctation. He was ventilated, inotropes commenced, PGE1 instituted with establishment of ductal flow on echo, and dialysis instituted. *Despite all these heroic*

*measures the baby could not be stabilized adequately for surgery and succumbed to severe multiorgan failure and ischemic enteropathy.* This case study reiterates the need for timely transfer.

#### Case Study 3

A term 30 day old neonate presented with severe respiratory distress and in circulatory shock but without organ dysfunction. He was intubated, ventilated and stabilized. Echo revealed critical aortic stenosis with severe left ventricular dysfunction (LVEF 10%). He underwent a successful emergency balloon aortic valvotomy with relief of critical aortic stenosis. He was successfully discharged 4 days later with a normal ventricular function.

In the case of hypoplastic heart syndrome, the option of palliative therapy must also be offered to the family in light of the dismal future prognosis. However, in the other two instances, non-surgical and surgical options today are available with acceptable immediate and long-term outcomes.

Thus, in summary, *neonates with duct dependant lesions like, dTGA pulmonary atresia or interrupted aortic arch are best transported under cover of a prostaglandin infusion (PGE1), especially if systemic oxygen saturation is low. A doctor familiar with neonatal resuscitation must accompany the neonate if a prostaglandin infusion is on, as apnea is a known complication with PGE1 infusion. However, it is only likely to occur with higher doses, and occurs soon after starting of the infusion. It is tempting to start high flow oxygen in a cyanosed neonate, however, oxygen may precipitate duct closure in a duct dependant lesion leading to worsening of the cyanosis or sudden collapse. Thus, it is important not to target for saturations greater than 80-85%.*<sup>6,8</sup>

### TAPVC

Many of these babies, especially those with obstructed TAPVC are very sick at the time of presentation and often need a brief period of medical stabilization prior to surgery. Intubation, ventilation with 100 percent oxygen, correction of metabolic acidosis and inotropic support all favorably impact surgical outcome. Currently, the survival of neonates operated for TAPVC is greater than 95 % in most Indian units.<sup>2</sup>

### Cardiac Failure (Large L-R Shunts, Pulmonary Overcirculation)

Once cardiac failure is diagnosed, these babies may be started on digoxin (currently contentious), a diuretic usually frusemide, and afterload reduction with

captopril or enalapril. The ACE inhibitor's help decrease the ratio of systemic vascular resistance to pulmonary vascular resistance thereby decreasing left to right shunting and pulmonary blood flow. These babies also need nutritional support, timely immunization and protection against RSV and other respiratory viruses to avoid a vicious circle of frequent respiratory infections, failure to thrive and more frequent infections.

Not infrequently, these babies may present with severe cardiac failure and secondary cardiogenic shock especially if there is a co-existent viral or bacterial infection as a trigger. Then, they need a period of aggressive medical stabilization including noninvasive or invasive ventilation and inotrope therapy until the acute event resolves. Once such an episode occurs, these babies need to be evaluated by a specialized pediatric cardiac team to further define a management strategy.<sup>3,6,8</sup>

### Arteriovenous Malformations

These neonates are often very sick present during the first couple of days of life in a state of high output cardiac failure and circulatory collapse. They often need a period of medical stabilization prior to either surgery or coil embolization. This usually involves intubation, ventilation and the use of high dose inotropes. Occasionally, preload regulation with nitroglycerine infusions are also helpful.<sup>3,6,8,16</sup>

### KEY POINTS TO PONDER

Thus to conclude, today a medical or surgical option with a satisfactory immediate and long-term outcome, can be offered to most babies with a structural heart defect even in our country.<sup>2,4</sup> However, prompt recognition of a neonate with a cardiac problem, immediate stabilization and early referral are crucial for a reasonable outcome. For purposes of clinical approach and subsequent management, it is useful for the pediatrician to identify a baby with an "urgent heart disease" as opposed to a baby with a "nonurgent heart disease". This approach also helps to demystify congenital heart disease in a neonate—which is often "perceived as an overwhelming difficulty" with no easy solution in sight.

An attempt has been made to lay down guidelines to stabilize sick neonates with suspected heart disease prior to "life saving catheter or surgical interventions". It is reiterated that prompt recognition by the primary caregiver who is usually a pediatrician or a neonatologist, early stabilization and timely referral, however, are crucial to an optimal outcome.

Progressive improvement in neonatal cardiac care in our country has resulted in "dramatic and almost

unbelievable outcomes" after neonatal cardiac interventions and surgery. Today, neonatal cardiac surgery with ~95% early survival is feasible in some of the cardiac centers in our country who work closely with pediatric and neonatal units.<sup>2,4,10</sup> It is expected that with time and the concerted and untiring efforts of pediatricians, neonatologists and cardiac units throughout the country that these outcomes will be achieved in many more cardiac centers across India.

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## INTRODUCTION

With the advent of neonatal intensive care, an increasing number of preterm babies develop renal insufficiency. Neonatal intensive care has changed the renal failure scenario over the years. Earlier, newborns used to present with renal failure as the only dysfunction. Nowadays renal failure is often seen in the setting of multiorgan dysfunction in a very sick neonate in the ICU. Another special setting is a neonate with renal failure following major surgery (e.g. cardiac surgery).

In the recent years, there have been many new developments in the field of acute renal failure presently known as acute kidney injury (AKI). A concerted effort has been made to standardize its definition and classification. There have been newer insights in understanding its molecular pathogenesis particularly in the ICU setting. Many tools and therapies which seem promising are being developed to improve the diagnosis and outcomes of acute kidney injury<sup>1</sup>, and this article aims to summarize them.

## PHYSIOLOGY

During fetal life the placenta performs all excretory functions and renal function is not mandatory for fetal survival. Renal function is low in the fetus and urine formation is needed only to maintain amniotic fluid volume which in turn is needed for lung development. Renal development starts by 5 weeks and though there is a full complement of nephrons by 36 weeks of gestation, the kidneys are immature at birth. The most important physiologic change during transition to the extrauterine life is reduction in renal vascular resistance and increase in renal blood flow (2-3 to 20% of cardiac output). GFR which is around 15-25 ml/min/1.73 m<sup>2</sup> at birth in a term baby doubles at one month and reaches adult values at one year of age. The tubules are limited in their diluting and concentrating ability and also in acidification. Hence any insult in the perinatal period may cause significant hemodynamic derangement leading to pre-renal azotemia which may

progress to intrinsic failure if severe or prolonged. Also because of nephron immaturity there may be more profound fluid and electrolyte disturbances.<sup>2</sup>

## DEFINITIONS OF AKI

After Homer Smith first coined the term acute renal failure in 1951, there have been at least 30 definitions of acute renal failure in literature.

Recently, a group of international experts (comprising nephrologists and intensivists) have developed a broad consensus on new definitions and terminology for acute renal failure. First known as the Acute Dialysis Quality Initiative (ADQI) and later as the Acute Kidney Injury Network (AKIN), this group has proposed the term 'acute kidney injury (AKI)' to redefine the entire spectrum of acute renal dysfunction, encompassing early and mild forms to severe forms requiring renal-replacement therapy.<sup>1</sup> This terminology will be used in this review.

## DEFINITION

Classically AKI is defined as abrupt onset (within hours to days) and prolonged renal dysfunction which is most often reversible. Older definitions included urine output less than 1 ml/kg/hour lasting more than 24 hours and/or serum creatinine above 1 mg/dl or blood urea above 40 mg/dL.<sup>3</sup> Another definition which considers gestational age is: oliguria (< 1 ml/kg/hour) and/or serum creatinine above the 95th percentile for that gestational age (Table 59.1).<sup>4</sup>

Modification of RIFLE criteria for children (pRIFLE)<sup>5</sup> and AKIN<sup>6</sup> criteria (Table 59.2) can be applied to children but have not been adapted to or studied in neonatal populations.

At present the diagnosis of AKI relies on two functional abnormalities: changes in serum creatinine [marker of glomerular filtration rate] and oliguria. Both are late consequences of injury. The ideal marker to detect AKI should be up-regulated shortly after an injury and be independent of GFR level. Currently no

**Table 59.1: Mean (95th percentile) serum creatinine (mg/dL) levels in term and preterm infants<sup>4</sup>**

Age (days)	< 28 wk	29-32 wk	33-36 wk	> 36 wk
7	0.95 (1.31)	0.94 (1.40)	0.77 (1.25)	0.56 (0.96)
14	0.81 (1.17)	0.78 (1.14)	0.62 (1.02)	0.43 (0.65)
28	0.66 (0.94)	0.59 (0.97)	0.40 (0.68)	0.34 (0.54)

**Table 59.2: AKIN and pRIFLE criteria**

Stage	Serum Creatinine	Adult AKIN* Urine output	Class	Pediatric pRIFLE** eCCI by Schwartz formula	Urine output
I	↑ SCr > 0.3 mg/dl or ↑ SCr >150–200% from baseline	< 0.5 ml/kg / hr × 6 hr	Risk	decrease by 25%	< 0.5 ml/kg per hr × 8 hr
II	↑ SCr to > 200-300%	< 0.5 ml/kg / hr > 12 hr	Injury	decrease by 50%	< 0.5 ml/kg/ hr ×16 hr
III	↑ SCr of > 300% from baseline or SCr > 4.0 mg/dL with an acute rise of at least 0.5 mg/dL	< 0.3 ml/kg / hr > 24 hr or anuria for > 12 hr	Failure	decrease by 75% or < 35 ml/min / 1.73 m <sup>2</sup> body surface area	< 0.3 ml/kg/ hr for 24 hr or anuric for 12 hr
			Loss ESRD	Failure > 4 weeks Failure > 3 months	

\*AKIN classification: an abrupt (within 48 h) reduction in kidney function required

\*\* pRIFLE staging: R, I and F represent increasing stages of AKI, ESRD: End stage renal disease

such marker is available in clinical practice. Serum creatinine is the most common method used to monitor renal function and to diagnose AKI, but has significant fallacies. Serum creatinine concentrations does not change until 50% of kidney function has been lost and it may take days before a significant rise is seen. At lower GFR, serum creatinine will overestimate renal function due to tubular secretion of creatinine. Creatinine is dialyzable and can no longer be used to assess kidney function after starting dialysis. One should also bear in mind that in the first 48-72 hours, neonatal serum creatinine may represent the maternal value.

Thus there is a need for creation of AKI definitions using early injury biomarkers which can ultimately predict morbidity and mortality. Until then our ability to recognize neonates with AKI early will be difficult.

## INCIDENCE

# 6

The incidence of acute kidney injury in the neonate has been found to be 10-30 percent in various studies and mortality rates are between 10% and 61%.<sup>7,8</sup> This

may be an underestimate as many non-oliguric forms (which constitute up to 50 % in some settings) of acute kidney injury may be missed. In addition, most studies that describe neonatal AKI use high levels of serum creatinine or need for dialysis to define AKI, which may miss a significant number of infants.<sup>9</sup> Our understanding of the epidemiology of neonatal AKI is based on small single center studies that usually focus on a subset (asphyxiated neonates,<sup>10,11</sup> those with sepsis,<sup>12</sup> postcardiac surgery etc) of the neonatal population. It should also be remembered that chronic kidney disease may present acutely in the newborn period (e.g. posterior urethral valves or dysplastic kidneys). But any renal dysfunction in the newborn is considered acute and reversible until proven otherwise.

## CAUSES OF NEONATAL AKI

Most neonates have prerenal kidney injury due to hypoperfusion of the kidneys (Table 59.3). The commonest causes of kidney injury are asphyxia, sepsis and respiratory distress syndrome (RDS). Most patients with prerenal injury have oliguria. Severe or prolonged renal hypoperfusion can cause acute tubular necrosis

**Table 59.3: Causes of kidney injury****1. Prerenal**

*Hypovolemia*—hemorrhage, dehydration, sepsis, necrotizing enterocolitis

*Hypoperfusion*—hypoxia / asphyxia, hypotension, RDS, cardiac failure, post-cardiac surgery, positive pressure ventilation

*Increased renal vascular resistance*—polycythemia, indomethacin, adrenergic drugs, (e.g. tolazoline)

**2. Renal**

*Congenital*—Bilateral renal dysplasia, renal agenesis, multicystic or polycystic kidneys, congenital nephrotic syndrome

*Acquired*—Intravascular coagulation, renal arterial or venous thrombosis, cortical/medullary necrosis following sustained hypoperfusion

*Ischemic*—shock, dehydration, hypotension, hypoxia

*Nephrotoxic*—aminoglycosides, methicillin, hemoglobin, myoglobin, bilirubin, contrast media

*Miscellaneous*—acidosis, hyperuricemia, polycythemia, pyelonephritis

**3. Postrenal causes**

*Congenital obstructive uropathy*: PUV, ureterocele, megaureter, PUJ obstruction, urethral diverticulum or stricture, neurogenic bladder, extrinsic tumor

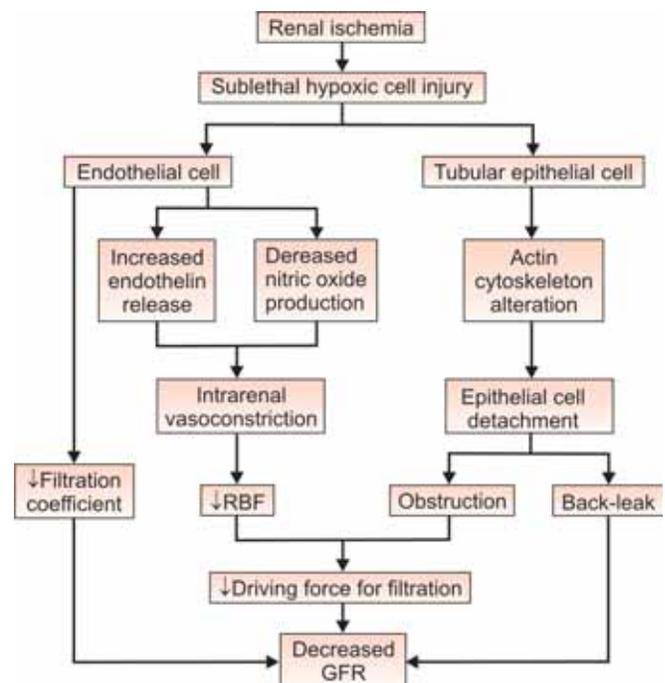
(ATN) or cortical necrosis and intrinsic kidney injury. Intrinsic kidney injury may also be due to drugs or toxins and structural renal defects. ATN in septic shock is due to systemic and regional hemodynamic alterations causing decreased renal perfusion and also cellular injury due to oxidative stress caused by inflammatory cytokines. Toxic ATN is commonly caused by antibiotics (especially aminoglycosides) or radiocontrast agents.<sup>2,7</sup> In neonates with RDS renal vascular resistance remains high and there is reduced plasma flow with low GFR. Mechanical ventilation in such babies causes further hypoperfusion by decreasing venous return and cardiac output. The kidneys recover at par with the improvement in lung function. Cardiac surgery and other major surgeries done in the neonate predispose to AKI. In the ICU setting, neonates receive a number of inotropes at maximal doses which by themselves might cause renal vasoconstriction leading to acute kidney injury.

Postrenal failure occurs from obstruction of the urinary tract. Oligohydramnios indicates renal agenesis, dysplastic kidneys, urethral obstruction or bilateral upper tract obstruction. At the present time most of the structural anomalies are diagnosed antenatally as ultrasound examination of pregnant woman has become very common.

**PATHOPHYSIOLOGY OF ATN**

The pathophysiology of ATN is schematically depicted in Flow chart 59.1.

When there is renal ischemia, there is a redistribution of blood supply from cortex to medulla, which even under normal conditions has very low oxygen supply. When ischemia is prolonged ATN sets in. The straight segment of the proximal tubule and medullary thick ascending limb bear the brunt of the damage. Endothelial cell ischemia liberates vasoconstrictors leading to intrarenal vasoconstriction and decreased renal blood flow reducing the GFR. Angiotensin II and other agents cause mesangial cell contraction thus reducing the filtration surface and filtration coefficient. In the tubular cells, there is actin cytoskeletal disruption leading to loss of cell polarity. The integrin molecules which attach the tubular cell to the basement membrane and are normally restricted to basolateral membrane move to the apical domains thus allowing detachment of cells. In the lumen, cells attach to each other and other intact tubular cells leading to cast formation that obstruct the tubules. Tubular obstruction increases intratubular pressure leading to back leak of filtrate through the denuded basement membrane. Back leak also causes interstitial edema which may compress the peritubular capillaries and the tubules. The

**Flow chart 59.1: Mechanism of development of acute tubular necrosis**

histologic changes are diffuse thinning of the tubular brush border and patchy loss of tubular cells leaving the basement membrane denuded. There are also tubular casts composed of proteins and cellular debris that obstruct the lumen of the distal nephron. The interstitium is edematous with an infiltrate of mononuclears, macrophages and occasional polymorphs. The lesions of ATN are patchy and essentially tubulointerstitial, the glomeruli being intact. In cortical necrosis there is complete loss of architecture with loss of glomeruli also.

AKI, by itself can cause dysfunction of many organ systems. In a nutshell, the dysmetabolism accompanying critical illness is exacerbated with coexistent AKI by loss of kidney homeostatic function.<sup>13,14</sup> Once established, these metabolic derangements, along with other potential pathways including endothelial dysfunction, interact with each other. The extent of interaction may be the decisive factor leading to recovery or death. These metabolic pathways represent potential therapeutic targets for improving outcomes.

### Phases of ATN

Clinically ATN has three phases: (i) Initiation phase lasting hours to days wherein the insult occurs, (ii) Maintenance phase lasting days to weeks where in (despite absence of the inciting agent) GFR remains low due to tubular dysfunction and tubuloglomerular feedback, and (iii) Recovery phase lasting few weeks where there is tubule cell regeneration and remodeling. In this stage usually diuresis occurs first followed by normalization of serum creatinine.

### CLINICAL APPROACH

Diagnosis and management go hand in hand and should proceed together. Two questions need to be answered while managing neonatal ARF:

1. Was the baby born with a normal urinary tract?
2. Is the renal perfusion all right?

### History

Family history of consanguinity or renal disease may give a clue to the underlying renal disorder. Maternal illnesses (infections, severe PIH), exposure to drugs and toxins is important. Non-steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors can cause fetal renal shut down when taken during pregnancy. In presence of oligohydramnios, the fetus should be evaluated for renal agenesis, dysplasia or obstructive uropathy. Even if none is found these fetuses have to be followed after birth as they are at

risk of postnatal pulmonary dysfunction due to lung hypoplasia.

History of severe pregnancy induced hypertension, antepartum hemorrhage, prolonged labor, birth injury, birth asphyxia are to be enquired into. History of umbilical artery or vein catheterization may be a clue to renal vascular obstruction. History of abnormalities in micturition like poor stream or dribbling indicate the presence of posterior urethral valves. A review of the medications may reveal use of nephrotoxic drugs in the neonate.

### Physical Examination

#### *Look for Congenital Anomalies*

One should look for renal disorders if a neonate has dysmorphism or congenital anomalies. The well known Potters facies (flattened nose, wide set eyes with inner canthic folds and low set ears) is associated with renal agenesis. These neonates often present with respiratory distress due to hypoplastic lungs. Small deformed ears and preauricular pits may be associated with renal dysgenesis. Likewise a single umbilical artery may be associated with renal dysplasia or extrophy of bladder. Normally the kidneys may be just palpable but should not be large. Large kidneys may indicate autosomal recessive polycystic kidney disease or pelviureteric junction (PUJ) obstruction. A palpable bladder after voiding indicates lower urinary tract obstruction. External genitalia should be examined for anomalies and the spine for dysraphism.

#### *Assess Hydration Status*

Signs of dehydration should be looked for. Blood pressure should be monitored either non-invasively or with intra-arterial cannula. Avoid umbilical artery cannulation. Edema may be normally present in preterm babies. Recent onset edema may indicate fluid overload or hypoproteinemia. Cardiomegaly, pulmonary congestion and large liver indicate fluid overload. Central venous pressure monitoring may be necessary in the very sick neonate.

Daily weight recording with a sensitive balance and meticulous urine output monitoring go a long way in assessing hydration status. Weighing of diapers is not adequate and perineal urinary bags or catheterization is necessary for monitoring urine output. Monitoring urine output is the easiest method of recognizing oliguric renal failure early.

Signs of sepsis should be looked for and also involvement of other organs especially if the baby had many interventions or had major surgery.

## Laboratory Evaluation

Renal function test must be interpreted in relation to gestational and postnatal age. Normal urine output after the first few days is 1-3 ml/kg/hour. Less than 1 ml/kg/hour is oliguria whereas more than 3 ml/kg/hour constitutes polyuria.

Urine testing including physical and biochemical examination and microscopy is useful. In ATN some protein and many renal tubular epithelial cells and few pus cells are seen. Predominant pyuria represents urinary tract infection. Presence of many red blood cells suggests renal artery or venous thrombosis.

Urinary/plasma indices are to be done before use of a diuretic and are given in Table 59.4. In prerenal state, the kidneys conserve sodium and water and urinary sodium is low and osmolality high. In ATN, there is increased sodium excretion in dilute urine (due to loss of concentrating ability). The indices of post-renal causes mimic those of ATN.

Blood sugar, blood urea nitrogen, serum creatinine, serum electrolytes, serum bicarbonate, serum calcium and serum phosphate have to be done and monitored regularly.

An ultrasound scan of the abdomen is a must to rule out congenital anomalies and postrenal causes and is essential in every neonate, even though pre-renal and renal factors are evident. The kidneys are normal in size or enlarged in ATN and pyelonephritis. Renal vascular thromboses can be delineated with Doppler studies.

Novel urinary biomarkers that can diagnose AKI within hours of an insult have been discovered. The original experience with these biomarkers occurred in neonates who required cardiopulmonary bypass surgery. These biomarkers will change our approach

to the diagnosis AKI and, hopefully, lead to better preventive and therapeutic interventions which will improve outcomes.<sup>15,16</sup>

Biomarkers are being explored to detect AKI early, to differentiate between the different causes and for prognostication. Currently, the most promising early non-invasive biomarkers of AKI are serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin-18 (IL-18),<sup>17</sup> kidney injury molecule-1 (KIM-1),<sup>18,19</sup> and serum cystatin C.

NGAL is the most strikingly up-regulated and over-expressed protein in the ischemic kidney. Serum and urinary levels are elevated in human models of AKI, including neonates undergoing cardiopulmonary bypass surgery and in a heterogeneous critically ill pediatric population. Lavery et al looked at baseline urinary NGAL in 20 premature infants (divided into four birth weight categories) and found that levels inversely correlated with both birth weight and gestational age. The wide baseline ranges narrowed over the course of 2 weeks, likely due to ongoing renal development.<sup>20</sup> This finding may be present for other biomarkers. Thus, one of the challenges in finding neonatal AKI biomarkers will be to account for the changes in renal development.

## MANAGEMENT

### Prerenal Kidney Injury

Neonates on restricted fluids for associated birth asphyxia, RDS, PDA, etc. are at increased risk of renal failure. If the neonate does not look volume overloaded and prerenal failure is suspected the first step is to give a fluid challenge of 20 ml/kg isotonic saline over 30 minutes. This should increase the urine output in such neonates. If not, one or two more challenges can be given followed by 1-2 mg/kg of intravenous furosemide. If there is no response to above measures, the neonate is presumed to have developed ATN and treated as below.<sup>21,22</sup>

### Intrinsic Kidney Injury (Acute Tubular Necrosis)

#### Maintenance of Fluid and Electrolyte Balance

Fluids (oral and intravenous) are restricted to insensible loss (40-50 ml/kg/day or 400 ml/square meter body surface) plus urine output. Of the insensible losses 1/3 is respiratory loss, which will not be present if the baby is ventilated with a humidifier. If the baby is nursed under a warmer fluid, requirement may increase by at least 20 ml/kg, and by a similar amount if the neonate is receiving phototherapy.

**Table 59.4: Urinary plasma indices in neonates with oliguria<sup>2</sup>**

Parameter	Acute prerenal failure	Intrinsic renal failure
Uosmo	> 400	< 400
Urine Na	< 40	> 40
U/P urea	> 20	< 10
U/P OSM	> 2	< 1
FeNa <sup>#</sup>	< 2	> 3
RFI	<1.5	> 6

# FeNa may be physiologically as high as 5% in extreme preterm babies

$$\text{FeNa (\%)} = \frac{\text{U Na}}{\text{P Na}} \times \frac{\text{Pcr}}{\text{Ucr}} \times 100 \quad \text{RFI} = \frac{\text{U Na} \times \text{Pcr}}{\text{U creatinine}}$$

**Type of fluid:** Once the diagnosis of intrinsic kidney injury is established the neonate is put on potassium free intravenous fluids, usually 10 percent dextrose. The concentration of dextrose is adjusted so as to prevent hypoglycemia. Maintenance sodium (2-3 mEq/kg/day) is added to the fluid.

**Electrolyte imbalance:** Hyperkalemia ( $K^+ > 6$  mEq/L) is managed with slow intravenous bolus of 10 percent calcium gluconate 1-2 ml/kg under ECG monitoring, followed by 1-2 ml/kg of sodium bicarbonate over 5-10 min. A glucose-insulin infusion is begun with a bolus of regular (plain) insulin 0.05 units/kg with 2 ml/kg of 10 percent dextrose; followed by an infusion of 10 percent dextrose at 2-4 ml/kg/hour and regular insulin 10 units/100 ml at 1 ml/hour (1 unit regular insulin for every 3-5 grams of glucose). Nebulized salbutamol can also be used. Kayexalate (ion exchange resin) given rectally as a retention enema at 1 g/kg dissolved in normal saline is very useful. Furosemide 1 mg/kg is given once renal function is adequate.

Hyponatremia can be corrected with hypertonic saline (1.6 to 3.0%) if the neonate is symptomatic with seizures. Otherwise fluid restriction is the ideal treatment as hyponatremia is due to excess free water. Hypernatremia will require 1/4 to 1/5 normal saline or dextrose solutions given in a graded manner in order to bring down the serum sodium gradually. However, peritoneal dialysis is often a better option for severe degrees of hypernatremia.

**Acidosis:** It is important to improve hemodynamic status and tissue perfusion which itself will ameliorate acidosis. The requirement of sodium bicarbonate is calculated by the formula- Base deficit  $\times 0.3 \times$  body weight and infused slowly over 4-6 hours with an aim to correct serum bicarbonate to 15-17 mEq/L.

**Calcium/phosphate abnormalities:** Hyperphosphatemia is seen especially in catabolic states. It can be corrected with oral phosphate binders (aluminum hydroxide or calcium carbonate) given with feeds and dialysis. Hypocalcemia is corrected with intravenous 10 percent calcium gluconate, particularly if the ionized calcium level is low. Care needs to be taken to prevent high calcium  $\times$  phosphate product which may cause metastatic calcifications. In chronic renal failure one also needs to provide 1,25 dihydroxy vitamin D or its analog.

### Dialysis Therapy

This is required when conservative measures are not enough. Dialysis is needed early in hypercatabolic

patients, (e.g. neonates with sepsis, post surgery, rhabdomyolysis).<sup>21,22,24</sup> The indications for dialysis include volume overload, anuria more than 48 hours (12 hours in critically ill), intractable hyperkalemia, intractable acidosis and progressive uremia.

**Peritoneal dialysis:** Conventionally peritoneal dialysis (PD) has been used in neonates. This is because of the ease of performing it. Peritoneal dialysis does not require vascular access, specialized dialysis machines, other equipment and skilled personnel.

A rigid catheter (Peritocath) is introduced over a stylet or flexible catheter (Cooke's) is introduced over a guide wire (Seldinger technique) into the peritoneal cavity. If one does not have small sized catheters, even a large IV cannula or a small intercostal drainage tube can be used for peritoneal dialysis. Standard peritoneal dialysis fluid (dextrose 1.7%; lactate based) at 25-30 ml/kg/cycle is put in and after a dwell time of 30-40 minutes is drained out. One can increase the concentration of glucose in the PD fluid to a maximum of 4.25 percent to achieve more ultrafiltration. After 10-15 cycles it is usual to add 1-2 mEq of potassium chloride to each liter of PD fluid to prevent hypokalemia. Heparin 500-1000 units per liter is added if there are fibrin clots which tend to block the PD catheter. Systemic heparinization does not occur as the heparin is not absorbed. Common problems with PD are inadequate drainage, fluid leak, bleeding, rarely perforation of an abdominal viscus and peritonitis. The procedure is done in hourly cycles for 48-72 hours. If continued longer the chances of peritonitis are high. Peritoneal dialysis can be repeated after 48-72 hours. Flexible catheters can be capped and left *in situ* whereas rigid catheters have to be replaced each time. If it is anticipated that the neonate will require dialysis for a prolonged period, a permanent cuffed Tenckhoff's catheter can be placed surgically. A cycler machine which does the exchanges automatically can be used to avoid frequent handling of the circuit (connections and disconnections), and consequent increased risk of infection.

### HEMOFILTRATION AND HEMODIALYSIS

If PD does not work or is not suitable (as in hypercatabolic state and post abdominal surgery) continuous renal replacement therapies, namely, continuous arteriovenous hemofiltration and continuous venovenous hemofiltration (CAVH/CVVH) or conventional hemodialysis (HD) are used. CAVH (Continuous arteriovenous hemofiltration) and CVVH (Continuous venovenous hemofiltration) done continuously over 48-72 hours are suitable for hemodynamically unstable neonates. CAVH entails placements of arterial catheter but does not require any

blood pump whereas CVVH requires venous catheters and a blood pump. Blood passes through a synthetic semipermeable filter which removes the solutes as an ultrafiltrate. The filtered blood is returned to the neonate with continuous replacement of needed volume with isotonic fluids. Better urea clearances can be obtained by running dialysis fluid through the dialysate chamber when the procedure is termed CAVHD (continuous arteriovenous hemodiafiltration) or CVVHD (continuous venovenous hemodiafiltration). The cost of the hemofilter limits its widespread use in our country.

*Conventional hemodialysis:* Conventional hemodialysis can be done in stable larger infants. It is performed over 3-4 hours, but requires a larger extracorporeal circuit and is not suitable for neonates with hemodynamic instability. Here solute exchange occurs by diffusion. Hemofiltration and hemodialysis require systemic heparinization and carry a risk of hemorrhagic complications.

#### BIOARTIFICIAL KIDNEY AND BIOENGINEERED MEMBRANES IN AKI

Current dialysis modalities removes waste products and corrects fluid/electrolyte imbalance, but does not perform the absorptive, metabolic, endocrine, and immunologic functions of normal renal tubule cells. Renal assist device (RAD) is an extracorporeal device fabricated with a standard hemofiltration cartridge containing approximately  $0.5$  to  $1.0 \times 10^8$  non-autologous human renal tubule cells grown along the inner surface of the hollow fibers. Early clinical studies of this device to provide renal cell therapy have demonstrated that these cells retain transport, metabolic, and endocrinologic activities.<sup>27</sup>

#### Nutrition

Maintenance of nutrition is a very important component of care of the sick neonate. Adequate calories (100 calories/kg) and protein (0.8 g/kg) should be given to promote growth and prevent protein catabolism. Expressed breast milk is still the best form of nutrition if the neonate can tolerate feeds. Parenteral nutrition may be needed if oral feeds are contraindicated or the neonate is very catabolic.

#### DRUGS IN RENAL FAILURE

Drug dosing needs to be modified in the presence of renal failure. Nephrotoxic drugs should be avoided. High dose furosemide has been used in early stage of ATN where it may convert oliguric form into non-

oliguric variety which is easier to manage. Furosemide given during the maintenance phase of ARF by resting the medullary thick ascending limb, may hasten recovery.<sup>23</sup> Overall, the benefits of diuretics in the management of incipient or established fluid overload in patients with oliguric and non-oliguric renal failure are limited.<sup>24</sup> Low dose dopamine (1-3 microgram/kg/minute) has been extensively used in management of ARF but is not proven to be beneficial. The use of mannitol as an osmotic diuretic is not recommended as it might result in sudden increase in serum osmolality with the risk of intraventricular hemorrhage and also cause volume overload.

#### RECENT TRENDS IN ARF THERAPY

Atrial natriuretic peptide (ANP) which inhibits sodium and water reabsorption in the distal tubule and maintains GFR by causing afferent arterial dilatation with efferent arteriolar constriction has been used in ARF. Though it has helped in increasing urine output it has had no impact on the overall outcome.<sup>25</sup>

During recovery from ATN surviving tubular cells regenerate and multiply to cover denuded areas. Receptors for growth factors like insulin like growth factor (IGF-1), epidermal growth factor (EGF) and hepatocyte growth factor (HGF) have been found in the regenerating tubule cells and there may be a role for these to hasten recovery. These agents are still experimental and human studies are needed.<sup>26</sup>

Apoptosis of renal tubular cells is well recognized event in the pathophysiology of ischemic/toxic AKI. Various antiapoptotic agents like caspase inhibitors and cysteine proteinase inhibitors have been tried but it is seen that simply blocking apoptotic pathway is ineffective as the damaged cells may not function appropriately or eventually undergo necrotic cell death. Recent evidences suggest that erythropoietin (EPO) which acts like a "multifunctional cytokine" provides cytoprotection by ameliorating oxidative stress directly (hemeoxygenase-1 and glutathione peroxidase). In addition, EPO may act indirectly by inducing iron depletion thus inhibiting iron-dependent oxidative injury. Red blood cell increase due to EPO may also reduce cellular oxidative stress as they have substantial antioxidative enzymes. Experimental models of AKI show that EPO reduces tubular cell death and dysfunction induced by ischemia reperfusion injury.<sup>28</sup>

#### STEM CELL THERAPY IN AKI

Several types of renal stem cells that are able to differentiate into tubular cells have been isolated from

both adult kidney and bone marrow. Chen et al<sup>29</sup> have reported that local mesenchymal stem cells (MSCs) can differentiate into endothelial lineage and participate in renal repair through the production of vascular endothelial growth factor.

Recently pluripotent embryonic stem (ES) termed iPS cells have been induced from adult skin fibroblasts and may be candidates for the cell therapy of AKI.

With above encouraging experiments, it needs to be addressed whether regenerative medicine is truly useful and practical in the treatment of clinical AKI and, if so, which cell population is best suited for this purpose.

### MANAGEMENT OF THE DIURETIC PHASE

Management of the diuretic phase is seldom given importance. Many neonates will have an intense diuresis, loose fluids and electrolytes and may become dehydrated. Intravenous supplementation will be necessary as oral intake may not suffice. Monitoring of fluid and electrolyte balance needs to continue diligently through this phase.

### PROGNOSIS

Prognosis depends on the cause of renal dysfunction. Pre-renal failure is almost always reversible. Intrinsic renal failure with multiorgan dysfunction carries a high mortality. Most babies with ATN usually recover completely. Those with cortical necrosis will be left with some degree of renal insufficiency. Often, even in those who normalize their serum creatinine, permanent concentrating and acidifying defects may be seen.

Various studies have shown that if renal failure alone is present, mortality is less than 20 percent. With involvement of more than 4 organs, mortality increases to more than 80 percent. Non-oliguric patients have a marginally better prognosis than oliguric patients and are easier to manage.<sup>2,7,12</sup>

### CONCLUSION

Acute kidney injury in the newborn is a common neonatal emergency often seen in the setting of multi-organ failure. Pre-renal and intrinsic kidney injury are the common causes though post-renal causes need to be excluded in every case. The management depends on removing the precipitating cause, maintaining fluid and electrolyte balance and initiating dialysis when required. The survival depends on associated multi-organ dysfunction, while long-term renal insufficiency is rare after recovery (except in the preterm babies).

We hope that biomarkers of acute kidney injury will soon replace serum creatinine not only for early diagnosis but for predicting outcomes as well.

Newer treatment strategies like EPO, various antiapoptotic agents and stem cells have been found useful in experimental models and its clinical translation is yet to be verified.

Renal assist devices (tubule cell therapy) have now been tested in phase II clinical studies and the results have been very encouraging. Let us hope that stem cell therapy and regenerative medicine in acute kidney injury may soon become a “dream come true”.

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Thermal protection of the newborn is the series of measures taken at birth and during the neonatal period to ensure that the newborn does not become cold and maintains a normal body temperature of 36.5-37.5°C. Hypothermia is a common problem and it contributes to the high perinatal mortality rate seen in the developing world.<sup>1</sup> It was present in 58% neonates admitted to a tertiary referral neonatal unit and was associated with five fold increase in the risk of fatality.<sup>2</sup>

Hyperthermia mostly occurs in the neonate because of overheating. Infections in neonates often cause hypothermia rather than hyperthermia.

Newborns, especially low birth weight babies, are at increased risk of heat loss due to their unique characteristics such as a large body surface area in relation to weight, a large head in proportion to the body, and little subcutaneous fat. When heat loss exceeds the baby's ability to produce heat, the body temperature drops below the normal range causing hypothermia.

### MECHANISMS OF HEAT LOSS

The sources of heat loss in neonates is reviewed in detail by Knobel and Holditch-Davis.<sup>3</sup>

Neonates can lose heat by radiation, convection, evaporation and conduction. Heat loss through radiation is related to the temperature of the surfaces surrounding but not in direct contact with the infant. The newborn infant emits heat energy in the form of infrared electromagnetic waves. The loss or gain of this 'radiant' energy is proportional to the temperature difference between the skin and the radiating body. Heat may be lost by radiation from the infant's body to a nearby cold wall. Heat may be gained from a source of radiant energy, such as a heat lamp placed near the infant. Heat loss from radiation may be the most important route of heat transfer in infants older than 28 weeks of gestation.

Heat loss occurs by convection if the baby is exposed to draught of air. It depends on temperature of air flowing over the baby's skin and rapidity of flow. Heat

is transferred by convection when air currents carry heat away from the body surface. If the infant's body surface is warmer than the surrounding air (as is almost always the case in the delivery room), heat is first conducted into the air and then carried away by the convective air currents.

Heat loss or gain via conduction occurs through direct contact with a surface with a different temperature. Direct transfer of heat occurs from the newborn to this surface. Heat can be lost directly to a colder surface or gained from a warmer surface, such as a warming mattress. The heat loss is directly proportional to the temperature gradient between baby's skin and the contiguous object.

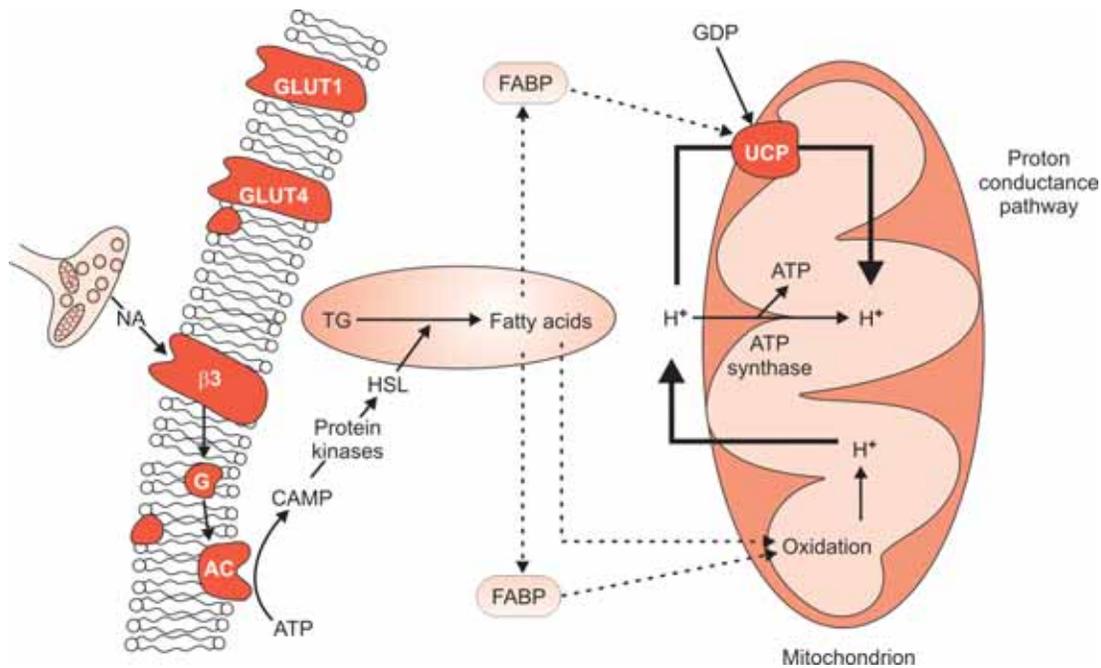
Evaporation occurs when water is lost from the skin. During evaporation, water is converted from liquid to gas, causing approximately 0.6 kcal of heat loss for every 1 g of water lost from the body.<sup>4</sup> In the extremely low birth weight (ELBW) infant, evaporative heat loss is the major form of heat loss during the first week of life. Transepidermal water loss in infants is inversely correlated with gestational age; infants born at 25 weeks gestation lose 15 times more water than term infants due to immature and thinner skin.<sup>5</sup> Heat loss by evaporation also occurs in neonates wet because of amniotic fluid, urine or bath water.

### RESPONSE TO COLD STRESS

*Behavioral response:* An older child will wake up and become restless when cold but the neonate may continue to sleep. However, cold stressed infants do tend to become sleepless, more active and assume flexed posture. This response is also seen in preterm infants.

*Physiological response:* Temperature sensors are present in skin (particularly on face), spinal cord and hypothalamus. Temperature information is processed in the hypothalamus. Norepinephrine (NE) is released in response to cold stress.

In newborn infants, non-shivering thermogenesis (oxidation of brown adipose tissue) is the major route

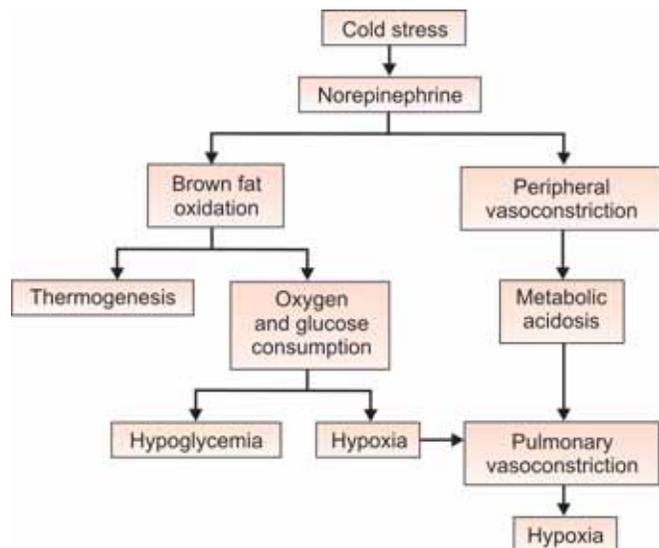


**Fig. 60.1:** A schematic presentation of thermogenesis in brown adipose tissue NA: noradrenaline,  $\beta_3$ :  $\beta_3$  adrenoceptors, G: G – binding proteins, AC: adenylyl cyclase, HSL: hormone-sensitive lipase, TG: triacylglycerols, FABP: fatty acid binding proteins, GDP: glucose biphosphate, UCP: uncoupling proteins

of a rapid increase of heat production in response to cold exposure. Brown fat is specialized unit of heat production and it is metabolically different from white fat. It is prominent in nuchal subcutaneous tissue, interscapular area, mediastinum, around kidney and along aorta. In neonate, brown fat constitutes 5% of body weight and can be identified by around 26 weeks gestational age. It contains a high concentration of stored triglycerides, a rich capillary network and is densely innervated with sympathetic nerve endings on the vessels and on each adipocyte. Each cell has numerous mitochondria with respiratory chain enzymes and the uncoupling protein that is the rate limiting enzyme in the process of heat production. When fat is oxidized heat is produced rather than energy rich phosphate bonds because of the uncoupling protein (Fig. 60.1). Blood flowing through brown fat becomes warm and circulates heat to other parts of body.

Norepinephrine released in response to cold stress acts directly on brown fat leading to non-shivering thermogenesis, increased oxygen consumption, peripheral vasoconstriction, metabolic acidosis, hypoglycemia and hypoxia (Flow chart 60.1). These are exaggerated in the preterm infant compared to the full-term infant. The preterm infant has less brown fat stores, poor vasomotor

**Flow chart 60.1:** Pathophysiology of hypothermia



response and less insulation to cope with a hypothermic event. Non-shivering thermogenesis is impaired in the first 12 hours, in sick babies following asphyxia, hypoxia and after sedative administration to mother.

## RISK FACTORS FOR HYPOTHERMIA

The newborn is most vulnerable to hypothermia during the first few hours after birth. It may occur later too, for example during bathing or transportation and if measures to keep the baby warm are inadequate. The following infants are at risk for cold stress:

- i. All infants within the first 12 hours of life.
- ii. Preterm infants and infants with intrauterine growth retardation.
- iii. Sick infants—birth asphyxia, hypoxia, hypoglycemia, sepsis, administration of sedatives to mother.
- iv. Infants with compromised integrity of skin—neural tube defects, omphalocele, gastroschisis or ichthyosis.
- v. Lack of awareness regarding thermal protection of the newborn among care givers.

A study on transported extramural hypothermic neonates found low birth weight, prematurity and presence of sickness to be associated with severe hypothermia.<sup>6</sup>

## SEVERITY OF HYPOTHERMIA: WHO CLASSIFICATION<sup>1</sup>

1. *Cold stress (mild hypothermia)*: The newborn with a temperature of 36.0-36.4°C is under cold stress (mild hypothermia) which should give rise to concern for the cause.
2. *Moderate hypothermia*: A baby with a temperature of 32.0-35.9°C has moderate hypothermia. It has been associated with danger to the neonate and warming is recommended.
3. *Severe hypothermia*: A temperature below 32°C is considered to be severe hypothermia.

It has been associated with grave outlook requiring urgent skilled care.

The site of measurement of temperature has not been specified in this classification. A study correlating the above classification with fatality found 39%, 51% and 80% fatality in mildly, moderately and severely hypothermic babies respectively.<sup>7</sup> Although the WHO classification is based solely on temperature of the newborn, sickness is a frequent association. Physiological derangements like hypoxia, hypoglycemia and shock set up a perpetuating cycle with hypothermia. Hence neonatal morbidities like birth asphyxia, sepsis and respiratory distress are important factors affecting the outcome in hypothermic neonates. The findings of a recent study suggest that the presence of birth weight <2000 grams, associated illness (perinatal asphyxia, sepsis and respiratory distress) and physiological derangements (hypoxia, hypoglycemia and shock) should be considered adverse factors. Their presence

should classify hypothermia in the next higher category of severity in WHO classification.<sup>7</sup>

## MEASURING OR ASSESSING THE NEWBORN'S TEMPERATURE

The sites for taking a baby's temperature include skin, axilla and rectum. Esophageal or tympanic membrane temperatures are impractical for general use.

*Tactile assessment* of temperature using the dorsum of examiner's hand can assess the newborn's temperature rapidly. It is a good screening method for assessment of temperature in hospital, at home and during transportation. If baby's palms and soles feel cold and the trunk is warm, it suggests cold stress. If periphery as well as trunk feels cold, the baby is hypothermic.

*Skin temperature using thermistor probe*: Skin temperature is usually measured with a thermistor probe taped to the skin over the liver/ in right hypochondrium. It provides continuous monitoring and is a good reflection of the core temperature as vasoconstriction does not occur in the abdominal skin.

*Measuring axillary and rectal temperatures*: A regular clinical thermometer that reads down to 35°C is good enough for routine checking of body temperature. If the level of mercury does not rise at all, it is an indication of moderate to severe hypothermia. Rewarming will be better guided by knowing the exact body temperature, and this can be done by using a low reading thermometer. Digital thermometers read down to 32°C, are widely available and measure body temperature in 60 seconds.

As a general rule, taking the axillary temperature is better than the rectal temperature because of safety, hygiene and ease. Taking the axillary temperature involves no risk to the infant and gives a good approximation of body core temperature. The clean thermometer should be placed high in the axilla, and the arm then held against the side of the baby for 3 to 5 minutes.

The rectal temperature is an accurate measure of the core temperature. However, rectal perforation is a serious complication with rectal thermometer. If taking the rectal temperature, the thermometer should be placed in the rectum to a maximum depth of 2 cm, where it should be held for at least three minutes. The baby should never be left alone with the thermometer in the rectum. Measurement of rectal temperature is not recommended for routine use in neonates.

## EFFECTS AND SIGNS OF HYPOTHERMIA

Prolonged hypothermia is linked to impaired growth<sup>8</sup> and may make the newborn more vulnerable to

infections.<sup>9</sup> Neonatal morbidities like perinatal asphyxia and sepsis frequently present with co existing hypothermia. Sick or low birth weight babies admitted to neonatal units with hypothermia are more likely to die than those admitted with normal temperatures.<sup>10</sup>

**Early signs:** An early sign of hypothermia is feet that are cold to the touch.<sup>11,12</sup> If hypothermia is allowed to continue, the skin becomes cold all over the body. The baby becomes less active, suckles poorly and has a weak cry.

**Late signs:** In severely hypothermic babies the face and extremities may develop a bright red color. Sclerema associated with reddening and edema—may occur on the back and limbs or over the whole body. The baby becomes lethargic and develops slow, shallow and irregular breathing and a slow heart beat. Hypoglycemia, metabolic acidosis, generalized internal bleeding (especially in the lungs) and respiratory distress may occur. Such a level of hypothermia is very dangerous and unless urgent measures are taken, the baby will die. However, all these signs are non-specific.

## MANAGEMENT OF HYPOTHERMIA IN HOSPITAL

The method used for rewarming depends on the severity of the hypothermia and the availability of staff and equipment.

All hypothermic babies may be rewarmed using the following methods:

- Radiant warmer:** It has become popular because it provides unimpeded access to neonates requiring intensive care. However, insensible water losses are large. Covering the infant with a plastic sheet or an acrylic shield can minimize this. Apneic spells do not occur during rewarming, as the air breathed is not warmed by the radiant warmer. For rewarming the baby, set the warmer temperature in the skin mode at 37°C (Flow chart 60.2).
- Incubator:** In a convectively heated incubator rewarming is done at set air temperature of 35-36°C. The heating of incubator air can be

controlled by a thermostat referenced to air temperature within the incubator or to infant skin temperature. Little data exists in selecting a single skin temperature as a control point in a servo-controlled system and any value between 35.5°C and 37°C could be defended. More apneic spells were observed in premature babies controlled to skin temperatures of 36.5°C as opposed to 36°C. Access to the baby is restricted.

- Warm room:** The temperature of the room should be 28-34°C (more if the baby is small or sick). This method of rewarming may not be suitable to the care providers and other larger neonates.
- Warm cot:** If a hot water bottle is used to heat the bed, it should be removed before the baby is put in.

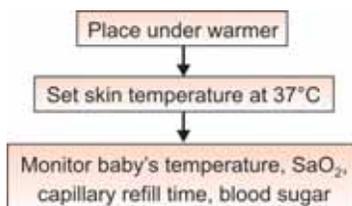
When a newborn is rewarmed in a warming device, its temperature as well as the temperature inside the device should be checked frequently. Once the baby's temperature reaches 34°C, the rewarming process in an air mode incubator should be closely monitored to avoid overheating.

## DURATION OF REWARMING

In cases of severe hypothermia fast rewarming is preferable to slow rewarming over several hours, as the latter is associated with high mortality.<sup>13-15</sup> Rewarming can be effectively achieved by using a servocontrolled open care radiant warmer in skin mode with skin temperature set at 37°C. Such equipment is now widely available in the health care facilities even at primary level. A study using this method estimated that the mean rewarming time required to reach normal abdominal skin temperature was 5 minutes, 17 minutes and 45 minutes for mild moderate and severe hypothermia respectively. The duration of rewarming did not differ significantly between the different weight and gestational age groups.<sup>7</sup>

In the absence of servocontrolled warming equipment with skin mode, an incubator or radiant warmer, with the air temperature set at 35-36°C or thermostatically-controlled heated mattress set at 37-38°C can also be used. However frequent adjustment of the set air temperature and monitoring of baby's temperature would be required to avoid over warming.

**Flow chart 60.2:** Rewarming with a radiant warmer



## Supportive Management

- Prevention of hypoglycemia:** Provide adequate fluids for age and sufficient glucose to prevent a drop in the blood glucose level which is a common problem in hypothermic infants. If hypoglycemia is detected then

treat it as per the protocols for treating neonatal hypoglycemia.

- b. *Maintaining perfusion:* If perfusion is poor give an intravenous bolus of Ringer lactate or normal saline (20 ml/kg) infused over 20-30 minutes.
- c. *Maintaining oxygenation:* Provide oxygen if baby is cyanosed or has a low oxygen tension on arterial blood gas. Pulse oximetry may provide fallaciously low values in hypothermic babies.
- d. *Monitoring for apnea:* Since some infants may develop apnea during rewarming; an infant should be carefully observed during rewarming.

### KANGAROO MOTHER CARE

Kangaroo mother care (KMC) is a method to meet baby's need for warmth. It is initiated in hospital and can be continued at home. It can be used to rewarm a baby with mild hypothermia. For best effect, the room should be warm (at least 25°C), the naked baby should be placed in skin-to-skin contact between the mother's breasts and both the mother and baby must be wrapped with shawl. The baby's head should be covered by a cap. Wet clothes should be replaced by dry pre-warmed clothes. There should be no draught of air. The rewarming process should be continued until the baby's temperature reaches the normal range or the baby's feet are no longer cold.

### MANAGEMENT AT HOME

Clothing has been shown to reduce the environmental temperature requirement by 4 to 8° C in low birth weight babies (Fig. 60.2).<sup>16</sup>

Warm room at 28-34° C can keep low birth weight babies warm. If hot water bottles are used to warm a cot, they should be removed before the baby is put in as they can be dangerous. They may easily cause burns,

as the blood circulation in the cold skin of babies is poor. The mother should continue breastfeeding as it helps in thermoregulation. While being transported, the baby should be in skin-to-skin contact with the mother or an adult during transportation.

### WARM CHAIN

The "warm chain" is a set of interlinked procedures to be taken at birth and during next few hours and in order to minimize heat loss in all newborns. Failure to implement any one of these procedures will break the chain and put the newborn infant at the risk of getting cold. The steps of warm chain are (1) warm delivery room, (2) immediate drying, (3) skin-to-skin contact, (4) breastfeeding, (5) bathing and weighing postponed, (6) appropriate clothing/bedding, (7) mother and baby together, (8) warm transportation, (9) warm resuscitation, (10) training and awareness raising.

### HYPERTHERMIA

Hyperthermia can be defined as a rectal temperature greater than 37.5°C. It may be important to distinguish between external sources of heat gain versus an actual febrile state. In a febrile state there is peripheral vasoconstriction associated with a higher abdominal skin temperature than the distal temperature of the foot. In the presence of overheating, the opposite would occur. Overheating is less common than accidental hypothermia in the newborn.

### PHYSIOLOGICAL RESPONSE TO HYPERTHERMIA

Infants in febrile state have hypothalamic dysfunction (raised set point temperature) leading to fever. A febrile infant behaves as if cold and makes physiological and behavioral responses which reduce heat loss, increase

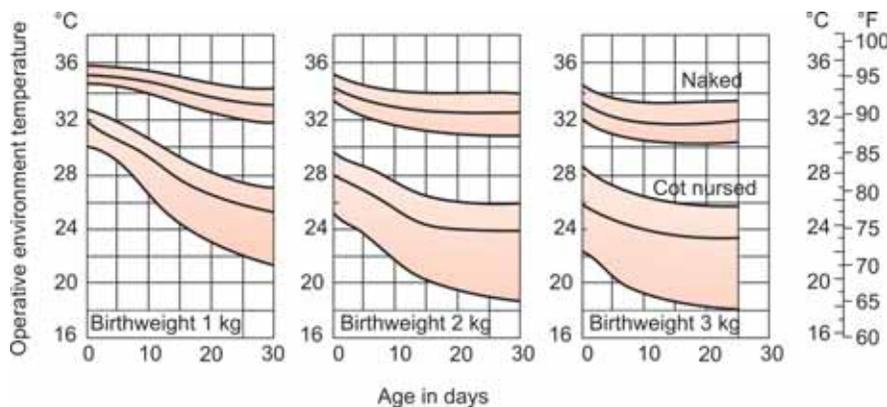


Fig. 60.2: Thermoneutral range for clothed and naked babies<sup>16</sup>

heat production and therefore raise body temperature. It is not known why serious infection in a newborn seems to elicit such a mild febrile response when mild infection in a toddler is often associated with a very high body temperature. In contrast, an overheated infant makes physiological and behavioral responses in an effort to increase heat loss and therefore lower body temperature. Either form of hyperthermia can cause increased metabolic demands on the neonate. The neonate may have increased oxygen requirements, apnea, dehydration, metabolic acidosis and in worse case scenarios heatstroke, brain damage, shock and death.

### CAUSES OF HYPERTHERMIA

Infection is not the only cause of raised set point temperature in a newborn; it is also caused by a severe cerebral abnormality, either congenital (holoprosencephaly, hydranencephaly, encephalocele) or acquired (birth asphyxia, intracranial hemorrhage). Hyperthermia usually occurs in the neonate by means of an external heating source and may cause hyper-pyrexia (rectal temperature above 41°C). Mild degrees of hyperthermia occur when active, large infants are overwrapped and left in a warm room, or when small infants are overheated by an incubator or a radiant warmer. Severe overheating occurs when there is malfunction of a warming device, or when an incubator is exposed to direct sunlight (this turns it into a greenhouse). It can also occur in hot summer months when the temperature is >41°C. Overheating is described in families with a history of malignant hyperpyrexia and anhidrotic ectodermal dysplasia.

### SYMPTOMS OF HYPERTHERMIA

The signs and symptoms of hyperthermia secondary to overheating are given in Table 60.1. The distinction between overheating and febrile state is an important one that can be made clinically (Table 60.2). Mild overheating has been suggested as a predisposing factor in apnea of prematurity. Severe overheating leading to hyperpyrexia has caused sudden death in the newborn without prior symptoms.

### MANAGEMENT

1. **Cool environment:** Overheated infants simply need a cooler environment. The heat stressed infant should be assisted in keeping metabolic heat production to a minimum. The infant who assumes an extended position should be left in this position in order to

**Table 60.1: Clinical features of hyperthermia**

Complaints	Signs
Irritability	Warm extremities
Diaphoresis	Tachycardia
Poor feeding	Hypotension
Lethargy	Apnea
Weak or absent cry	Hypotonia
Warm extremities	Extended posture
	Skin temperature greater than core temperature
	Flushing

**Table 60.2: Differences between a healthy infant who is over-heated and a febrile infant with a raised set point**

Overheated infant	Febrile infant
High rectal temperature	High rectal temperature
Warm hands and feet	Cool hands and feet
Abdominal exceeds hand skin temperature by less than 2°C	Abdominal exceeds hand skin temperature by more than 3°C
Pink skin	Pale skin
Extended posture	Lethargic
Healthy appearance	Looks unwell

encourage heat loss. Shift the baby to cooler environment and reduce clothing if inappropriate. Skin surfaces can be left exposed to enhance evaporative loss. Active temperature reduction methods should be kept at a minimum to prevent a dramatic loss of heat, potentially leading to cold stress and shock.

2. **Intravenous fluids:** Most neonates need extra fluid. Extra fluid to match the extent of dehydration should be provided. If in shock give intravenous fluid bolus of Ringer Lactate or Normal saline (20 ml/kg). Metabolic acidosis if present should also be corrected. Provide adequate fluids to maintain hydration and continue breastfeeding if baby is able to suck.
3. **Monitoring the baby:** Monitor baby's temperature, respiration (for apnea), capillary refill time and state of hydration. A febrile neonate should be investigated for the cause of fever and treated accordingly.
4. **Antibiotics:** Antibiotics are not normally indicated in all febrile neonates. However, if an infection focus is identified or if the index of suspicion for infection is high, antibiotics may be added to the supportive care outlined above till the availability of confirmatory evidence.

To conclude, thermoregulation of the newborn is part of essential newborn care. Disturbances in temperature can be due to the environmental temperature as well as underlying disease and both often coexist. It is important to attend urgently to the underlying disease as well as attempt to normalize the temperature.

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**INTRODUCTION**

Initial management of surgical emergencies in the newborn is frequently the neonatologist's domain. Many a time the diagnosis is made *in utero* and the delivery is planned with anticipatory preparedness. More commonly the diagnosis becomes evident after birth only. Surface lesions such as myelomeningocele and omphalocele are easy to diagnose. The other emergencies present with variable symptoms such as bilious vomiting or respiratory distress. Here diagnostic work up runs hand in hand with initial resuscitative measures. The neonatologist is the pivot around which the perioperative care of these babies revolves. This chapter aims to give an overview of common surgical emergencies in the newborn under the following headings:

1. Neonatal intestinal obstruction.
2. Abdominal wall defects.
3. Respiratory distress.
4. Posterior urethral valves (PUV).
5. Antenatal hydronephrosis.

**NEONATAL INTESTINAL OBSTRUCTION**

Several conditions causing bowel obstruction at different levels and by different mechanisms can present with similar clinical features in the neonatal period. While most of them are not dire emergencies and can be operated as planned acutes after fluid resuscitation and radiological diagnostic work-up. Malrotation with midgut volvulus is a fire brigade emergency requiring urgent laparotomy to untwist the bowel in order to save it from catastrophic necrosis. Although most cases have congenital mechanical obstruction, such as atresia or stenosis, functional obstruction such as Hirschsprung's disease is also common. Many cases with systemic sepsis present with ileus that may mimic mechanical obstruction. Neonatal necrotizing enterocolitis (NEC) is a rapidly progressive condition in the preterm, and may result in bowel loss due to inflammation, ischemia and necrosis.

The causes of neonatal intestinal obstruction are listed in Table 61.1.

*General Aspects of Clinical Presentation*

At birth the abdomen of a child is not distended as there is no gas in the bowel. As the child breathes gas is ingested and gradually fills the intestines over the next 24 hours. *Bile stained vomiting* and *abdominal distension* are the key features of neonatal intestinal obstruction.

**Table 61.1: Causes of neonatal intestinal obstruction****Common causes**

1. Duodenal atresia (post ampullary)
2. Jejunio-ileal atresia
3. Malrotation with or without volvulus (more common with volvulus)
4. Hirschsprung's' disease (HD) (functional obstruction)
5. Meconium disease of infancy (Meconium ileus, meconium peritonitis, cystic meconium peritonitis, small left colon syndrome, meconium plug syndrome.)
6. Obstructed inguinal hernia
7. Anorectal malformations (ARM) (Imperforate anus)
8. Congenital hypertrophic pyloric stenosis (CHPS)

**Uncommon causes**

1. Pyloric atresia, web
2. Annular pancreas causing duodenal obstruction (clinical presentation same as duodenal atresia)
3. Duodenal web with a hole causing partial duodenal obstruction
4. Windsock abnormality—duodenal diaphragm getting stretched into distal gut with chronic duodenal obstruction.
5. Pre-ampullary duodenal atresia (non-bilious vomiting with double bubble)
6. Colonic atresia
7. Rectal atresia
8. Neonatal intussusception

**Medical/systemic causes**

1. NEC
2. Systemic sepsis

**Bile stained vomiting** is always considered surgical unless proved otherwise. It should not be confused with small vomits of yellow fluid which is common because of the colostrum being yellowish and reflux being common in infancy. Obstructed bile is green and any amount is significant.

**Timing and degree of distension** varies depending on the level of obstruction (Figs 61.1 and 61.2). Proximal obstructions such as duodenal and jejunal atresia present with early vomiting but minimal distension. Ileal and colonic atresia present with gradual distension over one to two days and late vomiting. Distension at birth should arouse suspicion of congenital mass lesions (duplications, lymphangioma, large teratomas) or meconium disease of infancy especially giant cystic meconium peritonitis.

**Passage of meconium:** Most term neonates pass the first meconium within 24 hours of birth. In pre-terms this



**Fig. 61.2:** Major abdominal distension in a case of colonic atresia

extends to 48 hours. Delay should arouse the suspicion of Hirschsprung's disease. Most cases of intestinal atresia do pass some meconium for a few days (gut distal to atresia produces intestinal juice).

**General condition, feeding and systemic signs:** Most babies born with congenital bowel obstruction are otherwise healthy, active and systemically well. They will also accept first few feeds well only to develop vomiting and abdominal distension later. If a child is systemically ill with sepsis, he or she may develop features of intestinal obstruction due to paralytic ileus. In that case the systemic signs will precede intestinal symptoms. This may be observed in a clinical setting of premature rupture of membranes, maternal infections, and prolonged labor. If a child has passed milk stools, it rules out intestinal atresia.

A baby who was born normal and healthy and took feeds well but develops bilious vomiting on the third or fourth day and becomes limp and pale suddenly, is most likely to have acute midgut volvulus because of malrotation. Examination will reveal shock and pallor with minimal abdominal signs. Plain abdominal film may show paucity of distal gas with few proximal loops. This is the most feared entity and although an upper GI contrast study is indicated, there may not be enough time. It is a fire brigade emergency, requires quick fluid resuscitation and a prompt laparotomy to de-twist the small bowel. At times laparotomy is a part of ongoing resuscitation. Failure to act quickly may result in ischemic loss of the entire small bowel with dreaded consequences of short bowel syndrome.

### Imaging

**Plain X-ray of the abdomen is the most important imaging tool.** An anteroposterior view should be taken in supine position. Erect view is unnecessary and distressing to the neonate. Some generalities about the X-ray findings are as follows:



**Figs 61.1A and B:** Mild abdominal distension in jejunal atresia (A) and operative finding of jejunal atresia in the same patient (B)

1. Plain X-ray is actually a contrast X-ray, air being the contrast. At birth there is no air in the gut. As the child starts breathing, air is ingested and travels across the intestines. In about an hour it should reach the jejunum and in 24 hrs the rectum. Timing of X-ray is important. Distal ileal atresia may not become evident on X-ray in the first few hours of life. Timing of X-ray is of utmost importance in anorectal malformations, where it should be performed after 24 hours.
2. It is not possible to differentiate between small and large bowel loops in a neonate on plain film.
3. A loop more than 1 cm in size is considered dilated. Normal bowel gas pattern in a neonate is that of the entire abdomen filled with bowel loops, but of normal size. Loops localized to a particular area, fixed loop on serial films, and dilated loops indicate abnormality.
4. Presence of gas in rectum rules out proximal atresia. Stenosis however, still remains a possibility.
5. Different conditions can be diagnosed on plain film:
  - Only distended stomach and no distal gas—pyloric atresia.
  - Distended stomach and proximal duodenum (classical double bubble)—Duodenal atresia. The dimple in between two bubbles is because of the pyloric contraction (Fig. 61.3).
  - Proximal few bowel loops seen and no distal loops—Upper small bowel atresia/jejunal atresia (Fig. 61.4).



**Fig. 61.3:** X-ray appearance of duodenal atresia in supine view



**Fig. 61.4:** X-ray appearance of jejunal atresia. Note the few dilated bowel loops and paucity of distal gas



**Fig. 61.5:** X-ray in ileal atresia showing many dilated bowel loops

- Many distended loops—suggests some form of distal obstruction:
  - a. Ileal atresia: Many distended loops. Step ladder pattern, many levels on lateral view (Fig. 61.5).

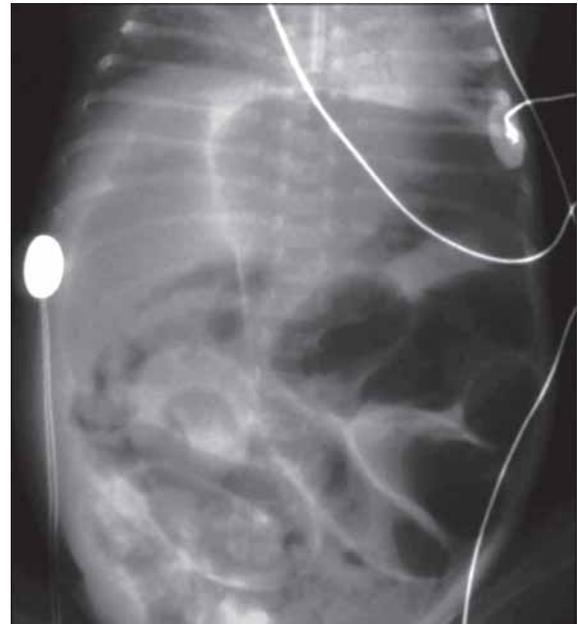


**Fig. 61.6:** X-ray in meconium peritonitis. Note the calcification in right iliac region



**Fig. 61.7:** X-ray in Hirschsprung's disease. Note the peripheral distended loops which are likely to be colonic loops

- b. Dilated proximal loops, soap bubble appearance and paucity of distal gas: Meconium ileus.
  - c. Picture of meconium ileus with calcification-meconium peritonitis (Fig. 61.6). Presence of calcification on plain film is an indication for ultrasound to look for other causes of calcification such as adrenal calcification, neuroblastoma, and teratomas.
  - d. Too many dilated loops with distended abdomen and gas filled loops reaching the periphery: Hirschsprung's disease/colonic atresia (Fig. 61.7).
6. **Free gas on supine film:** It is not necessary to get an erect film to pick up free gas. Large amount of free gas is expected in common conditions like gastric perforation or colonic perforations. This can be seen as *Foot ball sign* on a supine film (Fig. 61.8). The gas collects in the central abdomen and gets distributed on either side of the falciform ligament, which shows as an oblique shadow in the center of a big blob of gas (American Football), hence the name. *The liver shadow will not be dense* because of the overlying air. *Wriggler sign:* Gas on both sides of the bowel wall (intra-luminal and free extra-luminal) makes the bowel wall very bright and sharply defined. This is referred to as Wriggler sign (Fig. 61.9). *Scrotal gas:* Especially in preterm babies because of patent processus vaginalis.



**Fig. 61.8:** Foot ball sign

Small amount of free gas (as expected in NEC) may be missed on supine film. For this cross table view in left lateral decubitus position is taken. The child lies in lateral position on his left side, X-ray plate is kept against the back and the beam comes from the front. Small triangular pockets of free air



Fig. 61.9: Free gas depicting Wrigler sign

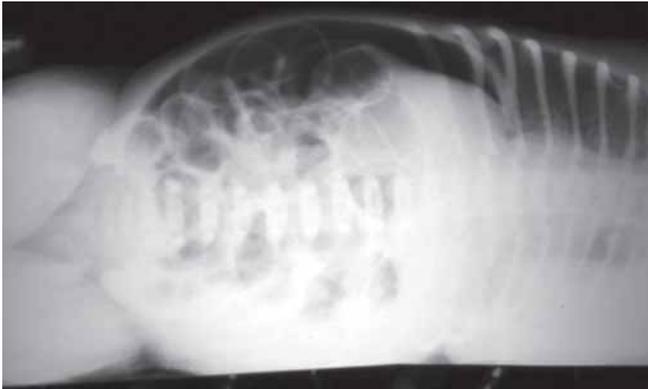


Fig. 61.10: Free gas seen on lateral decubitus X-ray

will be seen opposite the abdominal wall flanked by bowel loops. Free air may also be seen between the right edge of the liver and the right lateral abdominal wall (Fig. 61.10).

7. **Cross table lateral view in prone position (Fig. 61.11):** The child lies in prone position for two or three minutes with the pelvis elevated by 45 degrees on a soft wedge. X-ray plate is kept along the left or right thigh perpendicular to the table; X-ray beam comes from across the table, centered over the greater trochanter. So a dead lateral view is taken. This view is of importance in suspected Hirschsprung's disease and anorectal malforma-

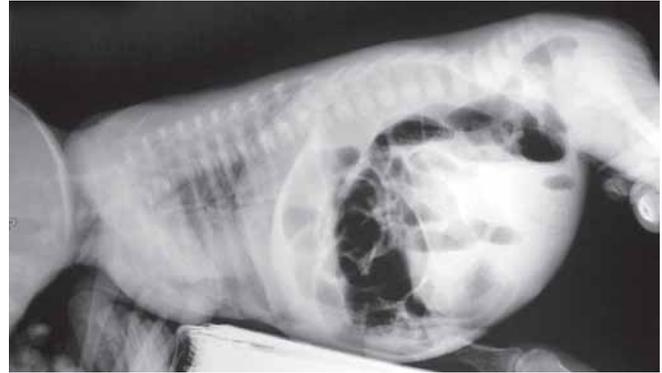


Fig. 61.11: Prone cross table lateral X-ray in HD showing dilated sigmoid but relatively collapsed rectum

tions. In the prone position with pelvis elevated the gas rises in the rectum. If X-ray shows rectal gas it almost rules out Hirschsprung's disease. In anorectal malformations the distance between the rectal gas and the skin is measured. If it is less than one cm, a primary perineal anoplasty operation can be done. If more than one cm, colostomy should be done and definitive repair deferred for few weeks.

8. **Invertogram:** The child is put in upside down position for two to three minutes before taking a lateral view with a purpose to know the type of anorectal malformation—high or low. It is very distressing to the child, invites aspiration if there is associated tracheo-esophageal fistula (association of ARM, esophageal atresia and duodenal atresia—triple atresia, is well known). Therefore, it has now become obsolete in favor of cross table prone lateral film.
9. **Plain X-ray in NEC:** In NEC X-ray findings are best interpreted on serial X-rays. Fixed loop at 12 hour interval, small amount of free gas, intramural gas (Fig. 61.12), and portal venous gas are the features of NEC.
10. **X-ray in peritonitis:** Normally the fat line in neonates is well appreciated in plain film because of the good interface being provided by pre-peritoneal fat that separates the anterior abdominal wall from the peritoneal cavity. In peritonitis this plane is lost due to peritoneal inflammation. So hazy fat line, inability to clearly see the psoas shadow and renal shadow indicate peritoneal inflammation.

Large amount of free gas is seen with rectal/colonic perforation, gastric perforation, and isolated ileal perforation without NEC.



**Fig. 61.12:** X-ray in a case of NEC showing intramural gas (arrow)



**Fig. 61.13:** Contrast enema showing microcolon. Note the filling defects due to meconium pellets

### Contrast Studies

Upper GI and lower GI contrast studies are indicated in certain situations to help in the diagnosis and sometimes in the management also. Which study to do depends on clinical suspicion and plain film findings. If upper bowel obstruction is suspected—upper GI contrast is indicated. If lower GI obstruction is suspected—contrast enema is needed. If there is too much gas on plain film a contrast enema will be helpful and vice-versa. Water soluble non-ionic contrast material should be used. Conray being highly osmolar can cause sudden fluid shifts into the bowel lumen leading to circulatory insufficiency. However, Conray or Gastrograffin should be used for therapeutic contrast enema for meconium ileus and small left colon syndrome. Before the study, adequate fluid resuscitation is a must to safely allow osmolar fluid shifts into the bowel lumen.

**Upper GI series:** Contrast is injected through the nasogastric tube and serial films taken. The most important indication is to confirm or exclude malrotation in a neonate presenting with bile stained vomiting. Normal location of the duodenojejunal junction (DJ) is above and to the left of transpyloric plane. Any abnormality in the location of DJ means malrotation irrespective of other findings. In a case of malrotation with volvulus one may see cork screw appearance of

proximal jejunal loops in addition to an abnormally located DJ. One more possible use of upper GI series is in partial upper small bowel obstruction such as duodenal or jejunal stenosis, band obstruction, and internal herniation. In such cases the presentation is usually not in the immediate neonatal period but a few weeks after birth.

**Lower GI study (contrast enema):** It is performed under antibiotic cover (triple antibiotic shot before the procedure). Initial contrast is always water soluble non ionic. Dye is instilled per rectum till the dilated loops are filled in. If the dye reaches the dilated loops it rules out atresia. In suspected meconium ileus there will be microcolon (colonic diameter less than 1 cm). The differential diagnosis of microcolon is:

1. *Meconium ileus and its variants:* Meconium pellets may be seen as filling defects (Fig. 61.13).
2. *Total colonic aganglionosis:* Microcolon with rounded splenic flexure.
3. *Distal ileal atresia:* dye fails to reach dilated segment.

Appearance of soap bubble appearance on plain film and microcolon in contrast enema calls for therapeutic enema with gastrograffin. Gastrograffin will dissolve the thick tenacious meconium from the terminal ileum which will be passed per rectum relieving the obstruction. Enema may have to be repeated several times for the first few days to completely relieve the obstruction.



**Fig. 61.14:** Contrast enema in HD showing rectosigmoid transition zone

Care should be taken to hydrate the patient well so that fluid disturbances do not occur. Being osmolar in nature the dye withdraws fluid into the lumen to dissolve the meconium thus causing fluid deficit in the intravascular compartment.

In suspected Hirschsprung's disease the contrast enema should be performed with the help of a non-lubricated end opening plain tube (not Foley catheter) placed in the distal rectum just about a cm from the anal verge. Dye is injected slowly under fluoroscopic guidance to see the filling of collapsed rectum followed by appearance of a funnel shaped dilatation (transition zone) and finally the dilated segment of proximal colon. Lateral views are taken (Fig. 61.14). On visualization of the transition zone further dye is not injected. Demonstration of an unmistakable transition zone should end the procedure. In doubtful cases a 24 hr film is taken to see clearance of the dye. HD can be diagnosed on contrast enema by a transition zone (classically at rectosigmoid, sometimes long segment and rarely total colonic). It is a myth that the transition zone disappears after bowel washout, per rectal examination and in neonates. In the author's experience transition zone is as evident in neonates as in a three months old managed with bowel washouts three times a day for three months. Ultrashort segment HD (also known as internal sphincter achalasia) cannot be

diagnosed by contrast enema and requires anorectal manometry. Funneling of distal rectum by contraction of external sphincter is normal and should not be mistaken for transition zone. The most common site for the transition zone is rectosigmoid.

#### *Ultrasound*

It has limited role for evaluation of neonatal obstructions. In suspected malrotation it is used to see the relationship of the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV). Normally the SMV is to the right of SMA (same as IVC and aorta). In malrotation this is reversed. One can also see cork screw appearance of jejunal loops in volvulus. Cystic and solid masses can be assessed with ultrasound. A child with distension at birth is a good indication for ultrasound. Rarely neonatal appendicitis and intussusception can be picked up.

#### *Principles of Preoperative Management*

1. Place the child under radiant warmer. Monitor SpO<sub>2</sub>, temperature and pulse.
2. Record birth history and sequence of events.
3. Pass NG tube and aspirate contents. Leave it on free drainage. Do this first thing after a focused physical examination.
4. Establish IV access and start fluid resuscitation with 20 ml/kg bolus of normal saline. Up to three boluses may be required. Continue with maintenance fluids usually N/5 in 5% Dextrose. (100 ml/kg/day). Replace NG losses by normal saline every 6 hours. Monitor fluid resuscitation by serum sodium levels and urine output. If the child is moderately fluid depleted, pass a urinary catheter for monitoring the urine output.
5. Monitor serum Na<sup>+</sup> and K<sup>+</sup> and urine output. Send blood sample for hematocrit, counts, urea, electrolytes.
6. Start broad spectrum antibiotics. A cephalosporin and metronidazole combination is sufficient in most cases.
7. Once hemodynamically stable, obtain a plain abdominal film in AP view. Consult the surgical team and decide if further contrast study is required.
8. Surgical management will depend on the condition. Table 61.2 gives a summary of the management of different conditions. Laparotomy should be planned only after adequate resuscitation and diagnostic workup. However, there is one exception—malrotation with midgut volvulus, which can be a dire emergency. A description of this anomaly follows for better understanding of the pathophysiology and the nature of emergency.

Table 61.2 Diagnosis and management of neonatal intestinal obstruction

Condition	Onset and clinical features	Imaging	Treatment	Remarks
<i>Duodenal atresia</i>	Within few hours after birth, bilious vomiting, no distension	Double bubble on plain film	Duodenoduodenostomy (diamond-shaped anastomosis)	<i>Etiology:</i> Failure of canalization. 25% have Down syndrome. <i>DD:</i> Annular pancreas, duodenal stenosis, duodenal diaphragm. Prognosis good if no Down syndrome
<i>Jejunal atresia</i>	Within 24 hours bilious vomiting, gradual mild distension Meconium passed	Few dilated bowel loops in upper abdomen	Resection of atresia and end-to-end anastomosis	<i>Etiology:</i> Intrauterine vascular accident. Prognosis good
<i>Ileal atresia</i>	24-48 hours, progressive distension, late vomiting, may pass meconium.	Many dilated loops with levels on plain film. Microcolon on contrast enema	Resection of atresia and end-to-end anastomosis	Resect about 5 cm on either side of atresia (poor myoelectric property) and to eliminate lumen disparity
<i>Meconium ileus</i>	Almost immediately after birth, distension and bilious vomiting. No meconium or very tenacious meconium.	Soap bubble appearance on plain film Microcolon on contrast enema	Gastrografin enema may be therapeutic. Laparotomy may be required for Bishop Koop or Santulli procedure.	Repeat Gastrografin enema may be required. Investigate for cystic fibrosis Exclude HD by rectal biopsy
<i>Hirschsprung's disease</i>	No meconium passed in 24 hours, gradual soft distension, no vomiting despite massive distension (distension because of colonic dilatation)	No rectal gas on cross table prone X-ray Transition zone on contrast enema	Rectal washouts for 6-8 weeks. Laparoscopic assisted trans-anal pull through at 6-8 weeks	Rectal biopsy diagnostic. Atypical presentation likely in total colonic aganglionosis. May present as acute small bowel obstruction requiring colostomy.
<i>Malrotation with midgut volvulus</i>	3-5 days sudden onset bile vomit, rapid deterioration to shock.	Plain film non-contributory, abnormal location of DJ on upper GI contrast study	Urgent Ladd's procedure, no time for imaging.	In 90% cases volvulus occurs within the first month of life. May also present with recurrent chronic duodenal obstruction

### Malrotation with Midgut Volvulus

This is a congenital abnormality that makes the midgut prone to twist in a clockwise manner around the superior mesenteric vessels due to a very narrow base of the mesentery. It results from failure of rotation and fixation of the midgut during 8-12 week of intrauterine life. The duodeno-jejunal junction is abnormally located to the right of midline, the duodenum and cecum are juxtaposed close to each other, and a band (Ladd band) runs from the retroperitoneum across the cecum and duodenum at the third part of the duodenum.

Clinical features may be due to volvulus of the small bowel around SMA (most common and most dreaded) or chronic duodenal obstruction due to Ladd bands or due to an intrinsic duodenal stenosis.

Volvulus of the midgut occurs most frequently within the first week of life with sudden onset of bile vomiting on 3-5th day. Rapid deterioration occurs because of gut ischemia and the child may present in shock. A quick resuscitation should be followed by an upper GI study if the child is resuscitable. Many a time laparotomy is required urgently as part of resuscitation. The key to surgery is the root of the mesentery. The volved gut is untwisted, mesentery is widened and Ladd band is divided.

### Duodenal Obstruction

Congenital duodenal obstruction can occur because of atresia, stenosis, perforate or imperforate webs and extrinsic compression by bands or duplication cysts. Annular pancreas can cause a total or partial obstruction and may be indistinguishable from atresia.

Duodenal atresia, the commonest cause of duodenal obstruction, occurs in 1 per 5000 live births. 25% have Down syndrome. In 80% cases the obstruction is distal to the ampulla of Vater resulting in bilious vomiting. In 20% it is pre-ampullary causing non-bilious vomiting. Antenatal ultrasound shows polyhydramnios and dilated stomach and duodenum. Duodenal atresia is the most frequently prenatal diagnosis amongst bowel obstructions. Since associated cardiac defects and Down syndrome are common, prenatal diagnosis becomes important to facilitate parental decision regarding medical termination of pregnancy. Therefore, detection of polyhydramnios with a dilated bowel loop on prenatal USG is an indication for amniocentesis for chromosomal analysis to screen for Down syndrome.

Treatment for atresia and annular pancreas is duodenoduodenostomy. Postoperatively it takes some days before the motility of the duodenum is restored and feeds can be started. Prognosis is good if Down syndrome is not associated.

### Jejunioileal Atresia

Intestinal atresia refers to a congenital absence of bowel lumen resulting in total obstruction. Jejunioileal atresia is caused by an intrauterine mesenteric vascular accident causing ischemic necrosis and resorption of the involved bowel segment.

The more proximal the lesion, the earlier and more prominent the bilious vomiting and electrolyte disturbances, and lesser the amount of air on plain film. If there is proximal obstruction (duodenal or jejunal) the decision for surgery is simple and could be taken based on plain X-ray alone. The approach may be quite different for distal ileal or colonic obstruction because surgery may not always be required urgently (as in meconium ileus, HD). A contrast enema is required to differentiate ileal atresia from meconium ileus, Hirschsprung's disease, and colonic atresia. In distal ileal atresia the dye will not reach the dilated segment and there will be microcolon. In HD a transition zone will be seen. In Meconium ileus, the gastrograffin enema may be therapeutic. Treatment of intestinal atresia is by resection of the atresia and end-to-end anastomosis.

Prognosis is good if excessive bowel is not resected.

### Hirschsprung's Disease (HD) in the Newborn

HD can present in the neonatal period in different ways:

1. **Failure to pass meconium within 24 hours:** This is the most common presentation. Gradually abdominal distension occurs. The child continues to accept feeds and there is no vomiting. Plain X-ray shows many gas filled loops all over the abdomen. Prone cross table lateral view shows no gas in the rectum. Diagnosis is made by contrast enema which shows typical transition zone (for details see section on imaging). Rectal biopsy provides the most definitive diagnosis. In the biopsy specimen the Acetyl choline-esterase (AChE) activity is raised, ganglion cells are absent and nerve bundles are hypertrophied.

*Management:* The baby is put on rectal washouts with normal saline twice or thrice daily to help bowel decompression. Oral feeds are given. Child is sent home on daily rectal washouts. At 6-8 weeks when the child has shown satisfactory growth a definitive pull through operation is performed. The current trend is to perform a primary pull through without a colostomy.

2. **Full blown small bowel obstruction** with bilious vomiting, distension and failed passage of meconium. Often it is difficult to differentiate from ileal atresia. This presentation is usually seen in total

colonic aganglionosis. Contrast enema is helpful in diagnosis. It shows micro-colon and the splenic flexure is rounded. For management an urgent laparotomy is required with creation of a colostomy.

### Meconium Ileus (MI)

It is characterized by retention of thick and tenacious meconium in the distal small bowel causing total obstruction. Pancreatic deficiency and cystic fibrosis (CF) are known to be associated in about 80%. Seen in 15 % cases of CF, MI is the earliest manifestation of CF. The meconium is rich in proteins making it thick and viscid. There is further contribution by decreased gut motility and defective secretory properties leading to increased mucin content in the meconium. The result is accumulation of viscid and thick meconium in the distal small bowel. Antenatally this can be picked up on ultrasound as hyperechoic bowel contents. Suspicion of MI with a family history of CF should lead to amniocentesis for evaluation of delta F 508 mutation on the CF gene, and DNA polymorphism. If positive, the pregnancy should be terminated. Postnatally the presentation may be that of *simple MI* or *complicated MI*. Simple MI presents with abdominal distension at birth, bilious vomiting, and failure to pass meconium. Distension gradually increases. The dilated bowel loops may be visible and may indent on pressure. Digital rectal examination is difficult as the small rectal caliber does not allow insertion of the finger. Complicated MI may have volvulus, atresia, perforation, meconium peritonitis or giant cystic meconium peritonitis. At birth severe abdominal distension is usually present with erythema of the wall. A palpable mass may be there suggesting a cyst formation. Plain X-ray in simple form shows a soap bubble appearance in the right lower abdomen due to mixing of air and meconium. Proximal loops are dilated but air fluid levels are not many. Complicated form may show calcification indicating antenatal bowel perforation. A mass effect may be seen due to cyst formation. Contrast enema shows micro-colon. The dye refluxes into the ileum showing meconium pellets as filling defects. In simple MI Gastrograffin enema may be therapeutic as described earlier. The criteria for attempting non-operative treatment with gastrograffin enema are:

- a. Other surgical causes should have been ruled out
- b. The child must be well hydrated and antibiotics must have been given.
- c. It should be attempted only in simple form of MI.
- d. Enema should be done under fluoroscopy control.
- e. Urgent surgery should be available in case of complication.

Gastrograffin is a hyperosmolar (1900 mOsm/L), water soluble, and radioopaque solution containing a detergent agent (Tween 80) with meglumine diatrizoate. When instilled as enema it draws fluid into the bowel lumen causing osmotic diarrhea. Once the dye reaches the dilated small bowel loops the procedure is ended. The child continues to pass liquefied meconium. The enema may have to be repeated at 12-24 hrs intervals. The effect may be supplemented by 10% N acetyl cystine solution (5 ml 6 hrly) through a nasogastric tube.

Possible complications are rectal and small bowel perforation, hypovolemic shock and NEC. Success rate with this approach is about 50-60% only. In the rest and in complicated variety of MI a laparotomy is indicated.

### Inguinal Hernia

The child presents with a swelling in the groin that enlarges on crying but reduces when the child is calm. It may require gentle pressure to reduce it (reducible hernia). Occasionally it fails to reduce on gentle pressure (irreducible hernia). An irreducible hernia may lead to intestinal obstruction, which if left untreated, will lead to strangulation.

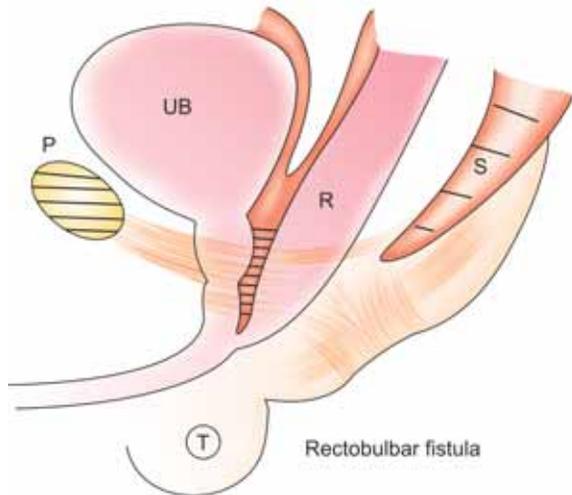
**Management of irreducible hernia:** Irreducible hernia should be reduced manually by **Taxis**. The child should be kept nil by mouth and good analgesia is given. Venous access is established and intravenous fluids started. Once the child is analgesed and sedated a gentle reduction is done by "Taxis". Once reduced, the hernia should be repaired after 24 hours. Taxis should not be attempted if there are established features of strangulation (long standing sick child, gross abdominal distension, and sepsis). Instead urgent operation should be performed after a quick resuscitation.

A non-reducible hernia in a girl child should *not* be subjected to taxis (manual reduction) as it may contain ovary which does not reduce well. Surgical repair should be performed urgently, lest the ovary should get strangulated.

**Management of reducible hernia:** If a hernia is noticed incidentally in a neonate in the neonatal unit, the repair should be performed before he is discharged from the medical point of view. Premature babies are prone to develop apneic spells following anesthesia. Hence they should be kept in the hospital overnight. Otherwise hernia repair can be done as a day care procedure.

### Anorectal Malformations

Anorectal malformations comprise a spectrum of congenital malformations in which the anus fails to



**Fig. 61.15:** Schematic diagram showing anatomy of rectobulbar fistula in a boy with anorectal malformation (UB = urinary bladder, R = rectum, T = testis, S = sacrum, P = symphysis pubis)

open normally on to the perineum. The rectum terminates either above (high malformation) or below (low malformation) the levator ani. In high malformations the rectum terminates in the urinary tract through a rectourinary fistula, the level of which may vary from rectobladder fistula to rectobulbar fistula. Rectobulbar fistula is the commonest malformation in boys (Fig. 61.15). In low malformations the rectum terminates within about a cm from the skin; there is no rectourinary communication; and often the meconium shows up in the perineum through a small opening (perineal fistula) either at the site of normal anus or along the median raphe in the scrotum (anocutaneous fistula) (Fig. 61.16). The diagnosis should be made in the delivery room by inspecting the perineum—no anal opening is found. The next step is observing for meconuria—passage of meconium in urine. Meconuria with absence of anal opening in the perineum invariably indicates a high malformation which requires a colostomy in the newborn period. Low malformations do not become evident until 24 hours (which is the time taken for meconium to descend down the gut), when the meconium may show in the perineal fistula. These defects can be managed by a perineal anoplasty without a colostomy in the newborn period.

**Associated malformations** are seen in 50-60% cases. 60% are genitourinary, 25% vertebral, 20% cardiac, 10% GI, 15% have VACTERL/CHARGE association. Severe



**Fig. 61.16:** Anocutaneous fistula. Note the long subepithelial tract along the median raphe

the malformation the higher the incidence of associated malformations.

Two most important questions that need an answer within the first 24 hours are:

1. Is the case suitable for a primary perineal anoplasty without a colostomy or an initial colostomy is required?
2. Is there any other life threatening association that needs more urgent attention—e.g. tracheo-esophageal fistula, severe cardiac malformation? Therefore, always pass a nasogastric tube to rule out esophageal atresia and leave it for gastric decompression.

#### *Clinical Features and Pathological Anatomy*

**Males:** Examine perineum (Figs 61.17 and 61.18): There is no anal opening. Look for gluteal fold, natal cleft, and palpate spine/sacrum. Is it a flat bottom? Is there a dimple at the anal site with pigmentation? Is anocutaneous reflex present? Is there a fold of skin under which you can pass a probe (Bucket handle deformity), is there any mass?, can you see a thin white epithelial thickening in the median raphe—suggests anocutaneous fistula, is there any speck of meconium in the perineum—perineal fistula?

Is there any abnormality of the external genitalia—bifid scrotum, hypospadias, and undescended testes? Look for evidence of meconuria—gas or meconium discharge per urethra.

**Prone Cross table lateral shoot abdominal film** is required if clinical information at 24 hrs is insufficient to decide if a colostomy is needed.



**Fig. 61.17:** Perineal appearance in the most common male anorectal malformation, i.e. rectobulbar fistula. Note the pigmented dimple and good natal cleft



**Fig. 61.18:** Perineal appearance in rectoprostatic fistula. Note the flat perineum and less pigmented dimple

**Technique:**

Place a radioopaque marker at the anal site.  
 Prone position with pelvis elevated—leave in this position for 5 minutes before taking the X-ray (to allow gas to layer on the meconium)  
 Dead lateral view centering over the greater trochanter.

**Interpretation:**

See distance of rectal gas from the marker  
 < 1 cm: Suitable for primary repair  
 > 1 cm: Colostomy needed.

**Indicators of “high” anomaly (colostomy indicated):**

- No meconium in the perineum at 24 hours

- Flat bottom, absent anal dimple/pigmentation, absent anocutaneous reflex,
- Sacral abnormality
- Meconium in urine (or gas in bladder on X-ray)
- Suggestion of a pouch colon on plain abdominal film.
- Associated bifid scrotum, proximal hypospadias, bilateral undescended testes

**Indications of low anomaly (suitable for primary anoplasty):**

- Good perineum, pigmented dimple, anocutaneous reflex
- Visible fistula in the perineum
- Bucket-handle deformity—a bridge of skin over the anal site under which an instrument can be passed and meconium can be seen under the skin.

Although a prone cross table lateral shoot film is not required in majority, a plain abdominal film should be obtained in all cases to exclude pouch colon, which is common in northern India. A bowel pouch spanning more than 50% of transverse span of the abdomen suggests pouch colon. If so diagnosed, the child needs a laparotomy rather than a simple colostomy.

**Females:** Most anomalies are low. Look for the number of openings in the vulva/perineum:

*Three openings:* Anovestibular fistula (Commonest), recto-vestibular fistula, perineal fistula (Fig. 61.19), anterior ectopic anus



**Fig. 61.19:** Perineal fistula in a girl child with low anorectal malformation



Fig. 61.20: Cloaca

*Two openings:* Rectovaginal fistula. (rarely vestibular fistula with vaginal atresia).

*One opening:* Common Cloaca (Fig. 61.20).

Examine in good light keeping the legs apart. The vestibular opening is usually very small and may be hidden within the posterior fourchette.

**Management:** The preoperative medical management is aimed at excluding associated malformations, parental counseling and reassurance, nasogastric tube, broad spectrum antibiotic and general supportive treatment. The following investigations are arranged:

- Renal and spinal ultrasound: To look for renal malformations, tethered cord
- Echocardiography
- Chest and spine X-ray
- Sacral Pena ratio
- Chromosomal analysis

Surgical management involves initial colostomy for cloaca and rectovaginal fistula. For anovestibular fistula a single stage operation at few weeks of life is usually performed.

### Congenital Hypertrophic Pyloric Stenosis (CHPS)

The classic picture of CHPS is projectile non-bilious vomiting in an otherwise well infant 3 to 6 weeks of age. Sometimes the onset is at 1-2 weeks and gradually the symptoms progress. The child feels hungry after the vomiting and readily accepts a feed only to vomit again. Pathologically, there is hypertrophy of the pyloric muscle possibly related to (a) compensatory work hypertrophy, (b) gastrin hyper secretion, or (c) neuronal immaturity.

The stomach becomes enlarged and the peristaltic wave may be visible in the epigastrium from left to right. Malnutrition and metabolic alkalosis set in with persistent untreated pathology. Physical examination reveals visible peristaltic wave and a palpable “olive” in the upper abdomen. The child should be examined after gastric decompression in the mother’s lap with relaxed abdominal wall. Sometimes a test feed is required to elicit this sign. An assessment of hydration status should be made. The typical abnormality in these children is hypochloremic, hypokalemic, metabolic alkalosis with hyponatremia. The urine is alkaline but prolonged illness may cause paradoxical aciduria due to renal preservation of potassium ions in exchange for hydrogen ions.

Diagnosis is made by typical clinical features and confirmed by ultrasound, the diagnostic criteria being: Pyloric muscle thickness > 4 mm, pyloric channel length > 17 mm, and pyloric muscle diameter > 14 mm. Upper GI contrast study shows a narrow elongated pyloric canal known as “string sign”. Pyloric bulge into the stomach lumen may also show as a shouldering effect. Urine examination should be done for pH and nitrites (to exclude urinary infection). Arterial gas analysis shows a typical metabolic picture as described above.

Gastroesophageal reflux, sepsis and urinary infections are other common causes of vomiting in infancy, but forceful projectile vomiting is typical of CHPS.

### Management

1. Insert a nasogastric tube and leave it on free drainage. Give a stomach lavage. Keep the child nil by mouth.
2. Treat dehydration and metabolic abnormality. Half normal saline in 5% dextrose is given as 20 ml/kg bolus initially and then in maintenance dose. 20 meq per liter of potassium chloride is added once urine is passed. Replace NG losses with normal saline every six hours. Correction may take a few hours to few days depending upon severity. Monitor electrolytes every 12 hours. Surgery should be performed ONLY AFTER full correction of electrolytes and alkalosis.
3. **Surgery:** Ramstedt pyloromyotomy is the most favored operation. It can be performed through open or laparoscopic surgery. The pyloric muscle is incised full length till the mucosa pouts out. Post operatively feeds are started at 6 hours and gradually built up. Patient can be discharged after 24 hours.

Postoperative mild vomiting is common due to gastroesophageal reflux.

### Necrotizing Enterocolitis

It is characterized by variable degree of mucosal or transmural necrosis of intestines commonly affecting the terminal ileum and the ascending colon. Of all the established cases, 90-95% are preterm making it the single most important risk factor. It is 10 times more common in babies who have been fed. Clinical presentation may vary from general signs of systemic sepsis to specific gastrointestinal symptoms such as intolerance to feeds, abdominal distension, bloody stools and gastric aspirates. General symptoms in a preterm baby should prompt for early evaluation for NEC by clinical and radiological means. Mechanical bowel obstruction forms a differential diagnosis but chronology of symptoms helps in reaching the diagnosis. NEC starts with general symptoms while mechanical obstruction starts with GI symptoms. Abdominal examination findings may include distension, thin stretched out abdominal wall, erythema and edema of abdominal wall, and tenderness. A palpable mass is a late feature indicating abscess formation. Blood picture is that of sepsis and metabolic and respiratory acidosis. Plain abdominal film shows distended bowel loops with features of peritoneal inflammation (loss of fat line and loss of psoas shadows indicating free fluid and tissue edema). Intramural gas is the hall mark of diagnosis (see Fig. 61.12). Other features are portal venous gas and free gas.

#### Management

Management is largely medical and comprises of rest to the gut, intravenous fluids, electrolytes and nutrition, antibiotics and general supportive therapy.

Indications of surgery are shown in Table 61.3. Patients on medical therapy usually show a trend in the first 24 hours. No improvement or deterioration calls for surgery. Free gas is an absolute indication. Management is individualized in the setting of portal

**Table 61.3: Indications of surgery in NEC**

1. Absolute indication  
*Pneumoperitoneum*
2. Relative indications  
*Dilated fixed loop on serial X-ray*  
*Mass which is tender*  
*Abdominal wall cellulitis*  
*Portal venous gas*  
*Deterioration on medical therapy*

venous gas, fixed loop, mass and general deterioration. Decision making may be helped by a paracentesis. If the paracentesis fluid is blood tinged with bacteria it indicates gangrene in the bowel and the patient is taken up for surgery.

Surgery for NEC may comprise of the following:

1. Laparotomy and resection of non viable bowel with anastomosis-only a minority will qualify for this.
2. Laparotomy with resection of non viable bowel and stoma formation—most frequently performed.
3. Laparotomy with no resection in the first instance, second look laparotomy after 24 hours for definitive resection—usually done in severe NEC involving entire small bowel.
4. High jejunostomy to divert intestinal secretions and give the bowel rest—done in diffuse but non necrotic involvement of small bowel or when multiple resections would be required.
5. When the child is not suitable for anesthesia (extreme prematurity, circulatory instability etc), bilateral flank drains should be put under local anesthesia in the neonatal unit itself. With this approach a rule of thirds applies. About 33% will improve to wellness, 33% will improve to undergo laparotomy and the rest will die.

**Isolated ileal perforation without NEC** is rare. It occurs in premature babies with cardiac malformation having right to left shunts. Possible cause is vascular micro-embolization into terminal arteries in the mesenteric circulation. Intravenous therapy in babies with right to left shunt should be given through a filter in the IV line to prevent iatrogenic embolization.

### ABDOMINAL WALL DEFECTS

#### Exomphalos and Gastroschisis (Figs 61.21 and 61.22)

The salient features of these two common abdominal wall defects are shown in Table 61.4.

Antenatal diagnosis of exomphalos is possible in the first trimester although confusion may arise from the natural state of evisceration of mid gut during early first trimester. However, the fact that the liver is never a part of physiological herniation provides a clue. Decision for termination of pregnancy should be taken only if the diagnosis has been confirmed and amniocentesis shows abnormal karyotype, or there is associated cardiac defect. If pregnancy is continued it should be carried to term to prevent ill effects of prematurity. The delivery may have to be planned by an elective cesarean section at a tertiary care center.

**Table 61.4: Exomphalos and gastroschisis**

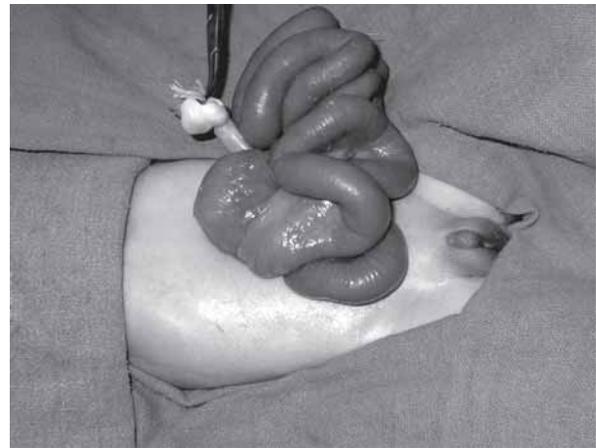
Criteria	Exomphalos	Gastroschisis
Definition	Herniation of intraabdominal viscera through an open umbilical ring into the base of the umbilical cord	Antenatal evisceration of bowel through a defect of the anterior abdominal wall to the right of the intact umbilical cord
Covering	Three layered: parietal peritoneum, Wharton jelly and amnion.	None. Gut lies bare.
Contents	Liver and intestines	Only intestines. Matted loops due to exposure to amniotic fluid
Associations	More common (40%) Cardiac, chromosomal (Trisomy 18), Beckwith Wiedemann syndrome	Uncommon. Only intestinal problems like stenosis and atresia are more common due to local effects.
Treatment	Primary closure/Merbromin application	Primary closure/skin closure/Silo pouch
Prognosis	Depends on associated malformations	Depends upon intestinal factors: ability to start enteral nutrition



**Fig. 61.21:** Exomphalos. Merbromin has been applied on the surface

#### *Immediate Postnatal Management*

The aim is to prevent evaporative fluid loss, infection and trauma to the gut. Nurse the baby in a warm and clean atmosphere. Warm saline soaked gauze is wrapped around the defect or exteriorized bowel. Side supports should be provided to avoid traction on the mesentery. In gastroschisis a cling film may be wrapped around the gut. Intravenous access should be obtained and antibiotics started. Give a fluid bolus to prevent dehydration. Do a quick survey for associated malformations. Surgery should be carried out soon. Large exomphalos with intact covering membrane may also be managed conservatively by application of merbromin or betadine solution. It results in gradual



**Fig. 61.22A:** Gastroschisis. Note a normal umbilicus on the left of the defect



**Fig. 61.22B:** Skin closure in the same patient of gastroschisis

epithelialization to provide a skin cover. Fascial closure can be done at a later date.

### Exstrophy Bladder and Cloacal Exstrophy

The defect in bladder exstrophy is quite obvious. The child is born with an exposed inner lining of the bladder and the ureteric orifices. The surrounding paraexstrophy skin is thin and shiny. In the classical exstrophy epispadias complex the defect extends from the dome of the bladder to the tip of urethra. The anus is anteriorly placed. In the male the penis is short and dorsally curved with separation of corporal bodies. In the female the clitoris is bifid. Vaginal stenosis and duplication may occur. The pubic bones are set wide apart (pubic diastasis). The anomaly looks gross but the child is otherwise normal, accepts feeds and there is no urinary obstruction.

Prenatal diagnosis is suggested by sonographic absence of a normal bladder, anterior abdominal wall mass and low set umbilicus.

#### Management in the Newborn

1. Ligate umbilical cord with a long thread rather than clamp (clamp may traumatize the delicate bladder)
2. Cover the exposed bladder by thin clear plastic sheet such as cling film. Gauge may adhere and damage the epithelium. Avoid petroleum jelly or saline soaked gauge on the bladder. Put diapers over the cling film.
3. Start gentamycin and a cephalosporin in anticipation of surgical closure within 24-48 hours.
4. Obtain a renal ultrasound to exclude upper tract anomalies such as duplex system.
5. Surgical closure should be performed within 24-72 hours once the parents have been counseled and consented.

**Cloacal exstrophy** is a rare but complex anomaly comprising of a large exomphalos, two exposed hemibladders one on each side of a prolapsing terminal ileum in the center (often termed as elephant trunk appearance), two appendiceal orifices and two ureteric orifices one on each hemibladder. There is no anal opening in the perineum. Unlike classic bladder exstrophy, associated malformations are frequent. Neonatal work up includes assessment for associated malformations and detailed discussion with parents about the outcomes. Surgical reconstruction is complex.

## 6 SURGICAL CAUSES OF RESPIRATORY DISTRESS IN THE NEWBORN

The common surgical causes of respiratory distress are shown in Table 61.5.

**Table 61.5: Surgical causes of respiratory distress**

1. Congenital diaphragmatic hernia
2. Esophageal atresia and tracheo-esophageal fistula
3. Congenital lung lesions
  - CLE
  - CCAM
4. Upper airway lesions
  - Choanal atresia
  - Pierre Robin syndrome
  - Cystic hygroma
  - Laryngeal cysts
  - Tracheal stenosis
5. Pneumothorax

### Congenital Diaphragmatic Hernia (CDH)

CDH results from failed closure of the embryonic pleuroperitoneal canal. The incidence is 1 in 2000 live births. Males and females are equally affected. It is largely sporadic and non-syndromic.

There are three anatomical types:

1. Posterolateral hernia through the Bochdalek foramen (90%)
2. Anterior subcostal or retrosternal Morgagni hernia (6%)
3. Paraesophageal hernia (4%).

#### Left Bochdalek Hernia is the Commonest

**Clinical features:** It presents in a wide spectrum ranging from severe respiratory distress at birth to no symptoms at all. Cases with an antenatal diagnosis before 34 weeks often die *in utero* resulting in still birth. The symptoms in a newborn are:

- Respiratory distress
- Scaphoid abdomen (most bowel loops are in the chest)
- Large chest
- Apex beat on right
- CXR shows bowel loops in the chest with obliteration of the diaphragm (Fig. 61.23). The mediastinum is shifted to the opposite side. An important differential diagnosis on X-ray is congenital cystadenomatoid malformation.

**Pathophysiology:** The following factors contribute to the pathophysiology of CDH

- Pulmonary hypoplasia
  - Reduced lung mass
  - Reduced cross sectional area of pulmonary vasculature
  - Thick muscle of pulmonary arteries
  - Pulmonary arteries are hypersensitive to hypoxia



Fig. 61.23: Left diaphragmatic hernia

- Persistent pulmonary hypertension resulting from persistent fetal circulation
- Mechanical compression of the lung by intestines
- Possible surfactant deficiency.

The most important feature in pathophysiology is pulmonary hypertension due to thick muscular pulmonary arteries, which are extrasensitive to hypoxia. With minor variation in inspired oxygen concentration the pulmonary arteries may go into disproportionately severe spasm occluding pulmonary flow. The aim of preoperative management is to lower pulmonary vascular resistance by improving oxygenation, vasodilators and ventilatory therapy.

#### **Initial management**

- Nurse under radiant warmer with head elevated.
- Pass a nasogastric tube and leave it on free drainage.
- **Endotracheal intubation:** Do not mask ventilate as it would cause further bowel distension and lung compression.
- Paralyze and ventilate with high rates, low pressures, low tidal volume and high  $\text{FiO}_2$ . Allow permissive hypercapnia for better pulmonary function. Newer modes of ventilation like high frequency oscillatory ventilation (HFOV) and jet ventilation may have to be employed if conventional ventilation fails. Adequate ventilation is the key to lower the pulmonary arterial pressure.
- 100% oxygen to begin with. Very slow and gradual reduction as the child improves.
- Decrease pulmonary vascular resistance to stop R-L shunting.
- Volume expansion and inotropes to maintain systemic blood pressure.

- Pulmonary vasodilators.
- Correct metabolic acidosis.
- **Monitoring:** Arterial lines should be put in the right radial artery and the umbilical artery to monitor pre- and postductal  $\text{PaO}_2$ . The aim of ventilatory management should be to achieve postductal  $\text{PaO}_2 > 60$  mm Hg,  $\text{PaCO}_2 < 30$  mm Hg and pH 7.45. The difference in pre and postductal  $\text{PaO}_2$  should not be more than 20.
- In refractory cases inhaled NO may be used as a potent vasodilator.
- ECMO support in selected cases.

Surgical correction of diaphragmatic hernia should be undertaken only after stabilization. Hypoxia should have been corrected. There should be no acidosis on blood gas analysis. If pneumothorax is detected as a cause for deterioration on medical management, intercostal tube thoracostomy should be performed. Surgery entails abdominal exploration and reduction of contents into the abdomen. The ipsilateral hypoplastic lung does not expand immediately and occupies the apex of the chest, the rest of the hemithorax being occupied by air. The defect in the diaphragm is closed. Postoperatively ventilatory support is continued with low pressures and high rates. The fragile lung is buttressed by the free air while it gently expands over the next few days. The air gets absorbed. Some surgeons prefer to put an intercostal tube to drain blood and serum. The ICD should be partially clamped (allowing 1-3 cm column movement) to prevent hypotension from wide swinging movements of the mediastinum, that would otherwise occur due to free transfer of transpleural gradient across an open chest tube.

Laparoscopic/thoracoscopic repair of diaphragmatic hernia is possible in neonates.

**In utero interventions:** The main reason for mortality in CDH is pulmonary hypoplasia and persistent pulmonary hypertension. Presence of fetal liver in the chest and fetal **LUNG to HEAD ratio (LHR) less than 1** universally indicate poor fetal prognosis justifying fetal intervention. Animal models in 1980s demonstrated that lung development could be achieved by surgically repairing the hernia in the second trimester through a fetal thoracotomy. However, there was a high mortality due to intrathoracic liver getting lacerated and from vascular kinking at umbilical veins. Alternate methods were then developed which aimed at pushing the thoracic contents down slowly by increasing the chest fluid. This was achieved by occluding the fetal trachea by a clip (**PLUG-Plug the Lung Until it Grows**). This prevented the tracheal fluid from

escaping—hence the bowel in the chest was pushed down and lung development ensured. However, at the time of delivery the tracheal clip had to be removed surgically at the time of birth before the cord was clamped (Extrauterine intrapartum techniques, i.e. **EXIT** procedure).

Tracheal occlusion by fetoscopic techniques using an expandable balloon at 26-28 weeks is currently the favored approach in fetal surgery. Thoracic liver and LHR < 1 are the indications. The balloon is removed at 34 weeks again by fetoscopic techniques. The fetus is delivered at term and the anatomical defect repaired.

### Esophageal Atresia and Tracheo-esophageal Fistula (EA and TEF)

The three most *common anatomical types* are: esophageal atresia with a fistula between the distal esophagus and trachea (86%), pure esophageal atresia without fistula (8%) and H type fistula without atresia (4%). Embryologically the respiratory tract originates from a ventral diverticulum of the primitive foregut. Incomplete separation of this diverticulum from the foregut results in the anomaly. This being a first trimester event (period of organogenesis) other associated malformations are seen in 50% cases. About 15% have VACTERL association (Vertebral, Anorectal, Cardiac, Tracheo-Esophageal, Renal, and Limb). The significance of VACTERL association is that these patients have a severer malformation and have higher complication and mortality rates.

The incidence is 1 in 5000 live births.

**Antenatal diagnosis:** Polyhydramnios and absent gastric bubble with a dilated upper esophageal pouch in the neck are the characteristic features in antenatal ultrasound. But it is seen in only 40% cases.

**Diagnosis at birth:** Since the outcome depends on early recognition and treatment, all neonates should be assessed for this anomaly by passing a orogastric tube into the stomach. In EA with or without TEF the tube typically gets stuck at about 10 cm from the lower gum and cannot be passed into the stomach. Passage of tube into stomach and aspiration of gastric secretions rules out esophageal atresia. Care should be used to pass a relatively stiff tube such as size 8-10 red rubber tube or the tubing of a mucus extractor. Softer feeding tubes often coil in the dilated upper pouch giving a false impression of through passage.

If the baby has not been tested in the delivery room, the child may have been given to the mother. Very soon the baby will develop typical clinical features which are as follows:

1. Drooling saliva and regurgitation of feeds—because of a total block in the esophagus no saliva or milk can be swallowed.
2. Respiratory distress contributed by (a) aspiration of saliva/milk into the airway causing pneumonitis; (b) reflux of acidic gastric contents through the lower pouch into the lungs; (c) diaphragmatic splinting by distended stomach and d) associated cardiac defects
3. Abdominal distension by escape of inhaled air through the fistula.
4. Choking on feeding.
5. Failure to pass a nasogastric tube beyond 10 cm.

It is not uncommon to see a late diagnosis (usually home deliveries) when the child presents with pneumonitis and TEF is detected during the course of examination and investigation.

#### Pitfalls

- a. Posterior pharyngeal perforation may mimic EA and TEF.
- b. In a sick preterm baby with EA and a large TEF the cough reflex may be weak. The nasogastric tube may be passed in the trachea and through the fistula into the stomach.
- c. In 14% cases of gasless abdomen, a fistula is present but obstructed by mucus.

#### X-ray Diagnosis

Plain chest X-ray including the abdomen should be taken with the tube in the upper esophageal pouch (Figs 61.24 and 61.25). The stiff tube should stretch the upper pouch to help assess the level of the pouch—it helps in planning the surgery. Presence of gas in the stomach establishes that there is a fistula between the distal esophagus and the trachea. Gas less abdomen means pure atresia, or rarely a blocked fistula. When a feeding tube is used it is often found coiled in the upper pouch. Putting about 3-5 ml of air through the feeding tube, may delineate the upper pouch better. Care should be taken to take the X-ray after doing upper pouch suction. X-ray may show pneumonitis and/or pneumothorax if complicated. A boot shaped cardiac silhouette may suggest tetralogy of Fallot. Dye studies are completely unnecessary and risk aspiration of contrast material. Triple atresia (Esophageal, duodenal and anorectal) can be diagnosed by an absent anus on examination, distended stomach and duodenum, but no distal gas on X-ray.

**Other investigations:** Echocardiography and renal ultrasound should be performed in all babies preferably preoperatively to pick up associated cardiac and renal defects. Presence of vertebral anomaly on X-ray calls for a spine ultrasound to check for tethered cord. Some



**Fig. 61.24:** Esophageal atresia with tracheo-esophageal fistula. Note the feeding tube in the upper pouch and plenty of abdominal gas



**Fig. 61.25:** Pure esophageal atresia. Note the tube in the upper pouch and a gas-less abdomen

units do preoperative bronchoscopy to define the anatomy, rule out proximal fistula, confirm pure atresia, and to block a large fistula to improve ventilation.

**Management:** Suck the upper pouch initially by a mucus sucker and later by a double lumen suction catheter (Replogle tube), which provides sump suction at low pressure without damaging the mucosa. The outer lumen should be flushed regularly to keep it patent. Baby should be kept nil orally. IV access should be obtained on the right hand. Blood samples should be drawn for hemoglobin, urea and electrolytes and blood grouping and cross matching. A cephalosporin and aminoglycoside combination is started. SpO<sub>2</sub> should be monitored and kept above 90 by oxygen hood. The baby should be nursed in a 30° degree head up position to prevent reflux of gastric contents into the respiratory tract. Humidification and chest physiotherapy should be instituted to optimize the lungs. Surgery should be performed soon after stabilization.

1. A primary repair through a thoracotomy is the most preferred operation for TEF. Most cases are dealt with this way after reasonable optimization of the chest. The fistula is taken down, trachea repaired and the esophageal ends anastomosed end to end.
2. If after fistula ligation the two ends of the esophagus cannot be brought together for anastomosis (long gap EA), gastrostomy and cervical esophagostomy is performed in the first sitting. Esophageal replacement is carried out few months later. If advanced ICU care facility is available, a delayed primary anastomosis may be possible. Several techniques to lengthen the esophagus are available to save the negative esophagus.
3. **Pure esophageal atresia:** Primary anastomosis is not possible because of the large gap. No thoracotomy is required at birth. Cervical esophagostomy and gastrostomy is done at birth and esophageal replacement performed at few months age. Again most western center would do a delayed primary repair at 8 weeks after the esophagus has lengthened enough to be brought together. Different esophageal lengthening procedure may be employed in the interim.
4. If the child is very sick and high risk for anesthesia at presentation (severe pneumonia, abdominal distension, low birth weight), an emergency thoracotomy to ligate the fistula is done and primary repair is delayed. Rarely a temporizing gastrostomy may be in order to decompress the stomach and improve ventilation.

In recent years thoracoscopic repair of EA and TEF has been started in some centers with results comparable to open surgery.

**Postoperative care after primary repair:** The baby is kept in the ICU. Chest physiotherapy is given gently. Oral

secretions need suction. The suction catheter should be marked so that it does not reach the anastomosis. If a transanastomotic tube has been put during surgery, feeds may be started about 48 hours post op. Antireflux treatment is also given. IV antibiotic is continued for about 5-7 days. On day 7 a contrast swallow is done to check for anastomotic patency and leak. Providing there is no leak the chest tube is removed. Antireflux treatment is continued for a few to several months.

Tracheomalacia causing barking cough, GER and chest infections are common postoperative complications.

### Congenital Lobar Emphysema (CLE)

This is relatively uncommon but an important cause of respiratory distress. It is characterized by over distension of a lung lobe by air trapping, causing compression of the normal lobes and herniation of the affected lobe to the opposite hemithorax. The upper lobes are predominantly affected (80%). The common causes are: intrinsic bronchial obstruction—abnormal cartilage or bronchomalacia, developmental abnormality of alveoli, or pulmonary alveolar hyperplasia.

Clinical findings are respiratory distress, asymmetric thorax, a shift in apex beat and focal hyperresonance and reduced breath sounds on the affected area. Most common presentation is within the first month. The diagnosis is established by a chest X-ray that shows lobar hyperinflation, mediastinal shift, and compression atelectasis of the adjacent lung lobe and flattening of the ipsilateral diaphragm (Fig. 61.26). The inexperienced may mistake it for pneumothorax and put in a chest tube into an emphysematous lobe with disastrous result. In pneumothorax the entire ipsilateral lung is collapsed into the hilum, while in CLE the adjacent compressed lung can almost always be seen. In CLE the lung markings may sometimes be seen; in pneumothorax they are never seen. The other differential diagnosis is congenital cystadenomatoid malformation (CCAM) and pneumatoceles. A CT scan is confirmatory (Fig. 61.27). Treatment is prompt resection of the offending lobe through a thoracotomy. Even if the diagnosis is made incidentally without much symptoms lobectomy should be performed early as the natural history is progressive. During anesthetic induction with positive pressure the hyperinflation may suddenly increase needing rapid thoracotomy. Postoperative care is simple and long term prognosis is good.

### 6 Congenital Cystadenomatoid Malformation (CCAM)

CCAM accounts for 25% of lung, malformations. It is characterized by an increase in the terminal respiratory



Fig. 61.26: X-ray chest in CLE

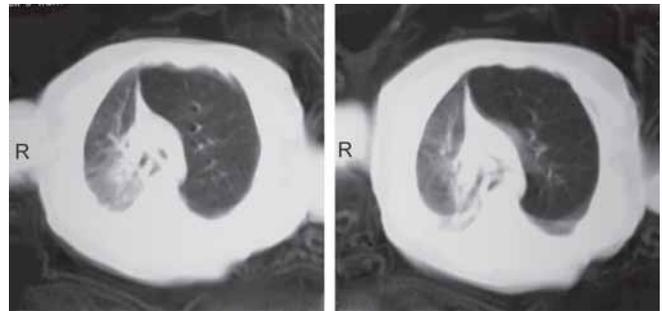


Fig. 61.27: CT appearance in CLE

bronchioles and the alveoli forming intercommunicating air filled cysts but with no connection with the lung mesenchyme, therefore no participation in gas exchange. The malformation can be macrocystic or microcystic. Prenatal ultrasound diagnosis is possible at 23-26 weeks. The typical lung lesion carries a bad prognosis if accompanied with polyhydramnios, ascites, hydrothorax and hydrops. Termination of pregnancy should be considered in such situation. Clinical presentation at birth or after few days/weeks is with varying degree of respiratory distress. Older children may present with recurrent chest infections. Figure 61.21 chest X-ray shows a sharply outlined radiolucent area with adjacent lung collapsed. The diaphragm may be pushed down, but adequately seen (unlike CDH where the diaphragm outline is lost). Microcystic variety may be difficult to pick on chest X-ray. Ultrasound is helpful in differentiating it from CDH. CT scan (Fig. 61.29) gives definite diagnosis and extent to plan surgery. Treatment is resection of the involved lobe of



Fig. 61.28: X-ray appearance in CCAM

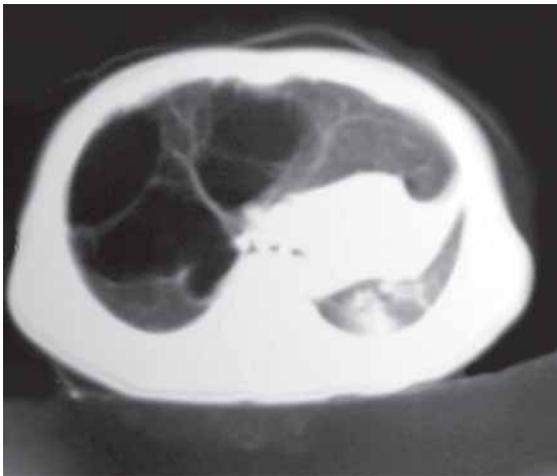


Fig. 61.29: CT appearance in CCAM

the lung. Prognosis is good in absence of associated malformations.

## Upper Airway Obstruction

### *Choanal Atresia*

Bilateral membranous or bony blockade of the posterior nasal passages is referred to as choanal atresia. A neonate is an obligate nasal breather except when crying. A baby who is well and pink when crying, but becomes cyanosed and distressed when at peace should be suspected of having bilateral choanal atresia. Unilateral choanal atresia is asymptomatic except when the functioning nostril is used for passing a nasogastric tube. Crying opens up the direct route of mouth

breathing. For the same reason they develop respiratory distress when feeding is attempted. Putting an oropharyngeal airway relieves them immediately.

Diagnosis is suspected when one is unable to introduce a feeding tube through the nostrils. CT scan is confirmatory. Emergency treatment is by passing an oropharyngeal airway for breathing and orogastric tube for feeding. Surgery should be performed expediently with release of bony or membranous obstruction and insertion of stents. If necessary the surgery may be delayed to allow weight gain.

### *Pierre Robin Syndrome*

This consists of micrognathia and retrognathia of the mandible, relative macroglossia and high arch palate with or without a cleft. The relatively large tongue tends to fall back causing airway obstruction. Feeding also is troublesome for the same reason. If the child can be pulled through initial 4-6 weeks, spontaneous improvement occurs by growth of the mandible and the child getting used to the abnormality. The neonate is nursed prone with head end down a little and neck extended. Feeding technique including breastfeeding should be individualized by a breastfeeding specialist. Alternatively gavage feeding may be resorted to. Application of a stitch to the tongue and fixing it to the chin is another option but is not usually necessary.

### *Miscellaneous Lesions*

Cystic hygromas in the neck may compress the airway from outside. Sudden distress may be caused by inflammation or bleeding in the lesion. Image guided aspiration of larger cysts may relieve the pressure partially. Emergency intubation may be required to establish a patent airway. Tracheostomy may be life saving if intubation fails. Laryngeal and tracheal cysts may produce stridor. Bronchoscopy is diagnostic and therapeutic aspiration may also be done. Recurrence, which is common, should also be treated by bronchoscopic aspiration. Flexible fiber-optic bronchoscopy using neonatal scope (2.5 mm wide for preterm and 3.5 mm for term) has revolutionized the diagnosis and management of laryngeal and tracheal pathology.

### *Pneumothorax*

Pneumothorax can be the cause of respiratory distress per se or more commonly it can cause sudden deterioration in an already distressed child. The common conditions that predispose to pneumothorax are HMD, MAS, TEF and CDH and babies on mechanical ventilation. Recognition should be prompt as delay in

therapy may be fatal. Clinically, it is recognized by sudden worsening of distress, unilateral hyperinflated chest, shift in apex beat, decreased breath sounds and a positive chest transillumination. When not sure it is advisable to assume it and treat with aspiration of air with a venflon inserted in the 2nd intercostal space in the anterior axillary line, or 5th intercostal space in the mid axillary line. The cannula is left inside the chest and connected to an underwater seal through an IV set. The free air escapes immediately in bubbles followed by small column movement in the tubing. Clinical relief should be dramatic. The thin cannula is likely to get blocked soon, so it is advisable to replace it with a formal intercostal tube put under local anesthetic in the unit. Once the column movements become minimal the ICD should be clamped for few hours and an X-ray repeated. If no further accumulation of air has occurred the tube can be removed. Broncho-pneural fistula, characterized by persistent bubbling, occasionally develops. In such situation suction should be applied (10-15 cm water) through a two bottle system connected to the ICD. Very rarely it may require further surgery. Bronchoscopic application of biological tissue sealants is another option.

*The neonatologist should be careful about the following situations:*

1. Congenital lobar emphysema (CLE) can be mistaken as pneumothorax. Chest tubes have been inserted into CLE on many occasions. The X-ray in CLE shows features of collapsed middle lobe (hazy cardiophrenic angle) in addition to emphysema-tous upper lobe. In pneumothorax the entire lung gets collapsed and lies along the mediastinum. A good quality X-ray in CLE may show some bronchovascular markings.
2. Spontaneous air leaks causing pneumothorax and pneumomediastinum are often asymptomatic. Up to 15% of a hemithorax maybe occupied by air without any symptoms or consequences. Such cases are managed conservatively unless IPPV is contemplated, when ICD should be inserted.

### POSTERIOR URETHRAL VALVES (PUV)

PUV is the most common obstructive uropathy of the lower urinary tract in a male neonate. About 30% of all patients of PUV present in the neonatal period. Out of them 50% will have antenatal ultrasound diagnosis suggested by bilateral upper tract dilatation, distended bladder, distended posterior urethra (key hole sign). Oligohydramnios and echogenic kidneys, when present indicate poorer prognosis. Besides urethral obstruction the key factors contributing to the overall morbidity are: bladder dysfunction, functional ureteric obstruction



**Fig. 61.30:** MCUG in a case of PUV. Note the dilated posterior urethra and vesicoureteric reflux

and varying degrees of genetically determined renal dysplasia.

At birth the child may be completely asymptomatic or may have poor urinary stream. A little older neonate may present with sepsis, azotemia, dyselectrolytemia dehydration and acidosis. Examination shows a palpable hard bladder even after micturition. This is because the bladder in a neonate is an abdominal organ and in PUV it gets hypertrophied due to distal obstruction. Kidneys may also be palpable. If oligohydramnios was significant the child may have respiratory distress (lung hypoplasia) and limb compression effects. The diagnosis should be established by postnatal ultrasound and micturating cystourethrogram (MCUG) (Fig. 61.30).

**Treatment components are:**

1. **Initial drainage** by a 6 Fr infant feeding tube placed per urethra. A Foley catheter should not be used as the balloon may occlude the ureteric orifices. Rarely the balloon of a Foley may be inflated in the dilated posterior urethra. If good urine flow is obtained and the upper tracts decompress on ultrasound, the prognosis is better. It also indicates that primary valve incision will be successful because the upper tracts specially the ureters have normal clearance. If the patient was azotemic the creatinine should fall by approximately 10% per day if the urinary flow is good. Failure to achieve upper tract decompression on urethral catheter is indicative of poor ureteric

clearance and hence a higher diversion in the form of ureterostomy or pyelostomy is needed.

2. **Fluid and electrolyte management:** Post obstruction diuresis can cause severe dehydration, hyponatremia and acidosis. A careful watch on the urinary output and electrolytes is mandatory. High sodium and fluid volumes are needed to offset the diuretic effect. Blood gas analysis should be repeated frequently to assess and treat acidosis.
3. **Management of sepsis and supportive treatment:** Antibiotics are given as per culture reports. Care should be taken to adjust the dose according to the serum creatinine values. General supportive care is provided. When not infected prophylaxis should start with cephalosporin. Trimethoprim should not be given for the first 2 months.
4. Definitive treatment is endoscopic valve ablation. Postoperatively urinary catheter is kept for 48 hours. Prophylaxis is continued and bladder function monitored. Oxybutynin is started to relax a hypertrophied bladder and prevent building up of high bladder pressures. Some surgeons including the author prefer to do circumcision in the same sitting.
5. **Vesicostomy:** If the response to catheter is good but the scopes are not available or the child is too small,

**Table 61.6. Prognostic factors in PUV**

Good prognosis	Poor prognosis
Late diagnosis	Early diagnosis
Non echogenic kidneys	Echogenic kidneys
Good liquor	Oligohydramnios
Good drainage on catheter	Poor drainage
Pop off mechanisms	
VURD syndrome	
Urinary ascites	
Cr < 0.8 mg% at one year	Cr > 0.8 mg% at one year

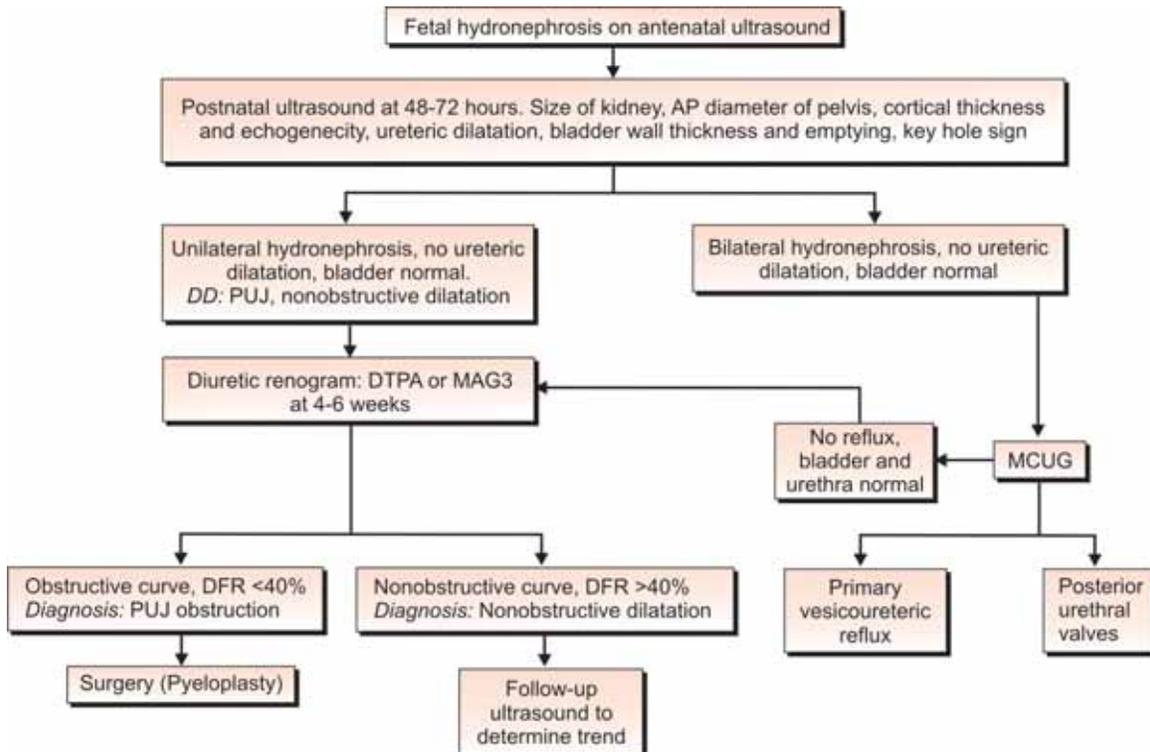
a vesicostomy is done to decompress the system temporarily.

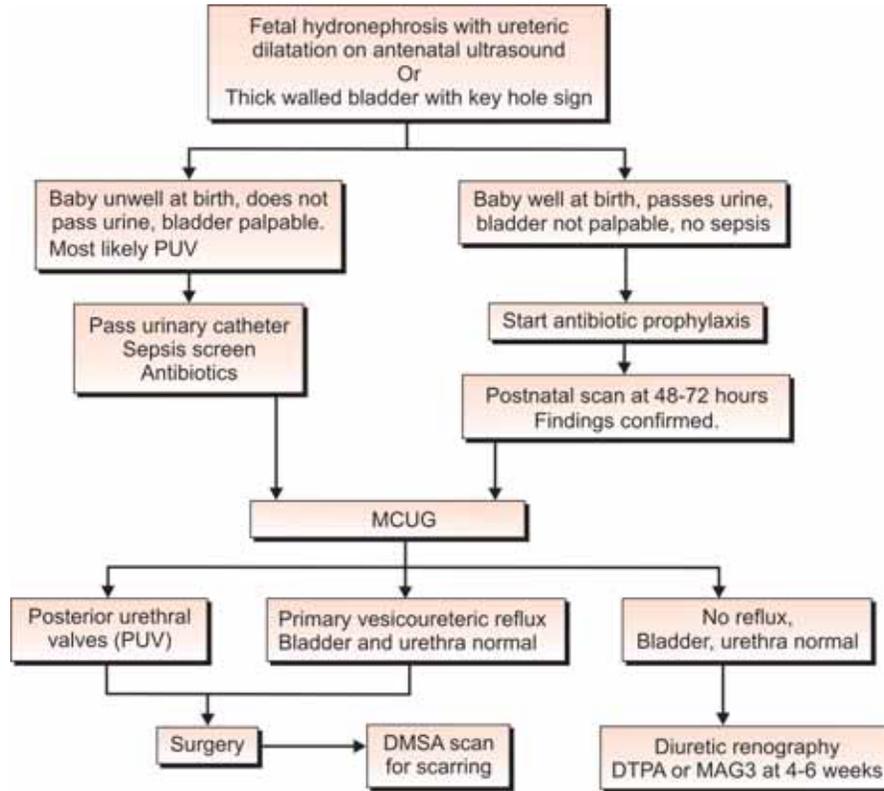
6. **High ureterostomy/pyelostomy:** This is indicated if the response to catheter is not good, azotemia persists and sepsis remains uncontrolled. Ureterostomy can be life saving in such situations. Definitive valve ablation is deferred for about one year. Prognostic indicators are highlighted in Table 61.6.

**ANTENATAL HYDRONEPHROSIS**

Unilateral hydronephrosis is the most common abnormality detected on antenatal ultrasound. This has

**Flow chart 61.1: Investigation of antenatal hydronephrosis**



**Flow chart 61.2:** Investigation of antenatal hydroureteronephrosis

resulted in an epidemic of radiological “PUJ” obstruction. It is frequently the cause of *in utero* referral for parental counseling and prognostication. 17% of all prenatal diagnosis refers to urinary tract. Half of these is upper tract dilatation (Hydro-nephrosis) equated with PUJ obstruction. Although 70-80% of antenatal hydronephrosis is nonobstructive dilatation not needing surgery, it requires evaluation in all to promptly identify those 20-30% that are truly obstructive and need surgery. An antenatal history and progression of dilatation is a good guide. There is a direct correlation between AP diameter of the renal pelvis and probability of obstruction. If the AP diameter is above 50 mm there is almost 100% chance of the baby needing surgery soon after birth. Investigative approach is shown in the Flow charts 61.1 and 61.2. Antenatally the expectant mother should be reassured and the delivery should take place in a referral unit. Indications of neonatal pyeloplasty in antenatal hydronephrosis are shown in Table 61.7.

If no indication for surgery is there, the baby is followed up with ultrasound scans very 3 months for the first year, every six months for the next year and yearly thereafter till the dilation normalizes.

**Table 61.7:** Indications of neonatal pyeloplasty in antenatally detected hydronephrosis

- Palpable kidney at birth with pelvic AP diameter > 50 mm
- Obstructive curve on diuretic renography
- Differential renal function <40%.
- Progressive dilatation on serial ultrasounds
- Progressive loss of cortex
- Falling differential renal function.

### Special Situations

#### **Bilateral upper tract dilatation on antenatal scan:**

Bilateral PUJ obstruction can occur in 20 % cases. Ureteric dilatation must be looked for every diligently to exclude lower urinary tract abnormality such as VUR and posterior urethral valves. MCUG is always performed for this purpose. The baby is put on prophylaxis. If bilateral PUJ obstruction is confirmed early pyeloplasty should be performed on the better functioning kidney first. Functional assessment is better done by GFR estimation on radionuclide scan than by differential renal function.

**Giant hydronephrosis with thin cortex and poor function:** These cases are better managed by an initial

percutaneous nephrostomy. Pyeloplasty is performed in about 8 weeks if there is functional recovery. Otherwise a nephrectomy is performed.

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## INTRODUCTION

Neonatal transport is an evolving concept in the Indian scenario. *In utero* transfer is the safest transfer but unfortunately, preterm delivery, perinatal illness and congenital malformations cannot always be anticipated, resulting in a continued need for transfer of babies after delivery.<sup>1</sup> These babies are often critically ill, and the outcome is partly dependent on the effectiveness of the transport system.<sup>2</sup> In developing countries the problem of transporting small and sick neonates is compounded by several practical constraints like:

1. Facilities are scarce and not easily available.
2. Families have poor resources.
3. Organized transport services are not available. At times the baby may have to be transported on foot or on bullock cart.
4. No health provider is available to accompany the baby.
5. Facilities are not fully geared up to receive sick neonates.
6. Communication systems are non-existent or inefficient.

Thus, transporting neonates in developing countries is a formidable challenge. In spite of the best planning, babies will develop serious problems during transport to a higher level of care. Care providers should, therefore, be ready and confident to handle this responsibility.

In India, however, almost two-thirds of births take place in the community. Antenatal care is inadequate. Thus we are faced with the problem of shifting sick neonates born in the community to the nearest equipped hospital, which is compounded by a poorly developed virtually non-existent neonatal transport system. As a result most of the referred neonates reach the hospital in a critical state; the mortality risk amongst these neonates being at least 5 fold higher than amongst those delivered in hospitals or referred in a stable condition. There is thus a need for all those involved in the care of neonates to be familiar with the principles of neonatal transportation.

## WHY IS TRANSPORT OF SICK PATIENTS NECESSARY?

Transportation of the sick or preterm babies to the center with expertise and facilities for the provision of multi-organ intensive care has been shown to improve outcomes.<sup>3</sup> In India, majority of the deliveries still occur at home (approximately 60% in rural areas as per NFHS 3) and only 1 out of 7 home deliveries are attended by skilled birth attendant. Prematurity, asphyxia and sepsis are the most common cause of neonatal mortality in our setting.<sup>4</sup> With the initiative of state governments in developing Special Care Newborn Units (SCNU) at District Hospitals, many of the sick neonates can be provided better newborn care if they are timely transported in a stable condition.

## CLINICAL PRESENTATION OF TRANSPORTED BABIES

Common indications for babies transported include prematurity (82%), hyaline membrane disease (62%), sepsis (54%) and birth asphyxia (16%).<sup>5</sup>

In India, the onus of transport usually lies with the parents, who, are barely informed about the condition of their baby and the indications of transfer. Mir et al<sup>6</sup> observed that attendants traveled distances varying from 2-100 km. Transport vehicles used were cars (73%), rickshaws (10.8%), open jeeps (6.4%), and buses (5.4%), and in only 3 percent by ambulances (Fig. 62.1).



Fig. 62.1: A bullock cart being used to transport a neonate

Hypothermia has emerged as the major cause of morbidity and mortality especially in preterm babies during transport. In babies transported by referring hospitals, at time of admission 38.4% of babies were hypothermic. Other abnormal parameters at time of admission include low oxygen saturation (21.7%), hypoglycemia (20.5%), hyperglycemia (20.5%), hyperthermia (15.3%)<sup>5</sup> Singh et al,<sup>7</sup> noted hypothermia in 14.5 percent of neonates transported to their institutions with a mortality of 56.2 percent as compared to an overall mortality of 26.3 percent. The neonates were usually brought to the emergency department wrapped in cotton (24.5%), blanket (25.4%), quilt (11.8%) or just in towels without any external source to provide warmth. Very rarely Kangaroo care was provided to keep the babies warm. A secure intravenous (IV) access was almost always lacking. Oxygen was provided only to those babies who were brought in an ambulance equipped with cylinders, thereby increasing their mortality.

Observations on transported neonates at our institution show that on arrival 26.2 percent were hypothermic (34.8% were shifted wrapped only in cotton), 15.4 percent had hypoglycemia and 13 percent had poor perfusion. Also 31.4 percent of babies had no IV access and only 6.8 percent of babies came with some form of oxygen supplementation. The mortality amongst transported babies was 52 percent compared to 10 percent amongst intramural births.

### TYPES OF TRANSPORT<sup>8</sup>

There is widespread agreement that neonates should have access to facilities appropriate to their care needs and that movement to different care destinations should be provided by staff trained to move them swiftly, but safely to such facilities.

Neonatal transfers can be categorized as follows:

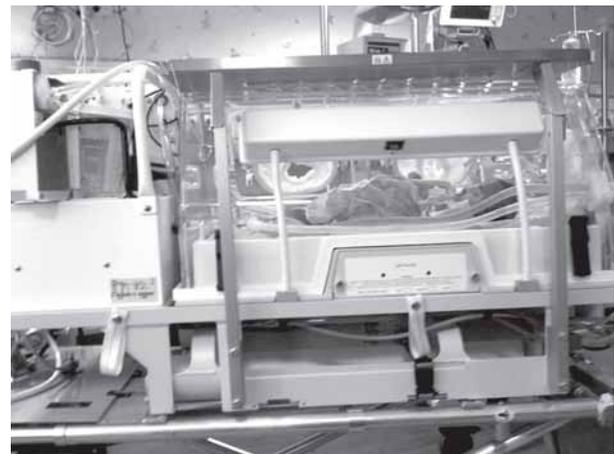
1. Intrahospital transport (including delivery suites, theaters) (Figs 62.2 and 62.3).
2. To facilitate specialist management of the neonate (movement to a regional center for cardiac, neurological, renal or surgical opinion) (Fig. 62.4).
3. Retrieval from a peripheral hospital for ongoing intensive care within a level 3 unit (when mothers deliver prematurely without warning).
4. Returning infants to local neonatal units following care elsewhere (either locally or long distance) – reverse transport.

### REGIONALIZATION OF NEONATAL HEALTH CARE FACILITIES

Neonatal transport programs require appropriate referral systems, management structures and trained



**Fig. 62.2:** Neonate transported to nursery wrapped in a towel in a thermocol box



**Fig. 62.3:** Intrahospital transfer of a neonate in a transport incubator

transport personnel. They need to utilize transport equipment, address transport logistics and have a quality improvement program. Local factors such as geography, population density and organization of perinatal services affect the manner in which different transport programs function.

There are various regionalized neonatal transport systems distributed all over the world. Among them, the popular ones are the neonatal transport system of New South Wales of Australia (NETS), various regionalized transport systems in United Kingdom and in United States of America.

In India, Hyderabad has tried to make a regionalized transport network where they are transporting babies in and around 250 kms of Hyderabad. In a retrospective analysis done over a period of 33 months they found that biochemical and temperature disturbances are more common in babies transported on their own and



**Figs 62.4A and B:** A cardiac ambulance used for road transport along with an air-transport plane

a specialized neonatal transport service could improve the survival of these babies.<sup>5</sup>

Similarly in India, Tamil Nadu and Madhya Pradesh and Gujarat are the other states where regionalized neonatal transport services are available.

### WHOM TO TRANSPORT

An important aspect of transportation is to be able to assess which babies would need transport. The following are broad indications for which neonatal transport should be considered:

- Very low birth weight infants especially below 1250 g.
- Prematurity:
- Respiratory distress or apnea
  - Requires supplemental O<sub>2</sub>
  - Apnea requiring bag and mask ventilation
- Cyanosis persisting despite oxygen therapy
- Hypoxic ischemic encephalopathy
  - Requires intubation and assisted ventilation
  - Develops seizures activity
  - Multi-organ involvement
- Sepsis with signs of systemic infection
- Jaundice with potential for exchange transfusion
- Active bleeding from any site
- Infant of diabetic mother or hypoglycemia unresponsive to recommended treatment
- Surgical conditions
- Congenital heart disease (antenatal diagnosis or suspected)
- Heart failure or arrhythmia
- Suspected metabolic disorder
- Severe electrolytes abnormalities
- Infants requiring special diagnostic and/or therapeutic service.

### WHERE TO TRANSPORT

After a decision is taken to transport a neonate, the next question that needs to be resolved is the place where the neonate is to be transported. The sick neonate needs to be referred to the nearest health facility that is appropriately equipped to provide for the needs of that particular infant. However, the distance and time to reach a health facility and the ability of the neonate to remain stable during transport may determine the choice. A sick newborn from home may need to travel the shortest distance to a health facility without an identified neonatal care service but this facility would still be better than being at home. In an urban setting, the transport may be from a smaller hospital to a larger tertiary care center. The rule of thumb in most cases is to *transport to the nearest place with desired facilities*. However, it is important to ensure that when the transportation is being made from one health facility to another, the referral hospital has prior intimation of the transportation and is ready to accommodate the sick neonate. Transporting a sick neonate from one facility to another in search of admitting facility invariably destabilizes the neonate with an adverse outcome.

### MODE OF TRANSPORT

The mode transport (ground, air) should be determined by the transferring institution in consultation with the referral hospital. The thumb rule is to use *the safest and fastest means of transport that is available*. The vehicle used would depend on the local terrain, condition of the neonate, distance to be traveled, safety and costs. The transport vehicle should be compatible with weather and traffic conditions. Appropriate



Fig. 62.5: A transport ambulance with an oxygen cylinder

climate control is essential while transporting neonates, who are at risk of hypothermia. It is desirable that a dedicated neonatal transport vehicle be available, that is provided with adequate working space, good lighting and power sources, safety equipment and life support system. Ground transport is useful for distances of 100-120 km, beyond which an aircraft is desirable. However, in places like India where proper ground transport is rarely available, air transport is utopian. Under such circumstances one has to choose the fastest possible mode of transport this may be a local bus, tractor, auto-rickshaw, minibus, car, scooter, etc.

The ambulance used for neonatal transport should, at a minimum, meet the requirements for a basic life support ambulance (Fig. 62.5). In order to accommodate neonates, the ambulance also must provide:

1. Secure fixation of the transport incubator to the cot rails.
2. Secure fastening of other equipment (e.g. oxygen and air tanks, monitoring equipment).
3. Independent power source to supplement equipment batteries to guarantee uninterrupted and fail-safe operation of the incubator and other monitoring and supportive equipment. Necessary adapters to access the ambulance power source should be readily available.
4. Environmental conditions that reduce the risk of temperature instability, excessive noise and vibration and infection.
5. Rapid and safe transport without compromising safety.

### TRANSPORT PERSONNEL

The need for creating a team for organized neonatal transport service or accompanying person in case of

community transport which could be ASHA worker, ANM, a paramedic trained/untrained or a family member. The accompanying person should be trained in ongoing essential newborn care during transport, identification of danger signs and their immediate remedy.

### LEADERSHIP

1. **Medical director:** A physician with specialty training in neonatology or equivalent expertise.
2. **Manager:** The manager working closely with the medical director and controls day-to-day management, budget and maintenance of equipment. The manager may be a nurse or paramedic personnel.

### TEAM MEMBERS

Most transport teams is a neonatal-trained registered nurse (RN). Other programs use respiratory therapists, paramedics or a combination of these three disciplines.<sup>9</sup> Physicians are frequently added to the basic team depending on the needs of the patient and the competency of team members. No difference in outcomes has been observed when neonates are transported by trained paramedics/RN or physicians.<sup>10,11</sup> Trained nurses or paramedics for transport services are not available in India. Most units involved in organized neonatal transport utilize the services of residents, fellows or staff nurse working in neonatology for this purpose.

For all of these items, the critical characteristic which differentiates them from standard neonatal unit equipment is a capability for freestanding independent function. The extent to which each item has totally independent supplies of power or gases is dependent on the overall equipment and vehicle configuration within which it has to function. For each item a balance may have to be decided on between independent function, the familiarity of staff with equipment models and the presence of safety functions. Comprehensive training and demonstrable competency is essential for all staff using such items. An alternating current 240 V power source can be provided in the ambulance by two methods, a dedicated generator or an inverter.

Gas supplies can be provided on an ambulance, sufficient for most journeys, by large cylinders connected to a piping system using standard fixings. A vehicle which experiences high levels of use or long journeys may need to replenish supplies regularly and it is probably best to use widely available cylinder sizes, which can be replaced, in any large hospital.

Newer generations of aluminium gas cylinders are significantly lighter and have greater capacity for

compressed gas, but at this stage are not widely available although they may become so.

### TRANSPORT EQUIPMENT

The transportation of neonates requires several equipment items.

#### Thermal Support Equipment and Supplies

1. Transport incubator.
2. Radiant warmer.
3. Thermometer and/ or temperature monitor and probes.
4. Plastic wrap.
5. Insulating blankets.
6. Heat shield.

#### Respiratory Support Equipment

1. Oxygen and air tanks with appropriate indicators of in-line pressure and gas content.
2. Flowmeters.
3. Oxygen tubing and adapters.
4. Oxygen hood.
5. Oxygen analyzer (pulse oximeter).
6. Neonatal oxygen masks, nasal cannula.
7. Neonatal positive pressure bags and masks with manometer.
8. Continuous positive airway apparatus: nasal prongs, endotracheal tube.
9. Mechanical ventilator with back up circuit.
10. Endotracheal tubes: 2.5, 3.0, 3.5, 4.0 mm.
11. Laryngoscope with size 00, 0 and 1 blades.
12. Laryngoscope batteries and extra lamps.
13. Endotracheal tube holders and tape to secure ET tube.

#### Suction Equipment

1. Bulb syringe.
2. Regulated suction with gauge limiting < 100 mm Hg or < 4 inches Hg.
3. Suction catheters (5, 6, 8, 10, 12 F).
4. Feeding tube (8 Fr) and 20 ml syringe for orogastric decompression.
5. Sterile gloves.
6. Sterile water for irrigation.

#### Monitoring Equipment

1. Stethoscope.
2. Cardiac monitor.
3. Pulse oximeter.
4. Glucometer for blood sugar evaluation.

#### Parenteral Infusion Equipment

1. Intravenous catheters (24, 26 guaze).
2. Syringes (2, 5, 10, 20, 50 ml).
3. Splint.
4. Transparent dressings or micropore.
5. Three way stopcocks.
6. Intravenous administration tubing compatible with infusion pump.
7. IV chamber sets.

#### Medications

1. Calcium gluconate 10%.
2. Epinephrine (1:10000) prefilled syringes.
3. Dopamine, dobutamine.
4. Sodium bicarbonate (8.5%).
5. Morphine.
6. Midazolam.
7. Normal saline.
8. Phenobarbitone.
9. Surfactant.

### SPECIFIC EQUIPMENT ITEMS

#### Ventilators

These include ventilators that are integral to the incubator system (Air-Shields Globetrotter TI500, Draeger Medical) or standalone systems (Pneupac® babyPAC™, Smiths Medical). These systems are now capable of functioning well at the full range of rates and inspiratory times required for neonatal practice, but this should always be checked when evaluating a new system.

At present, there is no commercially available ventilator which can deliver high-frequency oscillatory ventilation during prolonged transport, mainly because these ventilators require very high gas flow rates to operate.

#### CPAP DEVICES

During transfer, CPAP can be delivered into a single nasal prong using a ventilator. If a more powerful dedicated CPAP device is used, such as the binasal Infant flow driver, there will be a need for compressed air and oxygen cylinders both in the vehicle and on the trolley when moving the baby to and from the neonatal unit. These devices have high gas requirements which may be higher than those needed for ventilation and will usually require an ambulance with its own air and oxygen supply for all but the shortest transfers.

## INCUBATORS

There are many tried and tested transport incubator systems available, providing adequate temperature control with temperate external temperatures, (Airborne 750i, GE Health care; Air Shields Globetrotter TI 500, Draeger Medical) (Figs 62.6 and 62.7). Only a limited number of incubators provide humidity at levels which will help with preterm temperature control (e.g. Globetrotter TI 500).

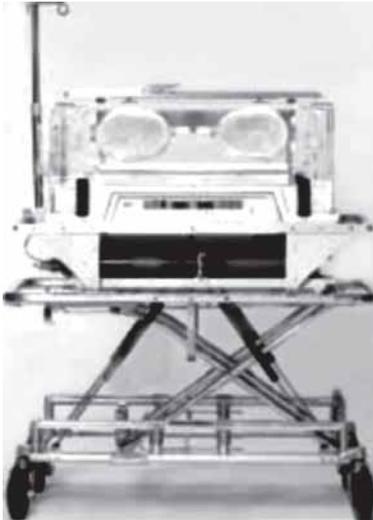


Fig. 62.6: Draeger—Air-shield globetrotter

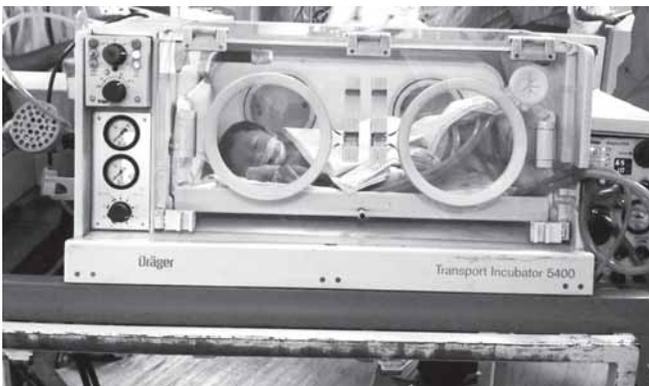


Fig. 62.7: Draeger—Transport Incubator 5400

A very simple solution to assist warming during transport is the use of phase-change gel mattresses which very effectively warm infants through release of latent heat of crystallization. So long as they are stored and activated at the correct temperature these devices can be one of the most effective ways to warm a cold infant during transfer.<sup>12</sup> In a slightly stable neonate KMC is a good, cost effective way of keeping the neonate warm



Fig. 62.8: Mother giving KMC during transport of their babies



Fig. 62.9: Twins can also be given KMC during transport

during the transport process. This can be given by the mother, father or any accompanying personnel (Figs 62.8 and 62.9).

## PRINCIPLES OF TRANSPORT

I. **Pre-transport stabilization:** Assess the baby and depending on facilities available check for temperature, airway, breathing, circulation and sugar.

- i. **Temperature:**
    1. Correct hypothermia if present before transport—KMC, provide warm clothing or under radiant warmer at stabilization unit or referring center, as most transport incubators are not able to actively warm the hypothermic baby.
  - ii. **Airway:**
    2. Assess airway for presence of any secretions (suction if present) and position of neck (place shoulder roll).
  - iii. **Breathing:**
    3. Assess for respiratory distress.
    4. Assess whether baby requires ventilation (PPV device such as self inflating bag).
  - iv. **Circulation:**
    5. Check heart rate, CRT, urine output, blood pressure (if feasible).
    6. Assess the need of fluid bolus.
    7. Check what fluids baby is getting and whether baby is on inotropes.
    8. Adjust infusion of inotropes as per need.
  - v. **Sugar:**
    9. Check sugar with glucometer.
    10. If blood glucose < 40 mg/dL, give 2 ml/kg of 10% dextrose through intravenous line.
    11. Check the patency of IV cannula and start IV fluids. Preferably have a second iv line *in situ* in case problems arise with the first one during the transport.
  - vi. Laboratory workup: Check all investigations of baby.
  - vii. Check all the medications received.
- II. Transport personnel:** Mother/attendant/ASHA from community or basic health facility. Trained nurse, paramedic or physician at the referring hospital.
- III. Equipment:** Ambulance if available or any other vehicle preferably drought free.
- IV. Care during transport**
- a. **Temperature maintenance:**
    1. Kangaroo mother care (KMC) by mother or attendant. Kangaroo mother care is a good method of temperature maintenance during transport especially in resource limited conditions when transport incubators are not available.
    2. Adequate covering of baby.
    3. Improvised containers (thermocol box, basket, polythene covering).
    4. Transport incubator if available.
  - b. **Airway and breathing:**
    1. Keep neck of baby in slight extension.
    2. Do not cover baby's mouth and nose.
    3. Gently wipe secretions from the nose and the mouth with a cotton or cloth covered finger.
    4. Watch baby's breathing. If baby stops breathing, provide tactile stimulation as in NRP.
    5. If baby required PPV during resuscitation and respiratory distress is persisting then shift the baby with oxygen as required, or on ventilator or while ventilating with PPV device such as self inflating bag.
    6. If baby required PPV during resuscitation and is now stable, monitor breathing of baby while shifting and provide tactile stimulation if baby gets apnea or ventilate with bag and mask as required.
  - c. **Circulation:** If baby has been started on IV fluids, continue same.
  - d. **Check oxygenation:**
    1. Pulse oximeter (preferable).
    2. Looking for central cyanosis (Provide oxygen if central cyanosis is present. Give enough oxygen to make central cyanosis disappear).
  - e. Inform SCNU/NICU to arrange and organize baby cot and keep the over head radiant warmer on and provide a detailed referral note (Fig. 62.10).
  - f. Inform and counsel parents regarding the condition of the baby. Provide emotional support to family.
  - g. **Feeds:**
    1. If baby can accept provide breast feeds.
    2. If not give expressed breast milk (EBM) with spoon or paladay. If EBM not available give any available milk continue IV fluids if the baby is sick.

## MODULES FOR TRANSPORT

1. SAFER (Sugar, Arterial circulatory support, Family support, Environment, Respiratory support)<sup>13</sup>
2. STABLE (Sugar, Temperature, Artificial breathing, Blood pressure, Laboratory work, Emotional support)<sup>14</sup>
3. TOPS: Temperature, Oxygenation (Airway and Breathing), Perfusion, Sugar.

## COMPLICATIONS OF TRANSPORT

- Hyperventilation during manual ventilation may cause respiratory alkalosis, cardiac dysrhythmias and hypotension.
- Loss of PEEP/CPAP may result in hypoxemia.
- Position changes may result in hypotension, hypercarbia and hypoxemia which may increase the chances of intraventricular hemorrhage.

Date ..... Time .....

Address .....

.....

Name ..... Mother's Name ..... Father's Name .....

DOB ..... TOB ..... Sex .....

Duration of Pregnancy ..... LMP ..... EDD .....

*Birth Details*

Mode of Delivery ..... Attended by .....

Place of Delivery .....

Time of 1st Cry ..... Apgar 1 min ..... 5 min ..... 10 min .....

**Resuscitation details:** Tactile stimulation / Free flow oxygen/  
 Bag and Mask Ventilation / Chest compressions

Duration of: O<sub>2</sub> ..... Bag and Mask Vent. .... Chest compression .....

Birth weight ..... grams

*Clinical course*

Feeding well Yes / No, Breastfeeds Yes / No, Spoon Feeds Yes / No

Type of feeds EBM / Formula / Any other milk Diluted milk Yes / No

Passage of Urine Yes / No Stool Yes / No

**Reason for transfer:** LBW / Respiratory distress/ Not feeding well/ Convulsions/ Jaundice/ Malformation/ Any other

*Examination Findings*

Jaundice Yes / No Any congenital malformations .....

Soles Warm/Cold, Trunk Warm/ Cold Temperature ..... °C

Heart Rate ..... / min Resp Rate ..... / min Chest Retractions Yes / No

Central Cyanosis Yes / No CFT < 3 sec / > 3 sec

Receiving oxygen Yes / No With Nasal cannula / Face mask / Oxyhood FiO<sub>2</sub> .....%

SaO<sub>2</sub> .....% Dxtx ..... mg%

Time of Last Feed

*Investigations with date*

.....

.....

*Treatment Given*

.....

.....

Place to which being referred .....

Mode of transport ..... Accompanying person .....

Name and Phone number of person at Referral Hospital .....

.....

.....

Signatures, Name, Date and Time

Fig. 62.10: Sample referral note and documentation sheet

- Tachycardia and dysrhythmias may occur.
- Equipment failure can result.
- Inadvertent disconnection of intravenous drugs may result in hemodynamic instability.
- Movements may cause disconnection from ventilatory support and respiratory compromise.
- Movements may result in accidental extubation.
- Movements may result in accidental removal of vascular access.
- Loss of oxygen supply may lead to hypoxemia.

### FAMILY COUNSELING

The birth of an infant means many things to different families ranging from happiness to mixed feelings of hardship. When a newborn is sick, parents endure an ever more complicated crisis. Parental reactions are sometimes hard to interpret. It is important to approach the family in a non-judgmental manner and to watch carefully for their non-verbal cues. The family support before and during transport should include the following:

- a. Discuss the infant's problems and plan of care. The family is given as much information as possible about the condition of the baby, the need for transport and further treatment strategy. Allow time for the parents to ask questions.
- b. Inform the family members of the cost of care and transport. Assess whether the family has adequate manpower and financial resources to shoulder this added responsibility or needs help.
- c. Written consent is taken from the parents for transport and care.
- d. Family members, preferably the mother, should accompany the sick baby.
- e. The names and telephone numbers of the physician who will be involved in the care of their infant should be given to parents, whenever possible.

### COST OF TRANSPORT

In India there are very few dedicated well-equipped teams who are committed to transfers of sick newborns babies. The cost of transport is variable, but since expensive equipment (ambulance and transport incubator) and specialized personnel are needed, it tends to be high. Estimates for transporting newborns in India are that it is about Rs 30 per kilometer of travel plus Rs. 1000 for the accompanying doctor and Rs. 500 for the accompanying nurse. Not a very large sum for a life saved.

### AVIATION PHYSIOLOGY IN NEONATAL TRANSPORT

Air transport greatly improves the speed of specialized care delivery. Undoubtedly, much morbidity and mortality has been avoided or circumvented thanks to this expedient mode of transport. Flying, however, is not free of complications.

### KEY POINTS TO PONDER

Although the ideal transport mode for a problematic fetus is *in utero*, tertiary care centers will continue to be called upon to transport sick neonates when unanticipated complications arise after delivery or when the mother is too unstable to be transferred. Personnel involved in these transports should be highly proficient in all aspects of neonatal resuscitation. Further, because initial resuscitative efforts have to be provided by the staff at the level I or II hospitals, a concerted effort should be made to train adequate numbers of personnel in techniques for resuscitation so that a skilled person is available at every delivery. A regionalized transport network contributes to effective neonatal care and also helps in proper utilization of available resources. In India since regionalization is still in its nascent stage, the concept of a uniform neonatal transport system is yet to germinate. Pretransport stabilization of the neonates is the need of the hour. Stabilization of babies before transfer not only helps a better and smooth transport but also ensures a better overall outcome.

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S e c t i o n

7



## INTRODUCTION

The term “acute abdomen” is a loosely defined condition that refers to a medical emergency in which there is sudden and severe pain in the abdomen with accompanying signs and symptoms that focus on an abdominal involvement. It also refers to a situation where an emergency management is required for an abdominal pathology.<sup>1</sup> The symptomatic manifestation of this pathology may take the form of pain, vomiting, distension, obstipation, diarrhea, fever, hematemesis and/or melena and problems of micturition, in isolation or in various combinations. In addition, a variety of physical signs may be present.

The evaluation of acute abdomen is one of the most difficult and challenging clinical problems in pediatric medical or surgical practice.<sup>2</sup> This results from the fact that the nature of abdominal pathology may take various forms; it may be visceral or parietal; inflammatory or non-inflammatory; and may or may not involve the peritoneum. The presenting features obviously depend on the nature of the pathology and organ involvement. Hence, acute abdomen refers to a vast spectrum of disease processes, and therefore the clinician is faced with a complex situation requiring detailed and meticulous evaluation, persistent observation and monitoring and optimally timed appropriate medical or surgical intervention.

### *Difference from Adults*

The clinician's problems are increased due to the fact the child is very often irritable and unable to accurately describe his symptoms. The small size of the abdomen and inadequate development of the omentum also prevent proper localization of pain and inflammation, resulting in hesitancy on the part of the patient to allow proper examination. Despite all the attending problems, the clinician has to arrive at a working diagnosis on the basis of history and physical examination in order to evaluate the pathology further and to initiate treatment. Emergency investigations are useful and at times essential for diagnosis.

In this chapter we will briefly describe the evaluation of a child with acute abdomen, the clinical signs and symptoms of common gastrointestinal disorders that have an acute onset.

## EVALUATION OF THE CHILD WITH ACUTE ABDOMEN

The evaluation of a child with acute abdomen involves careful history taking, proper examination and ordering appropriate investigations.

### History

The five main symptom complexes in the history are pain, vomiting, bowel function, problems of micturition and fever. History is usually obtained from the parents but the child should also be questioned whenever possible. It is also important to document any recent trauma and other past medical or surgical history.

### *Characteristic of Pain*

Details regarding pain are important pointers to the abdominal pathology. Sudden acute abdominal pain is usually a feature of an underlying surgical cause. Factors, which increase or decrease pain should also be looked for. The nature of pain is important, although in young children it may be difficult to elicit. Intermittent colicky pain suggests intestinal obstruction and a continuous but moderately severe pain is present in appendicitis. Mesenteric adenitis presents with similar severity and can often be misdiagnosed as appendicitis. Acute bacillary dysentery or inflammatory bowel disease manifest with diffuse crampy pain, tenesmus and loose stools mixed with blood.

*Site:* Localization of pain is most often unhelpful in a child as he/she usually point to the periumbilical area. However, if the child is able to localize a pain then it indicates a local pathology, e.g. flank pain is characteristically present in renal pathology; epigastric

pain is seen with esophagitis, gastritis or acute pancreatitis.<sup>3</sup> Radiation to the shoulder is often seen with gallbladder disease and subdiaphragmatic abscess or to the back in acute pancreatitis. As a general rule, visceral pain is central (located in the epigastrium, mid-abdomen and hypogastrium); the pain is generally crampy, burning or gnawing in quality. Parietal pain (noxious stimuli in the parietal peritoneum) is generally more intense and more precisely localized to the site of the lesion, and it is often aggravated by movement or coughing. In females inflammation in the pelvis can present as an acute abdomen. Pain due to torsion of the pedicle of an ovarian cyst is acute, severe and continuous.

#### *Vomiting*

Vomiting is a sign of intestinal obstruction or peritoneal inflammation. Initially the vomiting may contain recently ingested food material, however after a few hours it usually turns bile stained in cases of abdominal obstruction. The frequency of vomiting, amount and nature of vomitus should be ascertained to assess the fluid and electrolytes requirements. Bilious vomiting indicates intestinal obstruction unless proved otherwise. Vomiting, which occurs after the onset of pain or abdominal distension usually indicates a surgical cause while it may precede or occur simultaneously in bacterial gastroenteritis, mesenteric adenitis, diabetic ketoacidosis, Henoch-Schönlein purpura or acute pancreatitis. In comatose children and young children and infants vomiting can be dangerous since they run the risk of aspiration. Therefore in these children a nasogastric tube must be inserted. Massive hematemesis is usually seen with portal hypertension and uncommonly with peptic ulcer disease.

#### *Bowel Function*

Complete information about stool habits before the onset of the acute abdominal symptoms is useful. The rule that adults with acute abdomen usually have no passage of stools does not hold true in infants and young children. Constipation is usually present with surgical conditions but localized peritonitis (in appendicitis or pelvic abscess) can lead to watery diarrhea. The enterocolitis of Hirschsprung disease also manifests with loose, watery, foul smelling stools accompanied by features of systemic toxemia. Blood in stools can be quite alarming and may range from streaks in acute bacillary dysentery, post-defecation drops in rectal polyps to massive lower gastrointestinal

hemorrhage in Meckel's diverticulum. Melena may be seen with esophagitis, gastritis, peptic ulcer and portal hypertension. A pelvic abscess should be suspected when lower abdominal pain and diarrhea are followed by lower abdominal pain and constipation.

#### *The Presence and Characteristics of Fever*

Fever, when present, can be helpful in suspected peritonitis. As a general rule, a temperature that rises slowly and progressively in parallel with the abdominal signs indicates peritoneal infection. Conversely, a temperature that rises rapidly, despite acute abdominal pain, indicates other and often self limited, non-surgical diseases like gastroenteritis.

#### *Micturition Problems*

Frequency, hematuria and dysuria are suggestive of genitourinary tract pathology. A history of oliguria is an important indicator of fluid losses leading to dehydration.

### Examination

The time spent on history taking should also be time spent on gaining the child's confidence. A little 'chitchat' about the child's school, friends or hobbies is a useful 'trick' if combined with patience and a cheerful disposition. The examination becomes much easier once the child's confidence is gained and even a very sick child can become surprisingly cooperative.

#### *Inspection*

The pale anxious expression is a good indicator of a serious abdominal disorder. Patients with intra-peritoneal bleeding are restless in contrast to patients with peritonitis who resist movement. These patients usually have an anxious, pale face, sweating, dilated pupils and shallow breathing. Bruising in the flanks will indicate possible acute pancreatitis (Grey-Turner's sign). This is due to exudation of fluid stained by pancreatic necrosis into the subcutaneous tissue. Similar discoloration in the periumbilical area is known as the Cullen sign. A distended abdomen should suggest ascites or intestinal obstruction. While examining the abdomen emphasis should be placed on inspection with regard to: (i) *Hernial sites*: Inguinal and femoral; (ii) *Contour*: The nature of abdominal distension, e.g. localized fullness may indicate a mass or phlegmon, while generalized fullness may be seen in intestinal obstruction along with visible peristalsis; (iii) *Movement with respiration*: Generalized limitation of movement

occurs with peritonitis, localized limitation with appendicitis or cholecystitis.

### Palpation

As a rule the abdominal examination should be started away from the area of pain and the involved area should be examined in the end. Light and deep palpation of the abdomen will indicate areas of local tenderness or whether generalized tenderness is present. Elicitation of rebound tenderness is best avoided because it has limited value and is extremely distressing to the child. A palpable tender mass in the right iliac fossa could be due to Crohn's disease or an appendiceal abscess. A pulsatile abdominal mass usually indicates the presence of an abdominal aortic aneurysm.

### Percussion

Percussion should be done carefully since it may aggravate the pain and antagonise the patient. Loss of hepatic dullness indicates the presence of air in the abdominal cavity.

### Auscultation

High-pitched bowel sounds, are an indication of an impending obstruction. Their absence, over a period of two minutes indicates the presence of paralytic ileus or peritonitis.

### Examination of Genitalia and Rectum

Examination of the genitalia and rectal examination should not be missed. The general physical and systemic examination should precede the rectal examination, since it is the most uncomfortable part of the whole examination.

### Abdominal Signs in Acute Abdomen

Table 63.1 summarizes the various signs commonly seen with acute abdominal conditions.

## CLASSIFICATION OF ETIOLOGIES

It is useful to study 'acute abdomen' in terms of both the location and the pathophysiology of the disease as both are necessary to know the nature and urgency of intervention. Acute abdomen can be classified on the basis of pathophysiological mechanisms into obstructive, hemorrhagic and peritoneal or on the basis of location into extra-abdominal, parietal and intra-abdominal causes.<sup>3</sup>

**Table 63.1: Abdominal signs in acute abdomen**

Abdominal signs	Condition
Hyperesthesia	Acute appendicitis, diaphragmatic pleuritis, basal pneumonia
Rovsing's sign	Acute appendicitis
Cope's psoas test	Acute appendicitis
Cope's obturator test	Acute appendicitis
Murphy's sign	Acute cholecystitis
Guarding	Peritoneal irritation
Rigidity	Peritonitis
Shifting dullness	Free fluid in abdomen
Loss of liver dullness	Perforation of hollow viscus with pneumoperitoneum

## Pathophysiology

### Obstructive

In this situation, a severe colicky pain develops when a hollow viscus has a blockage in the lumen which interferes with its normal motility pattern and its ability to deal with the luminal contents or secretions. Intestinal obstruction if left untreated will lead to perforation with signs of an acute abdomen.

### Peritoneal

This symptom complex is a result of an inflamed intra-abdominal viscus. The inflamed viscus causes irritation of the visceral peritoneum, initially causing vague central abdominal pain which may be difficult for the patient to localize. Continued inflammation or localized perforation leads to involvement of the parietal peritoneum. Pain becomes localized and is then associated with tenderness, guarding and rebound tenderness. Spread of infection generally throughout the abdominal cavity leads to a generalized abdominal wall rigidity, often associated with a rigid or board-like abdomen. Generalized systemic signs of sepsis are apparent at this stage with pyrexia, tachycardia and pallor. It is discussed in detail in a subsequent section.

### Hemorrhagic

Although this is not the commonest cause of acute abdominal pain, it must be considered because of its serious and often rapid progression. It is due to bleeding into the peritoneal cavity or retroperitoneum either due to a leaking major vessel (e.g. aortic aneurysm) or a ruptured vascular organ (e.g. spleen). Onset of the pain may be insidious and poorly localized at first. Soiling of the peritoneum with blood may simulate peritonitis. The bowel sounds may diminish

and ileus may be present. The patient will present with features of shock and the abdomen will distend as bleeding progresses.

## LOCATION OF UNDERLYING CAUSE

### Acute Abdomen Due to Intra-abdominal Conditions

Majority of the acute abdominal emergencies are due to intra-abdominal conditions. The problems associated with the nature of the pathology, organ involvement and anatomic variation in the pediatric patients have been mentioned earlier. However, there are two distinct groups of patients with acute abdomen due to intra-abdominal pathology: (i) those with evidence of peritoneal involvement, and (ii) those without evidence of peritoneal involvement.

During the period 1981-2000, the department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi treated more than 1500 patients with acute abdomen due to intra-abdominal conditions. These comprised almost 10 percent of all our admissions during this period. Surgical intervention was required in two-thirds of patients with peritoneal involvement but in only about one-third of patients without peritoneal involvement. The mortality was only ~2 percent; twice as much in patients with peritoneal involvement as compared to those without peritoneal involvement. It is clear from the above data that considerations regarding pathophysiology, management and prognosis are different in these two groups of patients.

### Intra-abdominal Pathology with Peritoneal Involvement

Peritoneal involvement may be localized or generalized. Localized peritoneal involvement is usually seen in patients with intra-abdominal abscesses, appendicitis, biliary and pancreatic diseases. The peritoneal involvement is secondary to either direct spread of an existing infection or as a response to an existing inflammatory process, which is localized with the help of the intestines and omentum. Generalized peritoneal involvement as seen in patients with primary peritonitis, secondary peritonitis and trauma is due to either a primary infection or in response to blood, bile, feces, urine or pancreatic juices within the peritoneal cavity.

#### *Localized Peritoneal Involvement*

These patients present with abdominal pain which is usually central to start with but shifts to the area of localization in due course of time. The initial pain is

visceral origin and is usually a constant dull ache but occasionally may be colicky as in obstructive appendicitis or biliary disease. The shift of the pain is an indicator of peritoneal involvement and the character of the pain also changes from that of visceral to severe persistent somatic pain. The pain is usually accompanied by other features of inflammation like fever, irritability, loss of appetite and toxemia. The fever is usually moderate but when abscess formation has already occurred it becomes high grade and persistent. Vomiting may be associated but is usually not a prominent feature.

Abdominal distension is usually not a feature of localized peritoneal involvement. It may, however, be evident when intestinal obstruction or paralytic ileus complicates the primary pathology. Upper abdominal distension may be seen with pancreatic pseudocysts or due to reflex pylorospasm and gastric dilatation.

The most important feature in this group of patients is the elicitation of guarding and tenderness on physical examination. In the initial stages, the tenderness may only be elicited on deep palpation but as peritoneum gets involved the guarding and tenderness become more evident.

Tenderness is commonly present in the right iliac fossa with acute appendicitis, mesenteric lymphadenitis and amebic typhlitis; in the left iliac fossa with amebic colitis; in the hypogastrum and per rectum with pelvic appendicitis and pelvic abscess; in the right hypochondrium with subhepatic appendicitis, cholecystitis and hepatitis; in the subcostal region with subdiaphragmatic abscess; in the epigastrum with pancreatitis and in the renal angle with genitourinary infections. Rebound tenderness is indicative of peritoneal involvement and is present in these conditions.

Acute appendicitis is the most common acute abdominal emergency causing localized peritoneal involvement.<sup>4,5</sup> It should be differentiated from mesenteric lymphadenitis, respiratory infections, ureteric colic, acute urinary tract infection, cholecystitis and hepatitis. In doubtful cases the patients should be admitted, kept under observation and examined repeatedly. History of upper respiratory tract infection, fever, vomiting and diarrhea is usually present in patients with mesenteric lymphadenitis; examination and X-ray chest differentiate respiratory infections; tenderness in the renal angle and along the course of the ureter, urinalysis and culture and X-ray abdomen diagnose genitourinary conditions; jaundice and altered liver function tests differentiate infective hepatitis from acute appendicitis, and ultrasonography is useful in identifying cholecystitis. Abdominal X-rays are most often normal in children

with acute appendicitis. High resolution ultrasonography is a good test for identifying non-perforated appendicitis. The diagnostic accuracy of the ultrasound will be much less during perforation because of guarding and localized ileus. It is important to note that the ultrasound findings should be interpreted along with the clinical findings. Computed tomography is a useful diagnostic modality for periappendiceal masses.<sup>6</sup>

#### *Generalized Peritoneal Involvement*

Generalized peritoneal involvement is usually seen with abdominal trauma or in patients with generalized peritonitis. The diagnosis of abdominal trauma is self evident from the history and the essential features in the evaluation and management are identification of injured organs and their treatment.

Generalized peritonitis can be primary or secondary to either perforation of a hollow viscus or spread from an existing intra-abdominal infection, the commonest being appendicitis.

Generalized peritonitis presents as a serious intra-abdominal condition. A preceding history of sore throat or nephrotic syndrome is available in a large number of patients with primary peritonitis. Rupture of an inflamed appendix leading to generalized peritonitis can be diagnosed on clinical features. The majority of cases with generalized peritonitis following rupture of a hollow viscus are due to typhoid ileal perforations. Ileal perforations can also be non-specific, ischemic or due to tuberculous enteritis. The presenting symptoms and signs for primary and secondary peritonitis are similar. The pain is severe, persistent, generalized and somatic in nature. Movement exacerbates the pain and these patients prefer to lie still in one position.

The abdominal pain is accompanied by vomiting and mild to moderate abdominal distension. Guarding and tenderness are generalized with board-like rigidity. The patients are usually toxic. It is neither necessary nor desirable to elicit shifting dullness but masking of the liver dullness should always be elicited to rule out perforation of a hollow viscus.

It is essential to differentiate primary peritonitis from secondary peritonitis because the former can be treated with antibiotics only but the latter requires surgical intervention. Apart from the clinical features, X-rays of the abdomen in the erect and/or lateral decubitus positions usually confirm perforation of a hollow viscus. Rarely, when the perforation gets sealed off in its initial stages there may not be free gas in the peritoneal cavity. Diagnostic paracentesis may be done in doubtful cases and Gram's staining and culture of the pus may reveal *Streptococcus hemolyticus* or pneumococcus—the two most

commonly found offending organisms in primary peritonitis. In girls with primary peritonitis vaginal swabs may show Pneumococcus. Blood culture should be done before starting antibiotics and Widal test should be done in patients with ileal perforations.

While the blood and pus culture and Widal test reports are awaited, it is advisable to start treatment with broad spectrum antibiotics. The most commonly used combination is cephalexin or ampicillin and gentamicin. Metronidazole should be added in cases of intestinal perforation.

#### **Intra-abdominal Pathology without Peritoneal Involvement**

This can present in various forms but there are four major groups of symptoms complexes. They are intestinal obstruction, which can be mechanical or adynamic, various non-surgical gastrointestinal diseases, genitourinary diseases that usually present as infection, obstruction or hemorrhage, and acute non-specific abdominal pain.

#### *Intestinal Obstruction*

The major causes of intestinal obstruction in children are abdominal tuberculosis, intussusception, bands and adhesions, incarcerated hernias, helminthiasis and Hirschsprung disease. Uncommon causes include pyloric stenosis, Meckel's diverticulum and foreign body ingestion (Table 63.2).

The main presenting features of intestinal obstruction are abdominal pain, vomiting, constipation and abdominal distension. The pain is colicky in the initial stages but later becomes a constant dull ache when

**Table 63.2: Common causes of intestinal obstruction**

<i>Mechanical</i>	
Intraluminal	Intussusception Fecal impaction Meconium plug syndrome Foreign bodies Ascariasis
Intramural	Atresias and stenosis Hirschsprung disease Tuberculous stricture
Extraluminal	Malrotation Masses Obstructed hernia
<i>Paralytic ileus</i>	Gastrointestinal perforation Necrotizing enterocolitis Septicemia, peritonitis Viral or bacterial gastroenteritis Hypokalemia, uremia, lead poisoning

bowel fatigue sets in and paralytic ileus occurs. The onset of vomiting and abdominal distension usually runs an inversely proportional course depending on the level of obstruction. The higher the level of obstruction the earlier. In duodenal obstruction, vomiting occurs as one of the earliest symptoms and distension is the onset of vomiting and lesser the distension. In duodenal obstruction, vomiting occurs is one of the earliest symptoms and distension is restricted to the epigastrium only. The opposite holds true for distal obstructions and in large bowel obstruction vomiting occurs at a very late stage or may not occur at all.

Constipation also depends on the level of obstruction. The patient may pass a few stools even after the obstruction has set in when the obstruction is in the proximal bowel, which is due to the residual bowel contents. In Hirschsprung disease on the other hand, constipation is the first complaint. The sequence of events in partial obstruction is pain, constipation, distension and vomiting with relief of symptoms following defecation and vomiting.

Physical findings also depend on the level of obstruction. Visible gastric peristalsis may be seen in the epigastrium with pyloric and duodenal obstructions whereas with distal small bowel obstruction the visible peristalsis is seen in the central abdomen. Bowel sounds are hyperperistaltic in both small and large bowel obstructions. In the early stages of acute obstruction, bowel sounds may be high pitched or 'tinkling' in character, but the sounds disappear when prolonged obstruction leads to perforation and peritonitis. Rectal examination reveals an empty rectum in mechanical obstruction. Presence of a hernia should always be looked for especially in small children.

Intussusception, in addition to the above features of mechanical obstruction, has certain specific features. There is usually a history of passage of red currant jelly stools, a sausage shaped mass palpable in the right upper quadrant or flank and occasionally the intussusceptum may be seen protruding from the anus or palpable on rectal examination.<sup>7,8</sup>

Paralytic ileus can sometimes be confused with mechanical obstruction especially in patients who develop constipation and abdominal distension following diarrhea and vomiting. The ileus in these patients is usually due to electrolyte imbalance or antimotility medications received by the patient. Bowel sounds are usually absent and, if present, tinkling in nature. Rectal examination reveals a dilated rectum with or without fecal matter. Hirschsprung's disease rarely presents as an acute obstruction in older children, unless complicated by enterocolitis. The patient presents with foul

smelling loose stools, fever, abdominal distension and toxemia.

All patients with intestinal obstruction progress to paralytic ileus if treatment measures are not instituted in time. This is due to the severe loss of fluid and electrolytes in the vomitus and sequestration into the distended bowel. Apart from dehydration and electrolyte imbalance, the distended and edematous bowel allows transmigration of bacteria to produce peritonitis and septicemia. This is particularly true if bowel wall ischemia and gangrene are also present. The distended bowel splints the diaphragm and may produce respiratory embarrassment.

The evaluation of patients with intestinal obstruction should include measurement of the hematocrit, blood urea and electrolytes, and a X-ray film of the abdomen in the erect and supine positions. The X-ray film also helps in differentiating paralytic ileus from mechanical obstruction. Barium enema is required for the diagnosis of Hirschsprung disease but is not necessary for the diagnosis of intussusception, although it may be used as a therapeutic tool. Subacute or partial obstruction especially due to tuberculosis may require barium meal or enema examination.

#### *Nonsurgical Gastrointestinal Diseases*

Bacterial enterocolitis and food poisoning manifest with sudden onset of fever and diffuse abdominal pain, which is followed by diarrhea. There may be gross blood or polymorphonuclear leukocytes in the stool. There is diffuse tenderness on palpation but no signs of peritoneal irritation. The condition may sometimes mimic acute appendicitis. About 10 percent of children with inflammatory bowel disease will have a fulminant onset, simulating acute bacterial enterocolitis.

Peptic ulcer disease that includes gastric or duodenal ulcers, gastroesophageal reflux and gastritis presents commonly in older children with epigastric pain characteristically following meals and awakens the child early morning. In younger children the pain is diffuse, atypical with no periodicity or relation to meals. Vomiting is often an accompanying feature. Gastritis or gastroduodenal ulcers have been classified as primary or secondary. The majority of the gastroduodenal inflammation, particularly in younger children is associated with severe systemic illness like extensive burns, head injury, sepsis, postoperatively or an acute viral illness. They are also known to occur in Zollinger-Ellison syndrome, Crohn's disease or cystic fibrosis. Secondary ulcers or gastritis can manifest as an acute abdomen or sometimes with severe gastrointestinal hemorrhage or perforation. The risk of gastritis and

ulcers, induced by use of NSAIDs and aspirin, in children is low. The present studies show that children with no other identifiable cause for the duodenal or gastric ulcers have primary disease caused by *Helicobacter pylori*.<sup>9,10</sup> Upper gastrointestinal endoscopy would be the procedure of choice for diagnosing mucosal abnormalities as contrast radiography has not been found to be reliable.<sup>11</sup> Continuous colicky pain, which increases in intensity over 5 to 20 minutes and then subsides over a few hours, is suggestive of biliary colic. The pain follows meals and is initially localized to the epigastrium or the right hypochondrium and becomes generalized when the inflammation increases. Younger children may point towards the periumbilical area. There are often complaints of referred pain to the lower right scapular area. Continuous pain for several hours is indicative of cholecystitis when Murphy's sign (Table 63.1) may be positive. There should be a high index of suspicion for cholangitis when pain is associated with shaking chills and high spiking fever.

A child with acute pancreatitis will have continuous midepigastric or periumbilical pain, which radiates to the back, lower abdomen, chest or the left shoulder. There is associated vomiting, and fever and eating aggravate the pain and vomiting. The child is restless and finds comfort in lying on his or her side in a knee-chest position. The abdomen is distended and tender with decreased or absent bowel sounds. The child may have mild jaundice and altered liver function tests. The pain and vomiting usually increase over a period of one to two days but is usually self limiting. The serum amylase and lipase levels may be raised or remain normal during an acute episode of pain.<sup>12</sup> Ultrasonography or computed tomography may be useful in assessing the pancreatic size and pseudocyst formation.

Diffuse abdominal pain and vomiting with or without hematochezia precedes or follows skin involvement in Henoch-Schönlein purpura. There may be associated joint pains, hematuria, and proteinuria; 10 percent children may have intussusception.

#### *Genitourinary Diseases*

Genitourinary disease usually present as chronic problems but few conditions like acute pyelonephritis and urinary calculi may occasionally present as acute abdominal emergencies with symptoms of infection and obstruction. Renal angle tenderness is present in infective conditions. Urolithiasis is characterized by colicky pain in the abdomen radiating to the flanks with or without microscopic or gross hematuria. Urinalysis, X-ray film of the abdomen, ultrasonography and

intravenous pyelography may be necessary for the diagnosis.

Acute unilateral abdominal pain with or without uterine bleeding at midpoint of the menstrual cycle indicates *mittelschmerz* while abdominal pain with back ache, thigh pain, nausea, vomiting and diarrhea is characteristic of dysmenorrhea.

Pelvic inflammatory disease should be considered in adolescent females if they present with lower abdominal pain and fever following a menstrual period. There may be associated irregular vaginal bleeding or discharge. Tubo-ovarian abscess following complicated salpingitis manifests with peritonitis and the child may come in shock. Fitz-Hugh Curtis syndrome is suspected when there is right upper quadrant pain due to inflammation of the liver capsule sometimes seen in association with salpingitis.

#### *Acute Nonspecific Abdominal Pain*

In clinical practice a large number of children are seen to have episodes of acute abdominal pain, the character of which is not adequately described on questioning and physical examination does not reveal significant localizing findings. In majority of them the pain subsides spontaneously in periods ranging from a few minutes to a few hours. Most of these children do not require hospitalization and investigation do not reveal an underlying pathology. In some children, however, the pain does not subside and hospitalization, for observation, necessary investigations and management may be required. Repeated physical examination is essential in order to diagnose the underlying condition. Despite this no organic pathology may be found and the pain may settle down in 24-48 hours. In some patients the initial episodes may be the harbinger of condition like appendicitis, Meckel's diverticulitis and pancreatitis. In others, parasitic infestations, genitourinary infections, metabolic disorders like diabetes and porphyria, poisonings and hematological disorders like acute hemolytic crises, sickle cell anemia or Henoch-Schönlein purpura may be found.<sup>7</sup>

#### **Acute Abdomen due to Parietal Conditions**

##### *Involvement of the Abdominal Wall with Conditions like Herpes Zoster*

Involvement of the abdominal wall with conditions like herpes zoster, abscess, cellulitis and injuries are easy to diagnose and treat. Patients with hemophilia may develop hemorrhage into the rectus sheath or retroperitoneal tissues. However, contusions of the abdominal

wall and deep-seated abscesses may pose diagnostic problems. Contusions of the abdominal wall may not be associated with superficial cuts and bruises, and the patient may present with generalized guarding and tenderness due to the reflex spasm of the abdominal musculature. A history of trauma is usually present and it is essential to rule out visceral injury in these patients.<sup>7</sup>

Deep seated abscesses often occur as a result of secondary infection or hematomas. Preceding history of trauma may not be available, because the injury is often trivial. Surrounding inflammation may produce local peritoneal reaction, which may be indistinguishable from local peritonitis. Abscesses present between the rectus abdominis and the posterior rectus sheath may be impossible to differentiate from intra-abdominal abscesses even on contracting the abdominal muscles. Ultrasonography is useful in localizing the site of abscess in such patients.

However, certain intra-abdominal conditions may be associated with abdominal wall involvement. Abscesses, necrotizing enterocolitis and peritonitis may produce abdominal wall erythema and cellulitis. In such conditions the abdominal wall involvement is subsequent to the intra-abdominal pathology and this can usually be elicited on the basis of history.

### Acute Abdomen due to Extra-abdominal Causes

A retrospective study was done on 1141 children between the ages of 2 to 12 years who presented in the emergency department or a clinic with complaints of abdominal pain which was  $\leq 3$  days.<sup>13</sup> The prevalence of acute abdominal pain was found to be 5.1%; interestingly, the six most prevalent final diagnosis which accounted for 57.5% of all final diagnosis were nonsurgical, extra-abdominal causes like upper respiratory tract infections/otitis, pharyngitis, viral fever, and acute febrile illnesses. Only 26.5% had an abdominal cause out of which 12 (1%) children required surgical intervention (10/12 were for appendicitis).

#### *Basal Pneumonia and Diaphragmatic Pleuritis*

Basal pneumonia and diaphragmatic pleuritis can produce features of acute abdomen.<sup>12</sup> Involvement of the lower pleura results in referral of symptoms along the lower thoracic nerve roots. A complete examination of the patient is therefore essential to recognize such a situation. Rapid and shallow respiration, restricted chest excursions during respiration and pleuritic pain during

deep breathing suggest the diagnosis. Diaphragmatic pleuritis may not be evident on auscultation but like basal pneumonia it produces upper abdominal pain, guarding and tenderness, which decrease on gentle but firm pressures over the abdomen. Shoulder pain may also be present. A chest X-ray is usually adequate to confirm the diagnosis.

It is important to note that upper abdominal inflammatory conditions like subdiaphragmatic abscess, cholecystitis, hepatitis, pancreatitis, etc. may produce a similar clinical picture.<sup>14</sup> Differentiation and diagnosis can usually be made on the basis of history and physical findings. Fluoroscopy and ultrasonography may be necessary, in the acute stage, to arrive at a diagnosis. Appropriate treatment of pneumonia produces a dramatic recovery from the abdominal symptoms and signs.

#### *Other Extra-abdominal Conditions Presenting as Acute Abdomen*

Other extra-abdominal conditions are summarized in Table 63.3.

**Table 63.3: Other extra-abdominal conditions presenting with acute abdomen**

Condition	Abdominal signs
Septicemia, meningitis	Distension, bilious vomiting, jaundice
Hypothyroidism	Prolonged jaundice, distension, constipation
Cardiac failure	Tender hepatomegaly, ascites
Diabetic ketoacidosis	Pain abdomen
Food poisoning	Pain, vomiting, diarrhea
Acute bacillary dysentery	Fever, colicky pain, blood and mucus in stools
Porphyria, lead toxicity	Pain, constipation
Herpes zoster	
Nerve root compression	
Acute pericarditis	

### EMERGENCY INVESTIGATIONS

Most of the important emergency investigations have been mentioned above. These investigations cannot replace clinical judgement and the information that is obtained from observation and repeated examination is usually far more valuable. The aim of investigations in acute abdominal emergencies is two-fold. The first is to confirm the clinical suspicion if a diagnosis is not possible on the basis of history and examination, and secondly, to assess the general condition of the patient

as regards anemia, dehydration and electrolyte imbalance. Investigations that are time consuming or those that are not absolutely essential should generally be avoided.

### *Radiological Investigations*

Accurate diagnosis of acute abdominal pain in children can be difficult, if one relies solely on clinical and laboratory findings, therefore, imaging plays an important role. Imaging in children with an acute abdomen is considered when there are confusing signs and symptoms or contradictory laboratory findings, and when surgery is being considered.

Ultrasound is the investigation of choice if acute cholecystitis, cholelithiasis, urolithiasis, cystic lesions of the gut or pelvis, or pancreatitis is suspected. It is advocated in view of the lower cost, less patient preparation and safety from ionizing radiation.<sup>15</sup> The CT scan of the abdomen and pelvis is useful in certain situations like suspected vascular lesions (aneurysms intra-abdominal retroperitoneal hemorrhages, portal vein thrombosis), and doubtful inflammatory lesions like appendicitis, pancreatitis or intra-abdominal abscess. It provides useful information about abnormal bowel gas patterns, calcifications and pneumoperitoneum.<sup>16</sup> Current evidence supports CT scan as the primary imaging modality, in view of the following benefits:<sup>15</sup>

- i. Significant decrease in the negative appendectomy rate
- ii. Decrease in perforation rate
- iii. Reduced inpatient observation days therefore reduced cost of therapy.
- iv. Useful in establishing alternative diagnosis
- v. Useful in obese patients.

The upper and lower GI endoscopy can be useful in evaluating the stomach, duodenum and the colon for ulcerations or inflammation.

## PRINCIPLES OF MANAGEMENT

Detailed description of the management is available in standard texts. The principles of management are discussed so as to provide guidelines that will determine which patients should be kept under observation, who should be treated medically and when should surgical intervention be considered.

### *Observation*

Observation is the hallmark of successful management in acute abdominal emergencies. The parameters that

need observation are the general condition, pulse, temperature, respiration, blood pressure, status of hydration, intake and output, abdominal girth and change in the symptoms and signs of the various conditions.

Oral feedings should be withheld whenever a child is vomiting or in situation when the bowel needs rest as in cases of intestinal obstruction, inflammatory conditions and when surgical intervention may be required. Nasogastric suction is required in obstructive, inflammatory and hemorrhagic states, and in poisonings. Intravenous fluids should be started when oral feeding is withheld. Urethral catheterization may be required in very sick children for the accurate record of urine output.

A large number of children, especially those presenting with acute abdominal pain and no localizing features may need nothing more than simple observation. The pain will subside without medication within 24-48 hours. But other conditions require specific medical or surgical management.

### *Medical Management*

Many acute abdominal emergencies like primary peritonitis, gastroenteritis, amebic infestations, genitourinary infection, and biliary and pancreatic inflammatory conditions usually subside with medical management. This includes, apart from general measures as discussed above, specific treatment for the conditions. In general broad-spectrum antibiotics are required for conditions with an infective etiology and for those of inflammatory etiology where superadded infection is a distinct possibility. Metronidazole is an effective agent for amebic infestations and for protection against anaerobic infections. Analgesics, antispasmodic and sedatives may be administered if necessary.

Some cases of intestinal obstruction can also be treated by medical measures. Postoperative adhesions, incarcerated hernias and subacute obstruction especially due to tuberculosis usually subside on medical management with bed rest, nasogastric decompression and intravenous fluids. Although medical management is usually successful in these conditions, some patients do not show any response up to 24-48 hours. In these circumstances surgical intervention may be contemplated.

Patients who develop abdominal distension and constipation following episodes of diarrhea and vomiting usually respond to treatment with antibiotics and correction of fluid and electrolyte imbalance.

### Surgical Management

Surgical intervention is indicated when medical measures fail to produce an improvement. However, in conditions like abscesses, acute appendicitis, peritonitis due to intestinal perforations and other infective lesions, intestinal obstruction, gastrointestinal hemorrhage due to Meckel's diverticulum, duplication cysts and polyps, and urinary calculi causing obstruction surgery is always indicated. It is not feasible to discuss the surgical management of each condition in detail. However, guidelines for emergency operative treatment are: (i) pus should be drained; (ii) infected lesions like an inflamed appendix should be removed; (iii) intestinal perforation should be closed; (iv) intestinal obstruction should be relieved; (v) diseased bowel should be either exteriorized, removed or bypassed; (vi) lesions causing hemorrhage and calculi causing obstruction should be removed; and (vii) the contaminated peritoneal cavity should be cleaned.

Treatment of intussusception by hydrostatic reduction is satisfactory but possible only in early and uncomplicated cases. While operative reduction is the other method available, few complicated cases may require bowel resection.

With the advent of ultrasonography it is now possible to drain percutaneously a number of intra-abdominal abscesses, which would have otherwise required surgical drainage.

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Urological emergencies in infants and children may present in one of several ways: (i) Urinary tract injuries; (ii) Retention of urine; (iii) Urosepsis in an obstructed system; (iv) Acute scrotum; and (v) Miscellaneous—paraphimosis, zipper entrapment etc.

This chapter aims to highlight important clinical aspects of each of these presentations and outline the principles of management.

### URINARY TRACT INJURIES

*Renal injuries* are the commonest, and occur as a result of blunt trauma. The clinical signs of renal trauma are nonspecific. Flank contusions must raise suspicion of renal injury. There may be tenderness in the renal fossa or an ill-defined flank mass due to perinephric blood or urine collection. The presence of hematuria may point to genitourinary trauma. Fortunately, renal injuries are mainly in the form of contusions, minor lacerations or subcapsular hematomas. Rarely, the collecting system is disrupted. The serious injuries are renal vessel injuries in which the symptoms and signs are even less specific.

When renal injuries are suspected, a contrast-enhanced CT scan is desirable. If renal vessel injury is identified, urgent surgery is necessary if the kidney is to be saved. Most other renal injuries can be managed non-operatively.<sup>1,2</sup>

*Bladder injuries* are uncommon in children and result from blunt trauma. Bladder rupture is more likely to occur if the bladder is full at the time of impact. The bladder is intra-abdominal in infants and children, in contrast to adults.

Hematuria may be only sign of bladder injury. Intraperitoneal leakage of urine may not produce many symptoms in the initial phase. Intraperitoneal bladder rupture requires laparotomy and repair of the bladder. Extraperitoneal ruptures, particularly if small, may be managed by Foley catheter drainage.<sup>1</sup>

*Urethral injuries* may not be life-threatening but have devastating sequelae if not identified early and treated appropriately. Any child with bloody discharge at the

external meatus, if associated with a perineal or scrotal hematoma must be presumed to have urethral injury till proved otherwise. Any aggressive attempt to catheterize such a child may convert a partial urethral rupture into a complete rupture with disastrous consequences. If suspected, children with urethral injury must quickly be referred to a center that can handle this emergency. If the child is unable to pass urine and the bladder is distended, a supra-pubic puncture and aspiration of urine will relieve the distress during transfer.

### RETENTION OF URINE

There are very few causes of acute retention of urine in children. These include:

- i. Cystitis.
- ii. Urethral calculus.
- iii. Urethral injury.
- iv. Prepuccial injury or infection.

Bladder outflow tract obstruction, as in posterior urethral valves does not usually present with acute retention. Also, contrary to common belief, phimosis is not a cause of urinary retention.

When evaluating a child with acute retention, it is important to take a detailed history. A preceding history of dysuria or fever may suggest cystitis. Cystitis is the most common cause of retention in girls. Pain radiating to tip of penis or a child pulling at his penis may suggest an impacted urethral calculus. Blood at the external meatus or scrotal hematoma is a sine qua non of urethral trauma. A close inspection of the penis may reveal prepuccial inflammation that may be the cause of urinary retention. Injudicious and forceful stretching of the prepuce may result in skin cracks that are painful and often make the child hold back urination.

A child who is in distress, and unable to pass urine becomes a source of great anxiety to his family. This anxiety only aggravates the problem, as all attention is focussed on the child in order to make him empty the bladder. Simple measures often help in easing the

situation. Warm compresses in the suprapubic region help, or simply putting the child in a tub of warm water helps him relax and void.<sup>3</sup> Simple analgesics (paracetamol) or mild sedatives (triclofos) also help by putting the child to sleep, and they often void while sleeping. If the child is still unable to void and the bladder is distended, much relief can be got by a suprapubic puncture and aspiration. Once the distended bladder is evacuated, subsequent voidings are easier. Bladder catheterization is more traumatic, particularly if done improperly, or if it is repeated. If repeated emptyings are required, it may be appropriate to leave an indwelling Foley catheter for 48 hours, provide symptomatic relief, correct the infection with oral antibiotics and, then, remove the catheter.

### UROSEPSIS

Urinary tract infection in the presence of obstructive uropathy can be very dangerous. Children with posterior urethral valves or hydronephrosis due to pelvi-ureteric junction obstruction who develop urinary infection become very sick very rapidly. They become septicemic, the renal function deteriorates and they present with acidosis. Urosepsis in obstructive uropathy needs to be treated very aggressively with intravenous broad spectrum antibiotics and urgent urinary tract decompression. Children with posterior urethral valves must have a bladder catheter. Children with pelvic ureteric junction obstruction, who do not improve with intravenous antibiotics, may need percutaneous nephrostomy.

### ACUTE SCROTUM

Conditions that cause acute swelling in the scrotum are listed in Table 64.1.

Torsion of the testis is the most common and the only true genitourinary emergency of childhood. In a boy who presents with a red, swollen and tender

**Table 64.1: Causes of acute scrotal swelling**

- Torsion of testis
- Torsion of testicular appendages
- Epididymo-orchitis
- Trauma
- Idiopathic scrotal edema
- Hydrocele/hernia
- Henoch Schönlein purpura
- Testicular tumor

hemiscrotum, it is important to exclude other causes quickly, since if testicular torsion is suspected, time is of essence. Prompt surgical detorsion is the only way to salvage the testicle. When precious time is lost in detailed clinical examination or organizing sophisticated investigations, the outcome is usually testicular loss. The adage most apt in acute scrotum is, “when in doubt, operate”.

There are no pathognomonic signs differentiating between testicular torsion, testicular appendage torsion or epididymo-orchitis. However, some helpful clinical features are outlined in Table 64.2.

In torsion of testicular appendages and epididymo-orchitis the local findings are less marked. The hemiscrotum may be red, swollen and tender, but with patient examination, it is usually possible to palpate the cord, testis and epididymis separately to arrive at a conclusion. The clinical features that suggest testicular torsion include the following:

- Sudden onset of pain, may be radiating upwards.
- Inflamed hemiscrotum with marked testicular tenderness.
- Absent cremasteric reflex ipsilaterally. This reflex may be elicited by stroking the upper inner aspect of the thigh. This results in contraction of the cremasteric muscle, pulling the ipsilateral testicle upwards. If the cremasteric reflex is intact, testicular torsion is unlikely.<sup>4</sup>

**Table 64.2: Clinical features in acute scrotum**

	<i>Testicular torsion</i>	<i>Testicular appendage torsion</i>	<i>Epididymo-orchitis</i>
Pain	Sudden onset, may radiate to inguinal canal or suprapubic area	Slow onset	Slow onset
Urinary symptoms	—	—	+
Fever	—	—	+
Tenderness	Marked, testicular	Less, pole of testis	Less, epididymal
Lie of testis	May be transverse	Normal	Normal
High testis	+	—	—
Cremasteric reflex	Absent	Present	Present

- High placed testis.
- Abnormal lie of the testis.

*Investigations* may help in differentiating the various causes of acute scrotum, though none is specific. Leukocytosis and pyuria may suggest epididymo-orchitis. Color Doppler examination for testicular blood flow and ultrasound examination may help exclude testicular torsion if the testicular arterial flows are shown to be normal.<sup>5</sup> Testicular scintigraphy with technetium-99m is of value in the diagnosis of acute scrotum. However, it is important to remember, if the testis is to be saved in testicular torsion, surgical detorsion must be completed within 6 to 9 hours. Manual detorsion can sometime be attempted after sedation; but the completeness of detorsion must be confirmed by a Doppler study.

*Treatment* of testicular torsion is early scrotal exploration and detorsion of the testis. If the testis is not viable at exploration, particularly if more than 12 hours have elapsed, it is best removed. Simultaneously, it may be prudent to fix the contralateral testis to protect it against future torsion.<sup>6</sup>

### Penile Conditions

The foreskin is not normally retractable in infants and young children up to 6-7 years of age.<sup>7</sup> This is physiological and cannot be termed phimosis. No attempt must be made to forcibly pull the prepuce back. Any such attempt results in pain, bleeding and painful micturition. The resulting raw area heals with scarring, making normal retraction of prepuce impossible.

*Circumcision is not routinely recommended for non-retractable prepuce.* The only indications would be recurrent balanitis, history of urinary infections or persistent ballooning of prepuce during voiding.

*Paraphimosis* occurs if the foreskin is retracted behind the glans and left there. This results in edema making

it difficult for the prepuce to be pulled back to its normal position. By applying steady continuous compression on the swollen prepuce, the edema can be reduced, allowing for manual reduction of the paraphimosis. This can be successfully achieved in most boys. In neglected cases, surgery in the form of division of the constricting band followed by circumcision may be necessary.

**Penile zipper entrapment** The prepuce or penile skin may sometimes be caught in the teeth of the zipper. No attempt must be made to pull the zipper forwards or backwards as this is extremely painful. It is advised to first infiltrate with injection plain xylocaine 2 percent locally, so that the procedure is not traumatic to the child.<sup>3</sup>

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### MAJOR TRAUMA

Trauma is the leading cause of death of American children more than 9 months of age. It remains the major factor in 40 percent of the deaths among children 1 to 4 years of age and 70 percent from 5 to 19 years.<sup>1</sup> Mortality in trauma has a trimodal distribution with more than 50 percent of deaths occurring due to fatal injuries at the site itself. Early deaths occur within hours of injury and account for about 30 percent of the deaths. Major cause of the early deaths is internal hemorrhage. Late deaths constitute the rest 20 percent.

In the absence of nationwide monitoring of such cases in India the exact magnitude of the problem is not known and non-fatal minor injuries have not been adequately studied.<sup>1</sup> However, studies have shown that accidents contribute to about 14 percent of the total children admitted.<sup>2</sup> Maximum number of accidents were seen to occur in the age group of 4-9 years.<sup>2,3</sup> Boys are affected more commonly than girls. The maximum cases in India are due to fall from height followed by road traffic accident.<sup>4</sup> More than half of the injuries take place at home followed by those on the streets.

### SPECTRUM OF TRAUMA

Trauma causes injuries that range from minimum to fatal, from a splinter to a severe injury caused by motor accident. It is imperative to categorize the injuries by:<sup>5</sup>

- i. Extent—Multiple or local.
- ii. Nature—Penetrating (sharp) or blunt.
- iii. Severity—Mild, moderate or severe.

For all practical purposes multiple trauma is defined as apparent injury to two or more body areas. Localized trauma involves only one anatomic region of the body irrespective of the severity of the injury. It is also necessary to distinguish between sharp and blunt trauma, as the information is useful in ascertaining the internal injuries of the child. Assessment of severity is likely to help in determining further course of treatment as well as the prognosis of the child.

### Triage

Triage<sup>5</sup> is a process of patient assessment, prioritization of treatment and selection of appropriate treatment location. The details of the accident sustained and the probable mechanism of injury must be ascertained. This would help in determining the possibilities of other injuries for which the patient should then be assessed.

Initial assessment is one of the most critical parts in the management of the child with multiple injuries. Failure to recognize the injuries, which may later become life-threatening, may lead to increase in morbidity and mortality. It is imperative that the treating pediatrician should single-mindedly focus on a sequence of priority items critical to survival.

Parents must be informed of events taking place.<sup>6</sup> They are more likely to trust and co-operate if they are kept abreast of the situation. It is reassuring both for the parents and the children to be kept together as far as possible. Nothing is more satisfying and reassuring for parents than to see their child's condition improving.

### Primary Survey

The priority sequence in the assessment of an injured child involves assessment of the A (Airway), B (Breathing) and C (Circulation).

### Airway

Pediatric airway is more readily obstructed than the adult one. So patency of the airway is to be ascertained and obstruction if any is to be corrected.<sup>7</sup> Care must be taken to stabilize the neck to protect the cervical spine from yet to be diagnosed spinal injury. The chin-lift jaw-thrust maneuver is often sufficient. Aspiration of the saliva, vomitus or other liquid may sometimes be necessary. A solid foreign body must be removed from the mouth or the pharynx. The patient should ideally be placed in a semiprone position. Even though this position is contraindicated in presence of cervical cord injury, the semiprone position would help in

keeping the tongue and jaw forward and permits easy suction of the oral secretions. Placement of an oropharyngeal airway or endotracheal intubation may be done if required to keep the airway patent. Intubation would also be needed in case of coma from head injury or if artificial respiration is likely to be required for a prolonged duration. A child should always be preoxygenated before intubation. Orotracheal route is usually preferred over nasotracheal route which is also contraindicated if a neck injury is suspected.<sup>8</sup> Emergency tracheostomy may be required in situations when facial or laryngeal trauma precludes the passage of an endotracheal tube.

It is seen that acute gastric dilatation is common complication of injury to thorax or abdomen in children. It is advisable to insert an orogastric tube to decompress the stomach. In cases of head injury care must be taken in inserting the nasogastric tube to avoid passage into the brain through a cribriform plate fracture. Continuous suction of this tube is preferable, but intermittent irrigation and suction may also suffice.

These steps are of greater importance in case of head injury where even minor degrees of hypoxia or hypercapnia may lead to rise in intracranial tension. Oxygen may be administered in cases of head injury whenever needed.

### Breathing

Once the airway is made patent, adequacy of the ventilation is to be assessed, more so in cases of head injury. Breathing is deemed acceptable only in the face of a patent airway and adequate gas exchange in the lungs. All patients with major trauma should receive supplemental oxygen therapy. Early monitoring of pulse oxymetry must be performed wherever possible. Presence of pneumothorax, tension pneumothorax, flail chest, hemothorax must be promptly recognized and managed when present. When associated with multiple injuries and particularly in presence of cerebral edema it is advisable that a radiographic examination be deferred for diagnosing pneumothorax and immediate drainage and/or chest tube insertion be done as indicated.

Compromise of the diaphragmatic excursion due to gastric dilatation is a special hazard in children due to increased importance of diaphragm in children. Early use of gastric decompression by an oro or nasogastric tube may be considered.

Ventilatory assistance may sometimes be needed in cases of central respiratory depression due to head injuries involving brainstem or medulla or due to an intracranial clot or cerebral edema. Although inter-

mittent positive pressure ventilation is the treatment of choice in cases of flail chest; this condition is however uncommon in children.

### Circulation

A child is likely to become hypovolemic even with a small hemorrhage as the total blood volume of a child is low.<sup>9</sup> In adults hypotension occurs when the blood loss is more than 25 percent of the total blood volume. However, in early phase hypovolemia is well tolerated in children and blood pressure is maintained by an effective vasoconstrictive mechanism.

An instant evaluation of circulation can be made on inspection. This is particularly true for children as they tend to have pallor (and sometimes excessive sweating) before tachycardia or hypotension are observed. In shock a child is also likely to have tachypnea, dyspnea, lethargy and hypotonia. Pulse pressure may sometimes be decreased and the capillary filling time elevated. Other neurological manifestations like agitation may sometimes be present due to cerebral hypoxia and signals the need for prompt action.

As the assessment is progressing, an intravenous access must be obtained. Although large bore cannulas are ideal, the size of the available veins should determine the size of the cannulas to be used. Jugular, subclavian, femoral, saphenous or antecubital cutdown may be carried out by skilled personnel to deliver fluids and medications in a hypotensive child. Early resuscitation may also be started by intraosseous infusion into the tibial marrow space by a bone marrow needle. A central venous line is desirable in order to monitor the CVP.

Hypovolemic shock is the most common form of shock after major trauma and should be treated with fluid resuscitation. The bleeding must be controlled as far as possible till specific measures can be undertaken. The colloids and/or crystalloids are administered as needed to correct the shock. Blood and blood products may be infused if required. The fluids and blood must be given rapidly enough to maintain stable vital signs and adequate urinary output. Vasopressors, steroids and sodium bicarbonate do not play a role in the initial treatment of hypovolemic shock.

Cardiogenic shock after major childhood injury is rare but could be seen after cardiac tamponade or direct cardiac injury. Neurologic shock may be suspected in patients with hypotension without tachycardia or vasoconstriction. Septic shock rarely occurs immediately after injury, even after abdominal contamination in abdominal injuries. These types of shocks should be appropriately managed.

The leads of ECG monitor with defibrillator should be attached to the patient as soon as possible. Defibrillation, external cardiac compression and rarely, open cardiac massage should not be delayed if needed.

In most instances the establishment of an arterial line is deferred until the child reaches the intensive care unit. Once the arterial blood gas analysis becomes available the degree of metabolic acidosis due to inadequate tissue perfusion may be determined.

After A (Airway), B (Breathing) and C (Circulation) comes D (Disability Assessment) and E (Exposure). Which means that the child's clothing should be removed and he should be examined for other injuries. The child is likely to be too sick or comatose to show his unwillingness to co-operate for the examination. However, he should be examined thoroughly without causing any further discomfort. A systematic examination of all organ systems must then be done.

Hypothermia is a special risk in injured children as they have relatively more surface area than an adult. The dangers of hypothermia are impaired circulatory dynamics, impaired coagulation, increased peripheral vascular resistance and hence increased metabolic demands. It is necessary to maintain normothermia in an injured child. Radiant warmers, air shields and IV fluid warmers are useful tools in maintaining adequate temperature.

### Exception to Sequence of Priority<sup>10</sup>

The following conditions are exceptions to the above sequence of resuscitation:

- A. Open chest wound—must immediately be closed keeping in mind development of tension pneumothorax, and
- B. A major external hemorrhage must be controlled immediately.

### Investigations

Immediate tests needed for a seriously injured child includes blood grouping and cross matching, hemoglobin and hematocrit estimation and conducting arterial blood gas and urine analysis.

In any child with major trauma caused by a blunt mechanism, a basic radiologic survey series should be considered. These include X-rays of cervical spine, chest, abdomen, pelvis and any extremity involved. In a stable patient the lateral X-ray of the cervical spine may be done before other X-rays are taken.

Emergency CT scans or ultrasonography of the abdomen are now increasingly used. Barium studies, intravenous pyelography (IVP) and micturating cystourethrogram (MCU) are also used in evaluation of a traumatized patient.

However, sophisticated tests usually serve only to confirm the clinical suspicions. Only rarely is the patient's survival determined by immediate availability of such tests; occasional exception being CT head.

### TRAUMA SCORES

In the early stages of assessment, precise diagnosis of the anatomic injury is impossible. Many injury severity scoring systems have been developed to identify patient at high-risk or with a potential for mortality which assist in the management of the injured child.<sup>11</sup> The following scales may be used:

- A. Glasgow coma scale of 12 or less is an indication for admission in emergency department.
- B. The CRAMS score (Circulation, Respiration, Abdomen, Motor and Speech) may be used for field triage.
- C. The revised trauma score is predictor of injury severity and can be used both for children and adults.
- D. The pediatric trauma score is designed to give added emphasis to the importance of patient sizes and airway control in an injured child and is therefore a better predictor for emergency department disposition. Scores of 8 or less are best managed in a pediatric trauma center.
- E. Champion trauma score<sup>11</sup> is the best known of the physiologically based trauma scales. It estimates injury severity and is based on initial vital signs and level of alertness. It can be used to compare predicted outcomes with observed ones and in evaluating trauma care systems.

### Organization of Trauma Services

The rationalization of trauma care in our country is still in its infancy. Most hospitals are likely to have only two or three physicians in the building and their ability to handle emergency trauma is hampered by lack of specific protocols. Each member of the team must have a well planned series of duties to be carried out with minimum discussion and delay. Each center must ideally have a critical care team with pediatric expertise. A trauma team should have a designated pediatrician in charge who is experienced in management of trauma. However, his specialty is less important than his ability to coordinate and obtain cooperation from all concerned. Other pediatricians would be needed to manage the airway and assist with the procedures. Nurses should be available for documentation and for other help needed in trauma resuscitation.

A trauma center also needs to have children transported from other places/hospitals. Although many ambulance crews are well trained; studies in US have shown that they feel uncomfortable in transporting critically ill children and need further training in this regard. A specialized pediatric team is the best choice for transportation of a critically ill child even if it takes longer to arrive. This dedicated team would be adept at pediatric and neonatal equipment and would lead to higher level of care of patients during transport.

## HEAD TRAUMA

Head injury is the leading cause of death and disability among pediatric trauma patients. More than half of children admitted with trauma are likely to have head injury of some degree as compared to orthopedic trauma which accounts for 10-15 percent of emergency department visits in hospitals.<sup>12</sup> In the United States head trauma accounts for approximately 2,50,000 hospital admissions and nearly 5 million visits to the emergency department leading to about 7000 deaths in a year. In India more than 2,00,000 children suffer from head injury every year. Falls account for the greatest incidence of head injury<sup>2</sup> in preschool children, while in school age children head injury is likely to be caused by sports related injuries or motor vehicle accidents.

Head trauma can be divided into penetrating or non-penetrating. These may further be classified on the basis of severity as mild, moderate or severe. Penetrating trauma includes injuries from sharp objects such as knives, darts and missiles. This is less common than blunt trauma but the incidence especially of gun shot injury is on the rise in US.<sup>13</sup> Blunt trauma to the head can lead to concussions, skull fractures (linear skull fractures, depressed skull fractures, basilar skull fractures, growing skull fractures), parenchymal injuries (cerebral contusions, intraparenchymal hematoma, diffuse axonal injuries), diffuse brain swelling, hematomas (epidural hematoma, subdural hematoma) and hemorrhages (subarachnoid hemorrhage). These types of injuries depend on the mechanism of injury as well as the age of the child.

Primary brain injury refers to the neural damage directly due to the traumatic insult. This type of injury occurs at the moment of impact, either by penetration of a foreign body or by nonimpact shear forces that occur during acceleration/deceleration injuries. Contusion or laceration of the brain tissue, damage to the neurons or penetration of the brain by a missile all constitute primary brain injury. Secondary brain injury

refers to subsequent injury to the erstwhile normal neurons after the trauma has occurred. The outcome of head injury to a large extent depends on the recognition and management of this preventable secondary damage to the brain. These potentially treatable factors such as hypoxia, hypercapnia, hypotension, seizures, metabolic derangements, increased intracranial tension, cerebral herniation syndromes, etc. should be prevented or minimized. Neuronal death after brain injury is a complex mechanism at cellular level, including dysfunction of ion pumps, intracellular accumulation of calcium sodium and chloride; intracellular swelling; glutamate accumulation; and release of phospholipids, oxygen free radicals, thromboxanes and leukotrienes.

Children are extremely labile in their response to head trauma and may deteriorate even when the injury is apparently small. The severity of the damage is not always proportional to the degree of trauma in a child and due to large proportionate head size a child is likely to have more damage to his brain than an adult undergoing similar traumatic conditions. Because their brains are softer with a higher water content, children are also more susceptible to acceleration/deceleration injuries. It is often difficult to decide when a child with head injury be admitted in a hospital.

Any child with a skull fracture or having unconsciousness or persistent drowsiness following head injury is a candidate for admission in a trauma center.<sup>14</sup> However, an exception can be made for children whose parents are sufficiently intelligent to carry out the necessary observation at home and report back when the child deteriorates. The warning signs that must then be looked for are deterioration in consciousness, progressive vomiting, visual disturbances, ataxia, seizures, dilatation and sluggish response to light in previously normal pupil, worsening of neurological deficit or appearance of signs of increased intracranial tension (ICT) or hemorrhage.

## Management of Head Injury

Wounds limited to the scalp and not entering the cranial vault are appropriate for primary repair. Mildly symptomatic patients without any neurologic deficit even with small cerebral contusions or hematomas may be kept for observation and subsequently discharged. As with other emergencies the management of head trauma also begins with ABC's of resuscitation. In addition to the steps already addressed, attention should also be focused on the need for brain specific therapies.

In all cases of head injury the potential for cervical cord injury should be recognized and the neck

immobilized manually or with a semirigid cervical collar till the cervical cord injury is ruled out. Keeping the head in the midline position has an added advantage of maintaining the jugular blood flow.

As soon as the airway is secure monitoring of vital signs like heart rate, respiratory rate, temperature, etc. should be undertaken. Blood pressure should also be checked in all cases of head injury. The blood pressure is unlikely to be on lower side. However, in babies and younger children hemorrhage even from a bleeding scalp wound may sometimes lead to excessive blood loss and subsequent hypotension. Other sources of bleeding must also be looked for in such cases and any bleeding lacerations should be occluded with direct pressure. Any penetrating objects still in place should not be removed in emergency because of the potential for serious hemorrhage.

Neurological assessment is crucial in detecting the extent of brain damage. The prognosis after severe head injury depends most on the level of neurological function at the time of presentation and on the presence or absence of other lesions. Glasgow coma scale (GCS) is usually used for this assessment. Some clinicians also use the modified GCS or the Children coma scale for pediatric patients.<sup>15</sup> Patients with a GCS in ranges of 3 to 5 have a low likelihood of a good functional outcome. For patients with better neurological status, the prognosis is influenced by the degree of brain damage sustained by the patient. It is seen that patients of head injury with intraparenchymal or subarachnoid hemorrhage or those with injuries involving both hemispheres do not have good prognosis.

X-ray of the skull is not essential in emergency situations and is more of medicolegal importance. However, it would help in detecting fractures and intracranial air indicative of compound fracture. In most cases of head injury CT scan of the head is worth the time spent in getting it performed. The goal of CT scan is usually to identify the injury and also any space occupying lesion that may need surgical intervention. With the increasing use of CT and MRI for patients with mild head trauma, an increasing number of contusions are being discovered in patients with none or mild symptoms.

In general ICT monitoring is advisable for any patient with a head injury who is comatose and has an abnormal CT head. ICT in these patients should be maintained at 20 mm Hg or less. An ICT between 20-40 mm Hg is considered moderate increase and requires treatment. If the ICT is more than 40 mm Hg then it is considered to be severely increased and potentially fatal unless managed urgently.

All seriously traumatized patients must be administered 100 percent oxygen until it is certain that supplemental oxygen is not required. Intubation and subsequent IPPV should be done if needed. If there is evidence of increased intracranial tension, therapeutic hyperventilation may be indicated along with the medical management (vide infra) of increased ICT. The aim of hyperventilation is to maintain the PaCO<sub>2</sub> of 30 to 35 mm Hg. No evidence exists that hyperventilation or medical therapy (mannitol, diuretics) prevents the development of brain edema. Corticosteroids also have not been shown to have any significant improvement in outcome of patients with head injury. Therefore prophylactic use of these drugs is not recommended. Anticonvulsant medications are indicated for patients with ongoing seizure activity. They are also used prophylactically in patients of head injury who have intracranial lesions associated with increased risk of seizures such as cerebral contusions, cerebral hemorrhage, subarachnoid hemorrhage or subdural hemorrhage. Patients without parenchymal injury having only epidural hemorrhage usually do not require prophylactic anticonvulsants.

Sedatives should be used as sparingly as possible, however, they may be required to prevent coughing or agitation which may lead to further elevation of the intrathoracic pressure and impaired venous drainage. Paralytic agents should be used only when sedating agents cannot be tolerated or when the maximum therapeutic dose is proving to be inadequate in controlling the patient's agitation. Patients with skull breach should be started on appropriate antibiotics. Many recommend that patient with basilar skull fracture and CSF leak should be admitted in the hospital for intravenous antibiotics.

All patients with intracranial hematomas exerting significant mass effect need an emergency operation to remove the hematoma. Smaller lesions may be initially managed nonoperatively but the patients must be monitored for any deterioration. Surgical intervention is usually necessary for compound or open depressed skull fractures especially in patients with lacerations of the dura mater. Surgery is also done though not necessary in emergency department, for patients with depressed skull fracture and underlying compression. Patients with a significant cosmetic difficulty are candidates for surgical repair as well.<sup>16</sup>

## MINOR TRAUMA AND LACERATIONS

It has been estimated that every year more than one crore wounds are treated in emergency departments in the United States. Lacerations account for more than

30-40 percent of all these injuries.<sup>17</sup> Data from India is hard to come by. Studies have revealed prevalence rates of 67 percent for minor injuries among underfives<sup>18</sup> and 14.2 percent in 4-9 years old children. The most common site of these injuries was head and trunk. Head and trunk had maximum of scratch and cut injuries or lacerations (53%) followed by abrasions (28%). Upper limbs and fingers had maximum of scratch and cut injuries (27% each). Lower limbs and toes had maximum of abrasions (67%). Overall maximum injuries took place at home (62.6%). Majority of injuries were self sustained (60%) and while playing (60.5%). It has been shown that wooden furniture, broken glass, concrete or other sharp objects are the usual causes of these injuries. Dog bites, monkey bites and other animal bites also account for some of these lacerations. Boys are injured twice as often as girls. The mechanism of injury also varies with age of the patient.

### Wound Healing

Scar formation is a complex process meant for restoring the strength of the skin. Scars are usually formed in wounds that are deeper than the dermis. Lacerations parallel to joint and normal skin folds usually heal more quickly with little scarring and have better cosmetic results. On the other hand wounds that are under a large amount of tension or those which cross joints or are perpendicular to skin folds, heal with formation of wide and ugly scars. A process like wound infection, which interferes with the laying down of collagen can lead to wound dehiscence and subsequent scarring. A scar may sometimes not be apparent until 6 months of injury and even then remodeling may occur to a period of one year.

Sutures are put to provide temporary support to the gapped wound till the skin can regenerate. Even with suturing, a laceration regains about 5 percent of its strength in two weeks, 30 percent in 6-8 weeks and full tensile strength in about 24-32 weeks after injury. However, infection, edema and poor nutrition can cause a delay in wound healing.

Wounds by sharp object are less likely to lead to infection compared to those by blunt objects. The blunt injuries involve larger force and lead to more amount of dead and devitalized tissue. They are thus more likely to become infected. Similarly, compression injuries cause the most tissue disruption and so lead to maximum infection and scarring. Wound infection also depends on the amount of bacteria on the skin. Wounds in areas colonized with high bacterial contamination like moist areas of the skin (axilla,

perineum), exposed areas (hands, feet) and high vascularity (scalp and face) are more prone to infection.

### Wound Assessment

As in case of major trauma, it is necessary to assess the mechanism of injury of the wound. An injury caused by a sharp object may be deeper though less extensive than that caused by a blunt trauma. The age of the wound should also be assessed. It should be determined whether any foreign body or material is present in the wound. This is especially important in case of a wound caused by a glass piece where glass pieces may be left behind in the wound. In such cases, radiograph of the respective areas may be obtained. Ultrasound may also be used for detecting and localizing larger foreign bodies. The environment in which the injury occurred may then be noted. This is particularly important in children as many injuries occur on the street and it is possible that the wounds are contaminated and some particulate matter gets embedded in the wound. It is also necessary to consider the patient's health status. History of allergy, diabetes, immunosuppression, bleeding disorders, chronic conditions, etc. must be noted. Intake of drugs like ibuprofen and steroids may have an impact on wound healing and should be determined. It is imperative to know the immunization status of the child for tetanus.

A careful physical examination is necessary before any anesthesia is administered to the child. A small external wound may be the only indication of a major injury at a location distant from the main wound. Any active bleeding site should be identified and the bleeding controlled with use of pressure, tourniquet or inflated blood pressure cuffs (applied for less than 2 hours duration). Any associated nerve or tendon damage should be looked for. Muscle functions must be assessed in the involved limb as far as possible. Nearby bones should be assessed for any crepitus or tenderness which might suggest underlying fracture.

### Wound Closure

It has been recommended that most wounds should be closed primarily as soon as possible after the injury. It has been seen that in children, wound infection only occurs in about 2 percent of all sutured wounds. If the primary closure is delayed, the risk of infection is seen to increase. Ideal period for primary closure is said to be six hours; however, clean cut wounds may be closed primarily within 12-18 hours. If the wounds are extensive or at high risk of infection, they must be referred to a pediatric surgeon. Smaller wounds which

are infected, ulcerated or due to animal bites are best left to heal by themselves (healing by secondary intention). A delayed primary closure or a tertiary closure is recommended after 3-5 days for wounds that are heavily contaminated or damaged, or those caused by crush injuries. In these cases, wounds should be cleaned and debrided at the onset and then re-assessed periodically.

The child and the family have to be reassured and given an age appropriate explanation of the procedures required. If the child is to be restrained then it is advisable to take the services of a hospital nurse or ward boy rather than the relatives. The child must be administered appropriate sedation and/or local anesthetics wherever required. The hair around the wound should be cut with scissors. Shaving the hair is likely to increase infection and must be avoided. The wound should be cleaned with a safe and effective antimicrobial agent like povidone iodine. Wound irrigation is an important step in containment of infection. This may be done with normal saline. Dirty wounds may require scrubbing or manual removal of foreign bodies. Surgical exploration may sometimes also be required depending on site of the wound. Any dead tissue should be removed, as it is likely to hinder the process of healing. The surrounding area must now be cleaned and draped before suturing the wound.

### Suturing

Sutures can be of various types and are best described in surgical textbooks. Sutures are put with a view to oppose the layers of the skin and avoid subsequent eversion of the margins. The wound should be stitched using appropriate needles and suture material. Nylon (Ethilon), Silk and Polypropylene (Prolene) being non-absorbable are mostly used for wound closure. Fine absorbable sutures like Vicryl may be used for suturing lower layers of the skin. However, absorbable sutures like gut may be used for stitching intraoral wounds or small lacerations on scalp where suture removal can be avoided.

Staples, or tissue adhesives<sup>19</sup> may also be used for wound closure. Staples and skin glues such as cyanoacrylates can be applied rapidly and have a lower rate of infection. They are however costly and can be applied only to superficial wound. They are also not universally available. Dressing is then done with a view to protect the wound from further injury or contamination. A proper and rigid dressing may also act as a splint. An absorbable dressing is sometimes required to absorb the secretions from the wound. Scalp wounds are usually not dressed. Some studies indicate that local

antibiotic ointments may be useful in reducing infection. They also act as a lubricant and prevent the dressing from sticking to the wound.

Systemic antibiotics have no proven benefit and are not recommended for routine use. Broad spectrum antibiotics may be considered for large, crushed or contaminated wounds. They may also be given if a secondary repair of the wound is done. Mild analgesics may be prescribed to the child if indicated. Tetanus toxoid and/or tetanus immunoglobulins may be given depending on the nature of the wound and the tetanus immunization status of the child.

The parents should be told about the warning signs, i.e. increase in pain, redness, edema or discharge. Wound must also be re-inspected if there is persistent fever or pain. Dressings should be changed after 1-2 days or earlier if wet or soiled. The child can have regular baths as long as wound is dried and dressed after bath. The sutures should be removed in 5 days (face, neck) to 10 days (limbs, trunk) depending on site of the wound. It may sometimes be necessary to put tape on the wound to prevent gaping.

If proper precautions are taken then complications like infection and hypertrophic scarring or keloid formation can be avoided.

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Acute orthopedic problems in children are unique because of the dynamic growth and development in the early years of life. Children are definitely not 'small adults'. The biochemical and physiologic differences of the child's skeleton from that of the adult lead to distinct presentations in an acute setting, such as trauma and infection. In an immature skeleton, different mechanisms of injury lead to unique fracture patterns; bone and joint infections may present in various ways. Moreover, every age group from neonate through adolescence has its own typical fracture patterns, also presentations of acute non-traumatic orthopedic disorders like bone and joint infections, which one should be able to anticipate. It is vital for the emergency physician to understand that early diagnosis and appropriate treatment are crucial in these emergencies, failing which, catastrophic consequences may result.

### IMMATURE SKELETON—BASIC

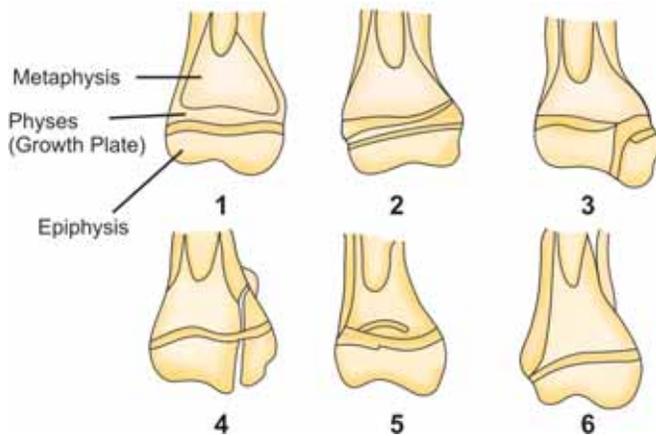
Between children and adults, there are definite anatomical, biochemical and physiological differences. Pediatric bone is less dense and more porous. The surrounding periosteum is thicker and stronger but loosely attached over diaphysis and hence, easily elevated because of trauma or infection. The periosteum, on the other hand, is well attached over the ends of long bones, thus stabilizing the growth plate or the physes in event of trauma. There is a greater probability of a plastic deformation due to low energy trauma in a pediatric long bone, because of decreased mineral content.<sup>1</sup> So, unique fracture patterns like torus or buckle fracture and greenstick fracture are seen. Generally, healing and bony union is faster in children. Moreover, a child's fracture has a remarkable remodeling potential, which allows for some longitudinal malalignment and greater degrees of angulation. Regarding pediatric fracture remodeling, new bone is laid down according to local forces, especially in the plane of motion in the joint. If a child has at least 2 years of growth remaining, a fracture adjacent to a hinged joint will remodel

acceptably if the angulation is less than 30 degrees in the plane of motion.<sup>2</sup> However, precise anatomic reduction is required for fractures with rotational deformities, excessive degrees of angulation, or intra-articular and displaced fractures. Fortunately, no significant stiffness of the joints is noticed in spite of lengthy immobilizations, and hence physiotherapy rarely is required in the management of pediatric fractures.

### PHYSES OR 'GROWTH PLATE'

Physes has cells responsible for bone growth (longitudinal) at the ends of long bones, and are oriented perpendicularly to its long axis. Most physes are extra-articular except femoral, proximal radial and a part of proximal femoral physes, which are intra-articular.

Physal arrest is commonest due to trauma. Although physes is the weakest area of the immature skeleton, only 20 percent of all children's fractures occur in this region.<sup>3</sup> The peak age for physal/growth-plate injury is early adolescence (10-12 years) and occurs more often in boys.<sup>4</sup> They are uncommon in children under 5 years. The most widely used classification for physal injuries is that of *Salter* and *Harris*.<sup>5</sup> The fractures are divided into V types with type VI added by Rang<sup>3</sup> (Fig. 66.1). Ogden went further and published the classification from VI to IX.<sup>6</sup> The growth plate is unaffected in types I and II, but may be affected in others. Type II constitutes 75 percent of all physal fractures. The significance of properly identifying a physal fracture is that growth disturbance may result, leading to angular deformities or shortened limb, depending upon the area of the growth plate affected. Closed reduction of displaced fractures across the growth plate needs to be gentle, to prevent further damage. Certain fracture patterns require operative realignment and stabilization to reduce likelihood of growth disturbance. Minimal soft tissue exposure near the physes and gentle handling, go a long way in preventing any iatrogenic arrest. Any screws used to fix the fracture should not cross the physes for the same



**Fig. 66.1:** Salter-Harris classification: (1) Transepiphyseal separation only; (2) Fracture-line through physes/growth-plate, exiting into metaphysis leaving a triangular portion attached to the plate (shaded on right side); (3) Intra-articular fracture traversing the physes and epiphysis; (4) Vertical fracture-line passing through epiphysis, physes and metaphysis; (5) Crush injury to physes not apparent in the initial X-rays; (6) Localized injury to a portion of perichondrial ring leading to subsequent bony-bar connecting metaphysis to epiphysis (across physes)

reason. Most importantly, parents need to be appraised of the relative risk of this problem surfacing during follow-up.

A special mention is necessary regarding the type VI, which occurs due to bruise, burn or avulsion of the stabilizing perichondrial ring. No technical damage occurs to the main part of the growth plate but problems occur as the healing process may cause bridging across the physes, tethering that area and restricting growth. Thus, a blunt injury near a joint such as knee may not necessarily be a trivial one and plain radiographs may look innocent. A guarded prognosis then is best, with subsequent early follow-up to pick-up the damage, if possible.

## GENERAL APPROACH

### History

An injured child is accompanied generally by a group of extremely worried individuals, with the parents in the forefront! A calm and gentle, yet firm approach is your best bet. Localizing the area of injury in a frightened and preverbal child is a great challenge. Mechanism of injury is extremely important to lead you towards the right tract. 'Pulled elbow' for example, will have a history suggesting a sudden traction to the forearm and not a direct injury to the elbow. The

physician can often predict the injury type through knowledge of the commonest types of injuries for the child's developmental level. Having stated this, the physician should have awareness regarding "child abuse".<sup>7</sup> A vague history not explaining the objective findings should ring the warning bells!

In a neonate, decreased movement of a limb coupled with a history of trauma, is highly suggestive of bone and joint infection. A very high degree of suspicion of infection must be entertained in all cases of premature neonates with low birth weight. Accompanying constitutional symptoms like fever, are commoner in an older child with infection. Pain is the commonest symptom, along with others, like refusal to bear weight, limp or simple disuse of the part.<sup>8</sup>

### Physical Examination

Keeping in mind a child's fear, pain, and developmental level, a gentle and systematic approach is best for evaluation and treatment. Administering appropriate analgesia will aid not only in reducing the child's pain and anxiety but also in examining the injured part. It pays to divert away your eyes from the obvious region of trauma and concentrate on the rest of the body. This reduces your chances to miss out on an associated trauma or any other significant finding.

Before palpating the injured area, one should examine the skin carefully for any breaks. Next, the physician should evaluate the neurovascular status of the limb carefully, especially before and after reduction and splinting. This is very important in supracondylar fracture of the humerus. Finally, one should examine the injured area by palpating the area of injury. For addition comfort, the injured limb should be splinted (include the joint above and below) before obtaining radiographs.

The radiographs must include the joint above and below the injury. The injured region should be radiographed using plain radiography in at least two different planes, usually anteroposterior (AP) and lateral views. There are some areas, such as the elbow or wrist, where oblique views are also obtained.

It is difficult to differentiate between the lesions due to accident or inflicted trauma. The physician therefore, should be knowledgeable in patterns of child's growth and development, as well as common injuries in children. A combination of the history given, behavior of the parent and, certain clinical manifestations serve as practical guideline for differentiating non-accidental injury from that associated with pathological conditions.

## Management

Some significant emergencies will be individually discussed subsequently.

## PEDIATRIC ORTHOPEDIC TRAUMA

### Polytrauma

It is important for the emergency physician to respond spontaneously to an unconscious road-side accident victim or a child having multiple fractures. Maintaining airways is the first priority, followed by restoring breathing and circulation by intubating if necessary, and infusing fluids/blood. A thorough clinical examination is necessary from head to toe. It is best to seek help from other relevant specialists as soon as possible.

### Open and Closed Fractures

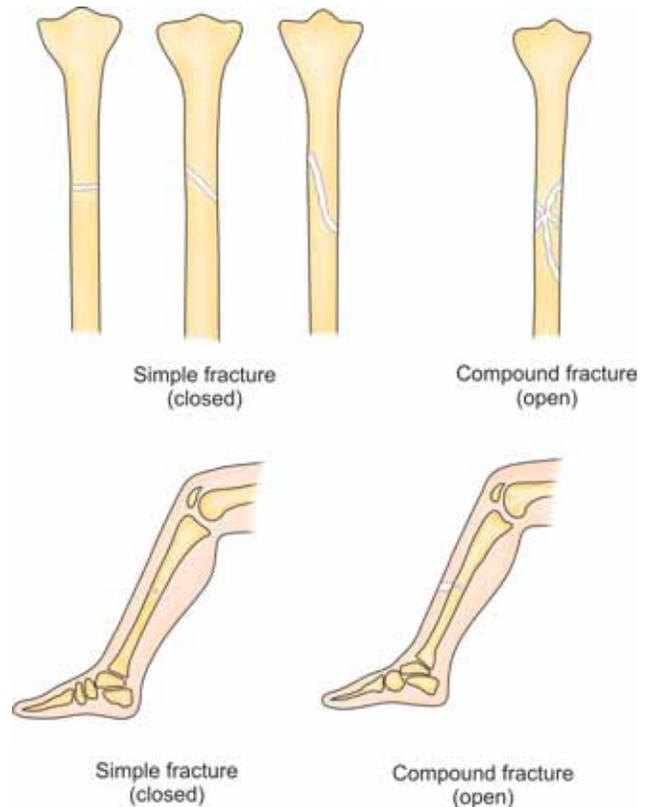
It is important to understand the differences between an open and a closed fracture (Fig. 66.2). In open fracture bone communicates with the outside environment. Chances of infection are increased in these fractures and they carry a relatively poorer prognosis. The limb may be obviously bleeding or may look ominously innocent with a trivial trickle from a puncture wound. A thorough wound toilet using plenty of saline goes a long way in reducing the chances of infection in the future. A special mention should be made regarding injuries with protruding bony fragments. Under no circumstance should the emergency personnel be in any hurry to reduce the fracture, as that just increases the chances of infection. It is better to leave the management to the orthopedic surgeon but, if the neurovascular status is being compromised, a thorough wound toilet is imperative before reduction. A broad-spectrum antibiotic coverage, preferably in combination, should be commenced in all open fractures. A closed fracture bone does not communicate with outside and has a better prognosis.

## FRACTURES AND DISLOCATIONS OF UPPER LIMB

### Around Shoulder

#### Clavicle

It is the commonest bone to fracture in the pediatric population.<sup>9,10</sup> It lies horizontally in the body and is commonly fractured in difficult normal deliveries. Newborns's lack of arm movements can be confused with branchial plexopathy or proximal humeral fracture. It is also a frequent fracture due to fall on an



**Fig. 66.2:** Open and closed fracture (Previously compounds and simple, respectively) of tibia

outstretched hand. It is important to check the neurovascular status of the limb. This fracture does not need reduction usually and unites well invariably.

#### Humerus: Upper End

The proximal humeral epiphysis is responsible for 80 percent of the longitudinal growth of the humerus.<sup>10</sup> Thus, for proper growth, diagnosis and treatment of physal fractures in this region are vital. Noteworthy, fractures to the proximal epiphysis are the major type of injury to the proximal humerus in children. *It is commonly mistaken for a shoulder dislocation in this age group* (Fig. 66.3). The usual history is that of a fall backward onto an extended arm. The humeral metaphysis is thus forced laterally and anteriorly.

A severe fracture or one in which the history is inconsistent with the injury should raise suspicion of abuse, especially in young children.<sup>7</sup> The entire shoulder girdle should be radiographed after the neurovascular examination. The physician should pay particular attention to possible axillary nerve damage with resulting abnormal deltoid function and paresthesia or anesthesia over the lateral shoulder.

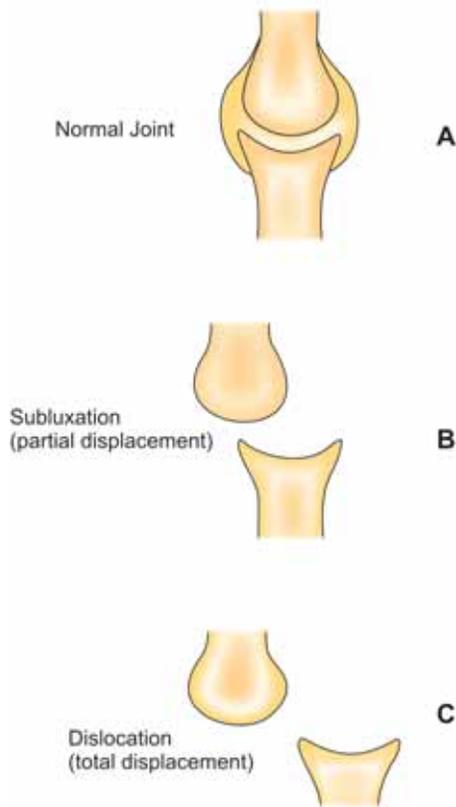


Fig. 66.3: Subluxation and dislocation

Most children can be treated with an arm sling if the separation is less than 1 cm, the angulation is less than 40 degrees, and there is no malrotation.<sup>9,10</sup> An orthopedic surgeon should evaluate the child as soon as possible.

### Around Elbow

#### *Supracondylar Fracture Humerus*

It is the commonest elbow fracture in pediatric patients. They typically occur between the ages of 3 and 10 years and more frequently in boys than girls. These fractures require treatment as an acute emergency, especially as flow through the brachial artery can be affected at the site of injury. Accurate diagnosis and prompt treatment are vital with supracondylar fracture to minimize morbidity.

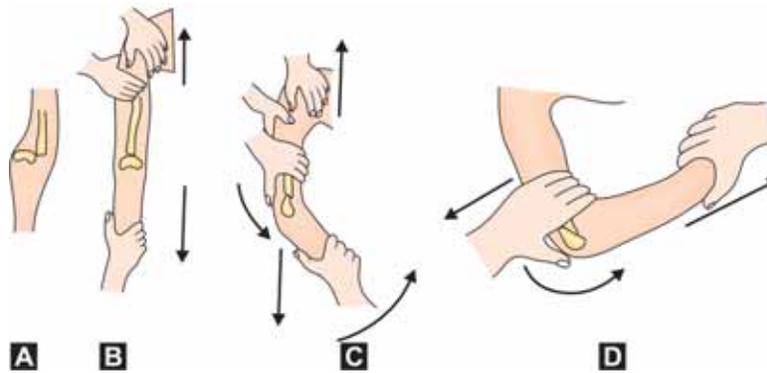
The typical history for a supracondylar fracture is a fall onto an extended arm and outstretched hand, which forces the distal fragment upward and posteriorly after fracturing the supracondylar area. The injured child will hold the arm in pronation and resist elbow flexion because of pain.

The physician who suspects a supracondylar fracture should do a careful neurovascular examination, checking for the five “Ps” of arterial injury or compromise: Pain, pallor (poor perfusion), weak radial pulse (to pulselessness), paralysis, and paresthesia.<sup>9</sup> Worsening pain or pain with passive extension of the fingers are also “red flags” for ischemia. An orthopedic surgeon must immediately evaluate and treat (reduce) a supracondylar fracture with any sign of ischemia. Compartment syndrome of the volar forearm can develop in less than 12 to 24 hours, with subsequent necrosis and fibrosis of the involved musculature. This ischemia/infarction can lead to Volkman’s ischemia contracture (VIC) subsequently, which is characterized by fixed elbow flexion, forearm pronation, wrist flexion, metacarpo phalangeal (MCP) joint extension, and interphalangeal flexion. *If no orthopedic surgeon is available and there is evidence of arterial injury or ischemia*, then the emergency physician must reduce the fracture.<sup>11</sup> The technique for fracture reduction is placement of the forearm in supination, then applying longitudinal traction, and direct pressure to the displaced fragment in a downward and anterior direction (Fig. 66.4). Majority of the displaced fractures can be managed by closed reduction and internal fixation by K-wires, using radiographic control (C-arm) preoperatively.

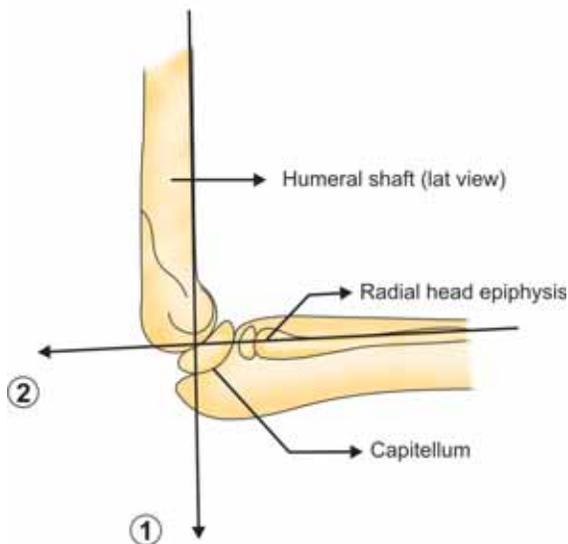
In a child without neurovascular compromise, an AP view in extension and a lateral view in 90° of flexion should be performed. Because the fracture line is often difficult to visualize, one can use the anterior humeral line and pathologic “fat pads” as indirect evidence of subtle fractures and both are visualized on lateral view.<sup>11</sup>

Anterior humeral line is a line that is visualized on the lateral view, being drawn down the anterior margin of the humerus. This line should intersect the capitellum in its posterior two thirds (Fig. 66.5). If this line intersects the anterior one third of the anterior capitellum or appears anterior to the capitellum, it is strongly suggestive of a supracondylar fracture with posterior displacement of the distal fragment. Additionally, one can use the fat pads as non-specific indicators of elbow joint effusion or hemorrhage that is seen with an occult elbow fracture. Both fat pads are visualized on the lateral elbow view. The *posterior fat pad* is recognized as radiolucency posterior to the distal humerus adjacent to the olecranon fossa; the presence of a posterior fat pad is always pathologic and indicative of elbow effusion. The interpretation of these is best left to concerned specialists.

An undisplaced supracondylar fracture without neurovascular compromise does not require immediate



**Fig. 66.4:** Technique of closed reduction of supracondylar fracture of humerus extension type (commonest, with distal fragment in extension or tilted posteriorly). Recommended for use by the emergency physician when no orthopedic help is available and there is neurovascular compromise. (A) Displaced supracondylar fracture. Before the maneuver, check the radial pulse whether palpable or not, and if palpable, compare the volume with that of the other side. (B) Bi-axial traction (using both hands over forearm and pulling both, one along the arm axis, and the other along the axis of forearm; keeping the elbow in 30° flexion) and counter-traction (by an assistant) given. Care should be taken not to take the elbow in full extension as this may further compromise the neurovascular status (C) Maintaining the traction and countertraction, gently flex the elbow till 90°-100°, using the thumb of the other arm to push the distal fragment anteriorly. If radial pulse disappears or becomes feeble during the procedure, *do not proceed* out bring the forearm back to 30° of flexion. (D) Do not flex beyond 100°, and keep the forearm in mid-prone position. Radial pulse may now be palpable or may increase in volume at this final position. Apply a posterior splint in this position and await the arrival of the orthopedic surgeon. Aim is to better the neurovascular status and not to achieve perfect reduction



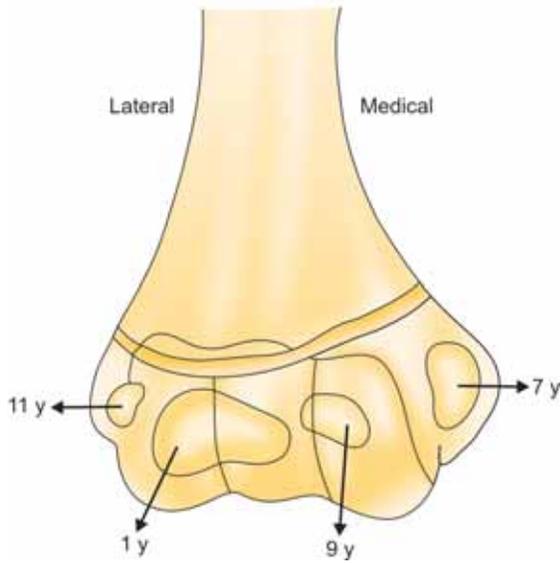
**Fig. 66.5:** Normal relationships around the elbow on lateral view: (1) Anterior humeral line passes through the junction between anterior 2/3 and posterior 1/3 of capitellum. Subtle supracondylar fractures of humerus (extension type) will have the line passing in the front. (2) Radio-capitellar relationship the long axis through the radial shaft passing through its head, always passes through the capitellum. This is true in all degrees of elbow flexion. This would be maintained in all supracondylar fractures and transepiphyseal separations of humerus. It would be disturbed in elbow dislocations and displaced lateral condyle fractures of humerus

orthopedic evaluation in the emergency. Rather, it can be gently splinted with the elbow flexed at 90°, with the forearm splinted in either pronation or a neutral position, posteriorly from the wrist to the axilla. One must always evaluate the neurovascular status of the forearm, wrist, and hand following splinting. These patients should be evaluated by an orthopedic surgeon within 24 hours.

Another injury that requires special mention is ‘fracture-separation of distal humeral physes.’<sup>12</sup> It is an injury of infants and can also be seen in a newborn. The diagnostic challenge lies in this age-group due to lack of ossification of the distal humeral epiphysis (Fig. 66.6). This injury can occur in 3 clinical settings: birth trauma, accidental trauma and child abuse. Diagnosis needs a good clinical examination and understanding of the relationship of proximal radius and ulna to the distal humerus (Fig. 66.5). It is important to realize that elbow dislocations are very rare in young children, especially in infants. Elbow arthrography can help to confirm the diagnosis.<sup>13</sup> Initial management is on similar lines as a supracondylar fracture.

### ‘PULLED ELBOW’

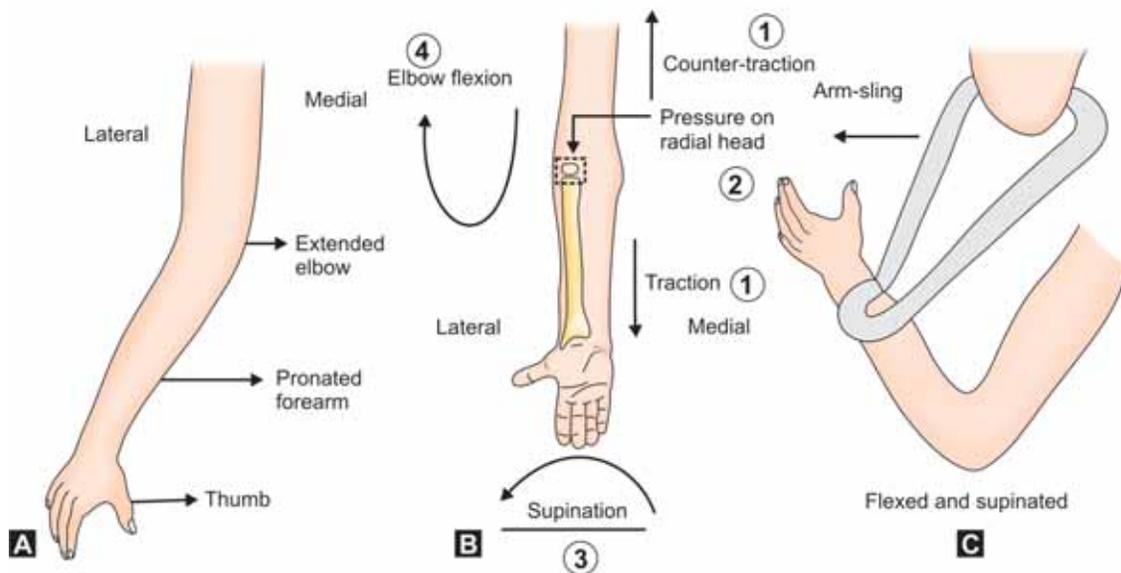
Radial head subluxation, commonly known as *nursemaid’s elbow*, is seen frequently in the emergency room because of parental concern over a child’s not moving his or her arm. This injury occurs primarily in toddlers



**Fig. 66.6:** Ossification of secondary centers of distal humerus (average ages are specified) Anticlockwise, from lateral to medial, lateral condyle, capitellum, trochlea and medial epicondyle have been depicted. The 1st three coalesce around 10-12 years and this, along with medial epicondyle fuses with the shaft between 13-16 years

but can appear in the infant or preschooler. Often, the history is difficult to obtain because the caretaker may not realize the cause of the injury. The typical mechanism is abrupt longitudinal traction on the child's pronated wrist or hand. This action forces the annular ligament over the radial head, lodging it between the radial head and the capitellum. Usually, the child refuses to move the affected arm, holding it close to his or her body with the elbow extended and the forearm pronated (Fig. 66.7A).

**Treatment:** After carefully examining the child's arm and shoulder girdle, the physician who is confident of a radial head subluxation can attempt reduction without obtaining any radiographs. If there is focal bony tenderness on examination, then one should obtain plain radiographs to rule out a fracture. Although there are many reduction techniques, supination is the integral part of most of the reduction methods. A popular method is for the physician to place his thumb of one hand over patient's radial head and with other hand holding the patient's wrist to pull the elbow into extension gently. Next, the physician should quickly supinate and flex the elbow (Figs 66.7B and C). In many cases, there is a palpable click over



**Figs 66.7A to C:** "Pulled Elbow": (A) Attitude of the upper limb after trauma. (B) *Reduction maneuver*—One hand holding the wrist gives gradual traction and the other hand holding the arm provides countertraction. The thumb of the hand holding the arm can be used to give posterior pressure over the region of the radial head. With this pressure maintained, supinate the forearm fully, and flex the elbow at the same time in one smooth fluid movement. *Supination is the crux of the procedure.* The head reduces with a palpable/audible click most of the time. (C) Final position after reduction. Cuff and collar sling may be given. *Refer immediately if the child isn't comfortable and doesn't move his/her limb actively with in 1/2 an hour of the maneuver*

the child's radial head when the annular ligament is reduced. In the absence of a click, the physician should fully pronate and extend the elbow, then repeat the supination and flexion maneuver. If no click is felt or heard at this time, the physician should allow the child to rest. A younger child should start to move his arm in less than 20 minutes. If the child fails to move his or her arm in that period, then further attempts to reduce should be deferred and the orthopedic surgeon should be called immediately. One should obtain radiographs (if not already obtained) and place the child in a posterior elbow splint.

Fortunately, most reduction attempts are successful, and the parents are usually impressed with their child's rapid return to normal. Because many parents do not realize the harm in lifting a child's entire body from the hand or wrist, the physician should explain the mechanism causing nursemaid's elbow and caution against lifting the child in this manner.

### Lateral Condylar Fracture Humerus

This is the 2nd most common elbow fracture with a peak age range of 5-10 years. This fracture can be caused by avulsion due to tension on the common extensor origin, or compression force from the radial head, both due to fall on an outstretched arm. There is bony tenderness over the lateral condylar region of the injured elbow. *This is complex fracture as it involves the physes as well as the articular cartilage.* Minimally displaced fractures may not be visible on standard AP and lateral views of elbow, and may require an oblique view with the arm internally rotated. Treatment depends on degree of initial displacement and assessment of fracture stability; and may range from simple cast immobilization to open reduction and internal fixation using couple of K-wires. Maintenance of articular congruity is important. Proper follow-up of these injuries is necessary when treated by casting alone, as there is a good chance of losing reduction and additional displacement.

### Forearm and Wrist Fractures

These are common and account for more than half of all children's fractures.<sup>14</sup> Most occur in children >5 years of age. The location of the fracture advances distally with the increasing age of the child. Distal radius and ulna are the sites for majority of forearm fractures.

*Galleazzi and Monteggia fracture dislocations* are special forearm fractures. Generally speaking, the former is the fracture shaft radius along with dislocation of distal

radioulnar joint; and the latter, fracture shaft of ulna along with dislocation of superior radioulnar joint. This just emphasizes the importance of including both the elbow and the wrist in the X-ray of any forearm fracture. Other variants may slow-up in these fracture-dislocations on X-ray, which needs to be recognized and managed by the orthopedic surgeon.

In these forearm fractures, the emphasis should be on proper splinting, checking on the neurovascular status, analgesics and proper radiographs, and the specialist should be called in at the earliest.

### Fractures and Dislocations of Lower Limb

#### Pelvis

Fractures of pelvis in children usually involve significant direct trauma to the child as occurs in road-side accidents. The immature pelvis is more malleable than that of an adult, largely because greater component is cartilage and the joints are more flexible. Greater energy hence, is absorbed during impact and the resultant fractures are less displaced and more stable. The cause being high-energy trauma, the attending physician should be vigilant regarding other associated fractures and injuries, like that of head and cervical spine, intra-abdominal injuries, other fractures and genitourinary trauma.<sup>3</sup>

A thorough physical examination, especially over bruised and contused areas is mandatory. These fractures can incur massive blood loss, which should be anticipated, monitored and replaced as soon as possible. Bed rest and protected weight bearing can manage most pediatric pelvic fractures.

#### Femoral Shaft and Supracondylar Fractures

These are common childhood fractures with a great variety in the types of treatment available. Fracture patterns like transverse, oblique, spiral and comminuted reflect on the mechanism of injury sustained. These injuries in children less than 4 years should alert the physician for child abuse.<sup>7</sup>

Most fractures have significant displacement and majority have breaks in the diaphyses. The supracondylar fractures of femur are similar and as dangerous as in humerus. Neurovascular compromise is always a strong possibility and hence a constant vigil on the same is needed. The role of emergency physician is also to replace fluids or blood, and give rest to the part using and appropriate splint. The orthopedic surgeon needs to take over as soon as possible.

## Tibial Fractures

### 'Toddlers's Fracture'

In infancy and early childhood, low-energy torsional forces like twisting of leg, can cause this fracture. Child refuses to walk on the affected leg and limps. Child is not averse to crawl and this eliminates a hip pathology. A point-tenderness is elicited in the distal one-third of tibial shaft. Fibula is not involved. Diagnosis is more by exclusion of other pathologies like that of hip, and tibial osteomyelitis. Radiographs may not be evident initially but will show-up after 10-14 days. A below-leg walking cast for around 3 weeks suffices.

### Ankle Fractures

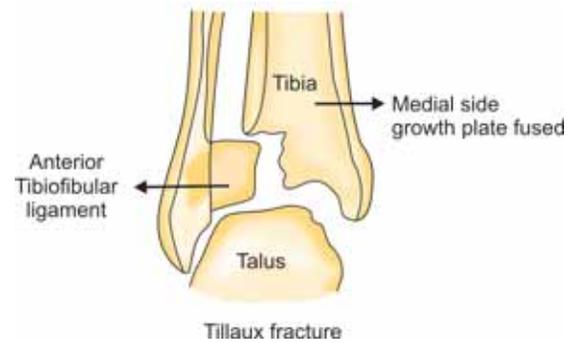
These are relatively common injuries in children and are usually due to indirect violence like a twisting strain. Distal tibial physis is a frequent site for physal separation, 2nd only to distal radius.<sup>3</sup> A special mention is warranted regarding transitional fractures seen only in adolescents because of incomplete physal closure. The mechanism of injury is external rotation. Tillaux and Triplaner fractures come under this category and are best evaluated by a CT scan (Fig. 66.8). These invariably require open reduction and internal fixation.

### Cervical Spinal Injuries

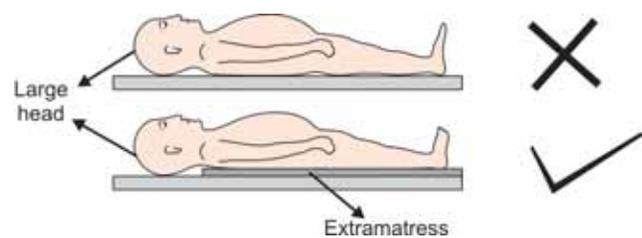
Traumatic spinal cord injuries in children are uncommon. However, cervical spine injuries in children have many unique characteristics that the physician must understand to limit morbidity and mortality in these patients. *In fact, up to 5 to 10 percent of lesions occur after the initial injury and during the early course of emergency management.*<sup>15</sup> With appropriate management in prehospital and emergency ward, the outcome is optimistic for many children with spinal cord lesions (Fig. 66.9).

The leading causes of spinal cord injury in children vary by age, but heading the list are motor vehicle-related injuries and falls. During the second decade of life, athletics, other recreational activities, and motor vehicle crashes cause most of the spinal cord injuries. Many children who sustain spinal cord injuries die from their injuries and the subsequent complications. Moreover, 60 percent of pediatric spinal cord injury patients also have associated significant head injuries.<sup>15</sup> As a corollary, in the presence of a head injury, the emergency physician should consider the possibility of a concomitant spinal injury.

The anatomic and biochemical differences in the immature cervical spine accounts for the differing patterns of injury between the pediatric and adult age



**Fig. 66.8:** Tillaux fracture: The closure of the distal tibial physes takes place around adolescence. It starts centrally and spreads posteromedially, anteromedially and finally laterally. The anterolateral quadrant of physes is last to fuse to the main shaft. During forced external rotation of the foot (twisting of ankle), anterior tibiofibular ligament stretches and avulses the lateral distal tibial epiphysis. It is a biplanar fracture and better visualized by a CT scan. This requires surgery to ensure accurate reduction and internal fixation



**Fig. 66.9:** Positioning of a young child with a suspected cervical spine injury (for example road-side accident). The upper diagram shows the child wrongly positioned on a firm board where the neck is forced into a kyphotic position due to the large head. The lower diagram shows the use of a mattress to elevate the chest and torso, thus allowing the large head to translate posteriorly. This avoids kyphosis and maintains normal cervical spinal position

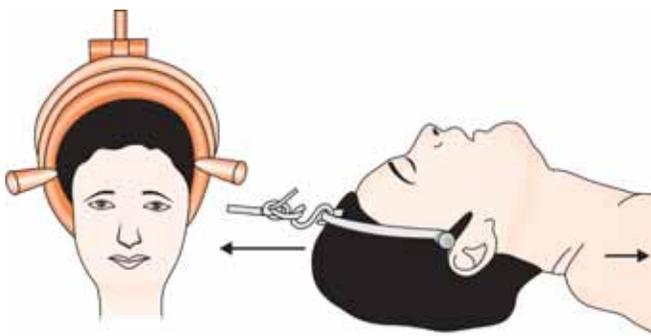
groups. *These differences are most notable in children younger than 8 years of age.* The most prominent differences are the predisposition for upper cervical spine injuries and a condition termed SCIWORA, an acronym for spinal cord injury without radiographic abnormality. Some of most notable characteristics are greater laxity of the intervertebral ligaments, disk annulus, and transverse ligament of the odontoid. Additionally, the articular surfaces of the vertebral bodies and facet joints are oriented horizontally, which allows for an increased susceptibility to subluxation. The immature cervical spine contains physes and incomplete ossification of the odontoid, making fracture through the cartilaginous structures more likely than ligamentous disruption.

Moreover, children have underdeveloped neck musculature and relatively large heads, which make the cervical spine at C2 and C3 susceptible. Thus, children suffer higher cervical spine lesions than do adults. The vertebral arteries in the pediatric cervical spine are more vulnerable to ischemia, perhaps in part due to the relative instability of the atlanto-occipital joint. Although younger children are more likely to have a high cervical spine injury, the commonest injury in all ages of children is a combined fracture and dislocation injury.<sup>11</sup>

### Evaluation and Treatment

Children with a history of significant trauma, including head, neck, or back injury, high-speed injury, or falls from heights, should be evaluated for possible spinal cord injury.

Basically, an injured child with one or more of the following findings should be immobilized (Fig. 66.10) and undergo cervical spine radiograph: *neck pain or tenderness, abnormal reflexes, diminished strength or sensation, history of neck trauma, limitation of neck mobility, and abnormal mental status.*<sup>16</sup> An additional tool for the evaluation of the potentially spinal cord injured patient is the mnemonic of the six Ps: pain, position sense, paralysis, paresthesias, ptosis, and priapism. Most of these Ps are self explanatory; however, ptosis is meant to be part of the miotic pupil, suggesting Horner's syndrome and cervical cord injury.<sup>11</sup>



**Fig. 66.10:** Skeletal traction (Gardner-Wells tongs, crutchfield tongs, etc) in a patient with injury to cervical spine (for example fracture dislocation). Countertraction is provided by the body weight with the head end of the bed elevated. (A) and (B) show the anterior and side view of the patient, respectively. Temporary immobilization may be provided with sand-bags on either side of head to prevent rotation, and positioning as shown

### Physical Examination

Obviously, vital signs and more specifically, airway management and oxygenation require initial management and emphasis. Spinal cord injury can produce apnea, loss of diaphragmatic breathing, or loss of abdominal or intercostal breathing.<sup>17</sup> Additionally, the emergency physician should be aware of the finding that children placed in supine position in spinal immobilization have reduction to a mean of 80 percent of FVC. Other vital signs can also be affected by spinal cord injury: hypotension with a relative bradycardia and hypothermia. These require aggressive management to limit further spinal cord damage and to ensure the best possible outcome for the patient.

The neurologic examination of the patient actually should begin with an assessment of the work of breathing by evaluating adequate chest wall excursion. Mental status should be quickly assessed. For a rapid gross motor examination, evaluation of dorsiflexion of the wrist and great toe, extension of the forearm and flexion of the lower leg at the knee are useful in all, except in young infants. In children with suspected spinal cord injury, evaluation should include sensory examination, deep tendon reflexes, and superficial reflexes. A rectal examination should be performed to evaluate for rectal tone and the bulbocavernosus reflex. The absence of the bulbocavernosus reflex is indicative of spinal (neurologic) shock.

### Radiographic Studies

Injured children who have clinical signs or symptoms of possible spinal cord injury require accurate radiographic evaluation. The radiographic cervical spine series is the same as that for adults, consisting of cross table lateral view (CTLV), AP, and the open-mouth (OM) odontoid views. When younger children are unco-operative for obtaining the OM view, one can substitute the Water's view, which allows one to visualize the odontoid through the foramen magnum.<sup>11</sup> Reports of the radiographs should be made available in the shortest possible time to decide on the next course of action. In cases where there is a neurologic deficit, a fracture, or the possibility of a fracture, further imaging of the spine is warranted. MRI has an important role in diagnosing pediatric cervical spine injury. In fact, it is the "gold standard" test for evaluating spinal cord injuries because it allows better visualization of the spinal cord and spinal canal than does CT scanning. In one study, evaluating children, it was demonstrated that in 19 percent of cases in which the practitioner had a suspicion for neck injury despite

negative plain cervical spine radiographs, the spinal MRI was positive.<sup>18</sup> Thus, consider using spinal MRI in pediatric patients when there is a high suspicion of spinal injury, especially very young and preverbal patients, or those with altered mental status.

### Spinal Cord Injury without Radiological Abnormality (SCIWORA)

SCIWORA is a phenomenon that is commonly seen in pediatric patients but much less commonly seen in adults. SCIWORA is defined as a spinal cord injury with significant neurological involvement, but without radiographic evidence of injury on plain spinal radiography, including flexion-extension views and spinal CT. A good example of SCIWORA is the central cord syndrome that is commonly seen in elderly patients after a hypertension injury. SCIWORA is commonly found in children because of their “elastic” and developing spinal column, which makes them more likely to sustain ligamentous, physeal, cartilaginous, and vascular injuries without findings on plain radiography. The reported incidence of SCIWORA varies between 4 percent and 65 percent, with the true incidence probably being around 20 percent of all pediatric spinal injuries.<sup>19</sup> SCIWORA can manifest itself initially after trauma as a profound or progressive paralysis, even up to 48 hours after the injury. Children who experience even mild transient SCIWORA with resolution before being seen in the emergency are susceptible to “recurrent” SCIWORA. Seemingly trivial transient neurological symptoms, such as shock-like sensations after trauma, should be a cause for concern, and the physician should thoroughly question for such symptoms. One half of all children with SCIWORA had delayed neurological deterioration, most likely due to repeated trauma in an unrecognized unstable spinal injury.<sup>20</sup> Children younger than 8 years old are particularly susceptible to SCIWORA and are more likely to have a complete spinal cord injury.<sup>11</sup> The child with a neurological deficit or a history of significant neurological symptoms (e.g. paralysis or anesthesia) with normal plain spinal radiography should be evaluated further, using preferably spinal MRI, or CT scan if one is unable to obtain a MRI. Patients with persistent or transient significant neurologic deficits or documented ligamentous instability require hospital admission and thorough assessment and appropriate spinal immobilization by the concerned specialist. Patients with minor transient symptoms, (e.g. bilateral paresthesias) who are neurologically intact and have a negative cervical spine radiographic series including flexion-extension views, need to be assessed by the specialist, and decided on the course of action on case-to-case basis.

### Treatment/Management

The goal in treating cervical spine injury is to limit neurologic injury by spinal immobilization and careful attention to cardiopulmonary function. Additionally, limiting hypoxia and hypotension is important. Hypothermia too, should be actively assessed and monitored. High-dose methylprednisolone, given within 8 hours of acute spinal cord injury as a 30 mg/kg bolus over 1 hour followed by 5.4 mg/kg/h for the next 23 hours, was associated with improved neurological recovery.<sup>21</sup> The physician treating a child with cervical spine injury, including SCIWORA, should strongly consider using methylprednisolone because it can affect the child’s outcome positively.

### Sports Medicine

#### Overuse Syndromes

This term categorizes several musculoskeletal maladies that are characterized by connective tissue failure in response to repetitive maximal loading. With repetition, musculoskeletal tissue hypertrophy occurs, which is the essence of athletic training. If the rate of tissue fatigue exceeds the reparative response, breakdown occurs.

#### Stress Fractures

These are partial or complete disruptions of bone secondary to an inability to withstand repetitive, non-violent loads. The proximal third of tibia is the most commonly affected site.<sup>22</sup> The other example is spondylolysis as a result of stress fracture of pars interarticularis, and is most commonly seen in young gymnasts. Stress fractures of proximal femur can have serious complications including avascular, necrosis if displacement occurs.

The typical history is one of insidious onset of pain in the area of fracture. This is relieved by rest initially, but eventually pain increases. Radiographs may be seemingly normal initially and use of bone scintigraphy may be required in highly suspect cases. It is important to remember that infections and some bony tumors can have presentations similar to stress fractures. The treatment involves breaking the cycle of repetitive trauma. In emergency, rest to part should be provided and analgesics given if required. Involving the orthopedic surgeon early is best.

#### Sports Trauma

The number of youth participating in sports, the amount of coaching and the intensity of training and

competition and steadily increasing. Injuries arising out of sports have gained importance. Contusions, sprains and simple fractures of upper extremity, account for most injuries in younger athletes.

Ankle sprains and painful unstable knees constitute the majority of these injuries. The initial management is the same as for any other orthopedic trauma. Orthopedic assessment is needed early.

#### *Pathological Fractures*

A fracture occurring over a diseased bone, due to a trivial trauma/impact is termed as pathological one.

The underlying pathology can be varied but broadly, three main causes which had to be mentioned *infections, tumors and Metabolic causes*. Osteomyelitis (Fig. 66.11), bone cysts (like unicameral, aneurysmal and fibrous dysplasia) and rickets, constitute examples of each category, respectively.

The principle of management of these fractures is the same as for any other fracture. History and radiographs give one a clue as to what exactly one is dealing with. Line of further management and future prognosis is best tackled by the orthopedic surgeon.

#### *Child Abuse*

It would be naive to think that “child abuse” is an entity limited to the western countries. In every metropolis with its fast and hectic pace, this aspect of medicine (or crime) is bound to surface.

There are many forms of child abuse but orthopedic injuries are the form in which abuse is most readily apparent. Orthopedic injuries, including soft tissue trauma, are the commonest presentation of child abuse, otherwise known as non-orthopedic accidental trauma (NAT). Abused children who are returned to their homes without social intervention face a 50 percent chance of repeated abuse and 10 percent chance of death.<sup>7</sup> Thus, making a prompt diagnosis of child abuse in the emergency is vital. Unfortunately, there is no easy or comfortable manner for the physician to initiate a child abuse investigation. *Not only does the physician have a moral obligation to report potential cases of child abuse; he or she also has a legal obligation.* Fractures from child abuse tend to occur in very young children. In fact, one-half of such skeletal injuries occur in babies 12 months old or younger.<sup>11</sup>

After necessary resuscitative efforts are completed, the physician should obtain a detailed history of the injury from the child’s caretaker. Suspicion should be raised if the mechanism of injury is inconsistent with the history or the child’s developmental stage. For



**Fig. 66.11:** *Pathological fracture:* Fracture of the distal femoral shaft on the right is seen on AP view. The femoral shaft has a fuzzy, mottled appearance (compare with normal on left side) due to osteomyelitis. Periosteal reaction is evident near the fracture. Fracture occurred in this weak and diseased bone due to mere weight-bearing

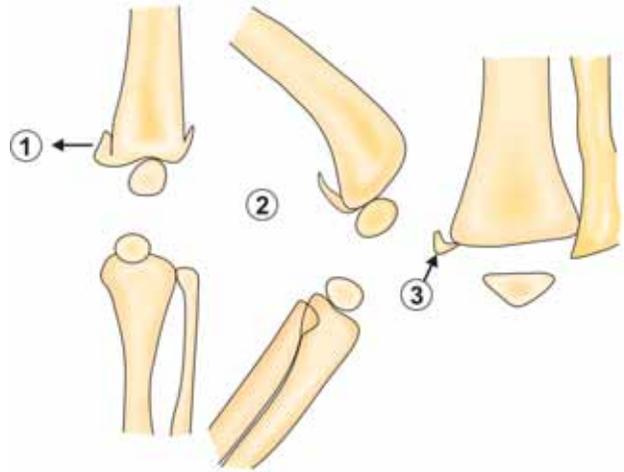
example, a baby who is obviously not yet walking should not be able to fracture his femur accidentally by falling down. Furthermore, a history of the mechanism of injury that changes should raise the examining physician’s suspicion. Likewise, the historian can also be evasive, inappropriately angry with the child or medical professionals, or obviously lying by being contradictory. If the child is verbal, the experienced physician can ask him or her about the injury in a non-threatening manner, without the presence of the attendants.

A thorough and gentle approach is best. The child should be examined head to toe, including the genitalia. Any scarring, ecchymosis, lacerations, burns, or other lesions should be documented carefully. The skeletal examination should be complete, considering that multiple fractures may be present. In the west, a complete skeletal survey is ordered for all physically abused children less than 2 years old and for infants suffering from neglect. A “babygram,” or an anteroposterior (AP) view of the entire child on one film, is an

unacceptable alternative, because it usually misses more subtle evidence of child abuse.<sup>11</sup> A skeletal survey in the west consists of the following: AP and lateral views of the extremities in total, AP and lateral views of thoracolumbar spine, and AP and lateral views of the skull. All positive findings should be evaluated in at least two planes. Additionally, oblique views may be necessary to reveal a suspected fracture not apparent on the biplane views. Radionuclide skeletal scintigraphy (bone scan) is often used as a screening tool for child abuse. Bone scanning is useful owing to its sensitivity for rib, spine, and subtle diaphyseal trauma, which may not be evident on plain films; however, bone scanning has limitations in that, symmetric fractures and epiphyseal-metaphyseal fractures can be missed. If bone scans are used, a physician knowledgeable in the interpretation of pediatric bone scans should evaluate the study. In the emergency, a bone scan is not generally necessary except as an adjunct to the skeletal survey. Another useful tool to evaluate the injuries of abuse is ultrasonography. In areas of incomplete ossification, such as the capital femoral epiphysis, ultrasound examination can help the physician define an injury.

#### *Distinctive Radiographic Features of Child Abuse*

Because the history of definite NAT is usually not present, the physician must understand the various fracture patterns that suggest NAT, otherwise he or she could overlook seemingly innocuous fractures that portend future injury. The finding of healing fractures of different ages found in a child is highly suspicious for NAT. Another finding highly specific for NAT is the classic metaphyseal lesion (CML), often termed a *corner or bucket-handle fracture*. The CML is a disk-like fragment of bone and calcified cartilage that is wider on the outer edges than it is centrally. This fracture is trans-metaphyseal through the primary spongiosa and leaves the disk-like fragment attached to the epiphysis. Corner and bucket-handle fractures are probably the same entity, just viewed in different planes (Fig. 66.12) Although these fractures appear relatively benign in terms of healing, it is the clear association with NAT that one needs to understand. These classic metaphyseal lesions are specific for abuse because of the mechanism that causes them, traction and torsional forces, rather than falling. Rib fractures in a young child without a history of significant trauma are telling of child abuse. Chest compressions from CPR have not been shown to cause rib fractures in children. Posterior rib fractures are highly specific for NAT. Complex skull fractures, again without history of significant trauma,



**Fig. 66.12:** Distinctive radiological features of child abuse-metaphyseal lesions: (1) Impaction fracture of distal end femur; (2) “Bucket-handle” fracture of distal femur on lateral view; (3) Metaphyseal corner fracture of distal tibia

are also highly specific for NAT. Although linear skull fractures are commonly seen in accidental trauma, they are also seen in child abuse.<sup>11</sup>

Other orthopedic injuries that are insensitive yet highly specific for NAT include scapular fractures, sternal fractures, spinous process, and vertebral body fractures, especially in the setting of an inconsistent history. Long-bone and clavicular fractures often occur in abuse, as well as unintentional injuries. If the history is inconsistent with the fracture pattern, NAT should be considered.

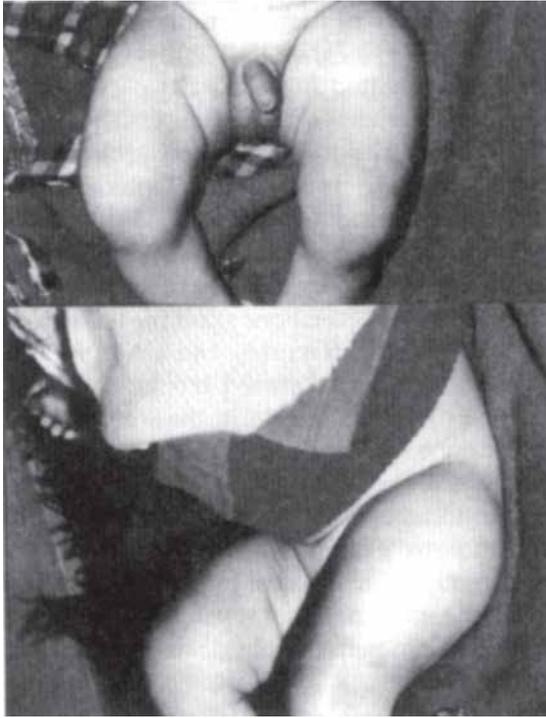
### Non-traumatic Emergencies

#### *Bone and Joint Infections*

Acute osteomyelitis and septic arthritis are acute infections affecting bone and joints, respectively. High index of suspicion and early diagnosis are paramount in order to start treatment early, to prevent their catastrophic consequences.

The commonest presentation in the emergency is a child or an infant not moving his/her limb. An older child may present with pain and a limp. This may not be preceded by constitutional symptoms like fever, especially in a neonate. A neonate may just be irritable and may refuse to feed.

A normal neonate has an immature immune system that makes him/her susceptible to a variety of organisms, which are less virulent under normal circumstances. Moreover, they do not have a normal inflammatory response creating the signs and symptoms, so



**Fig. 66.13:** Osteomyelitis: This 3-months old boy had a history of decreased left lower limb movements since 3 days. A history of irritability and “warm” body was elicited, but was not suggestive of any trauma. *Physical examination revealed an ill defined swelling, more apparent on the outer aspect of upper left thigh.* X-ray then was not suggestive of any pathology, but a whole body triphasic bone scan revealed increased uptake over left proximal femoral metaphysis

important for early diagnosis. One can now imagine the level of susceptibility to infection of a pre-term and low birth-weight neonate. In general, the infections are recognized in the hospital itself in these premature neonates whereas it is evident in normal neonates after discharge from nursery. The unique feature of neonatal bone and joint sepsis is the frequent association of contiguous bone and joint involvement and high morbidity due to subsequent destruction of growth plate or joint.<sup>23</sup> The message for the emergency physician is a diagnosed septic arthritis should warrant a thorough search for adjacent osteomyelitis (OM).

A careful history and thorough physical examination is crucial (Fig. 66.13). Physical examination of the infected joint reveals local erythema, warmth, and swelling. Examination of the affected limb should be gentle. A generalized circumferential swelling is commoner in early acute OM (a pointing localized swelling is more suggestive of an abscess). In septic arthritis, joint motions are extremely tender and this



**Fig. 66.14:** Complicated bone and joint infection around elbows. This 12 years old girl was improperly treated for a probable bilateral septic arthritis of elbows in her infancy. Proximal radius and ulna on both sides were infected. *At present, this girl has bilateral stiff (bony ankylosis) elbows in full extension, along with discharging sinuses (of pus), on both sides.* She could not feed or maintain personal hygiene, independently

needs to be borne in mind while examining. Pseudo-paralysis may be seen in neonates. Early diagnosis is the key. Neglect and improper treatment can lead to horrifying consequences (Fig. 66.14).

Blood work-up should include culture and sensitivity, complete blood counts, ESR and CRP. *The C-reactive protein (CRP) is more reliable than ESR, especially in a neonate.*<sup>23</sup>

The former is earlier to show a rise during infection and earlier to fall showing the response to treatment.

Radiographs may seem normal in the first few days of acute osteomyelitis. Periosteal reaction over the bone in osteomyelitis will only be visible after roughly 10-14 days. Dislocation or subluxation of the femoral head may be seen, particularly in neonates.<sup>24</sup>

Ultrasound examination, especially of the hips should be ordered early, and has been recognized as an invaluable tool to support the diagnosis of septic arthritis, and helps in taking early decisions on treatment.<sup>25</sup> An increase in the joint fluid detected on ultrasound, along with a positive history and clinical examination and also supported by the blood work-up, would point towards the diagnosis of acute septic arthritis. Immediate arthrotomy then, especially in cases of infected hip, may be the answer. A strong suspicion of infection is also an indication to order a 3-phase whole-body technetium bone scans. This is important in detecting multifocal involvement,<sup>26</sup> common in premature and low birth-weight infants. This is more specific for OM than septic arthritis, and the report

should be closely correlated to the condition of the child. Proper reporting by trained personnel is essential, especially when interpreting the same in a neonate or young infant.

Any further investigations (like MRI or CT) should be ordered in consultation with the orthopedic surgeon. Decision regarding joint aspiration to clinch the diagnosis is best left to the orthopedic surgeon. The well-established indications for surgical drainage in children with septic arthritis, based on several reports<sup>26-28</sup> include: (i) Involvement of the hip joint; (ii) The presence of large amounts of pus, fibrin, debris, or loculation within the joint space; and (iii) Lack of clinical improvement noted within 3 days of appropriate therapy.

The importance of early detection of hip infection need to be further emphasized. Hip joint merits huge importance as far as septic arthritis goes, as compared to any other synovial joint. This is mainly because of it being the weight bearing joint, and the high susceptibility of the femoral ossification nucleus to the presence of infection. *The natural course of an overlooked and untreated infective hip joint in a child would be a dislocated joint, destruction of femoral head and bony ankylosis (complete bony fusion). The whole idea is to anticipate and prevent the above-mentioned complication.*

Intravenous broad-spectrum antibiotics (in combination) should be started immediately, after blood has been sent for work-up, as mentioned above. Cases of septic arthritis and osteomyelitis should be initially treated with parenteral antibiotics to ensure adequate serum concentrations to control the infection. *Staphylococcus aureus* is the offending organism in majority of cases. In the case of septic arthritis in the neonate when no bacteria is identified in Gram's stain, treatment should be directed toward *S. aureus*, group B streptococci, and Gram-negative bacteria, especially *Escherichia coli*. A beta-lactamase resistant penicillin, such as cloxacillin, in combination with aminoglycoside or third-generation cephalosporin, such as cefotaxime, provides an excellent coverage. If methicillin-resistant *S. aureus* is suspected, vancomycin is preferred. The initial empiric antimicrobial therapy in uncomplicated cases of septic arthritis *beyond the neonatal period* must include an antistaphylococcal agent, either a beta-lactamase resistant penicillin or first-generation cephalosporin. Similarly, if methicillin-resistant *S. aureus* or *Pneumococcus* are suspected, vancomycin should be administered.<sup>26</sup>

The appropriate duration of therapy for septic arthritis is still controversial. It is advised, however, to treat a minimum of 4 weeks in both acute osteomyelitis

and septic arthritis.<sup>29</sup> Longer duration of therapy may be necessary for septic arthritis of the hip.<sup>23,24</sup> The choice of antibiotics is very important and a trained and experienced physician may well take this decision. Consensus is on sequential course of intravenous antibiotics followed by oral course, a total course of roughly, 4-8 weeks.<sup>23</sup> It is accepted nowadays that the transition from the IV route to oral needs to be based on case-to-case basis, depending on a regular clinical assessment as well as the blood work-up. Working in a tertiary center, we follow a protocol of 4-6 weeks of IV, followed by oral, for a total of 6-8 weeks of antibiotics. Regular blood counts, CRP and ESR, along with physical examination are imperative to support the effectiveness of antibiotics, their route of administration and duration. A central line (put from periphery preferably) ensures proper compliance of antibiotics and maintains its level in blood round the clock.

The affected part needs to be rested either by an external support like a splint or a POP slab. A balanced traction is a good alternative to provide rest. An orthopedic surgeon needs to be involved as early as possible in all suspected cases.

A special mention is warranted on an entity called "Caffey's disease" or infantile cortical hyperostosis. Although not very common, it's incidence in our set-up, is probably underrated. It is an important differential diagnosis of acute osteomyelitis in young infants. A febrile irritable child reluctant to move his upper limb, and with an increased ESR is one common presentation. Ulna and mandible are commonly affected.<sup>30</sup> This is a benign disease of unknown etiology and most recover spontaneously. It is always wise to manage all such cases as osteomyelitis, unless proved otherwise without doubt (by bone biopsy). This diagnosis is best made retrospectively in our set-up.

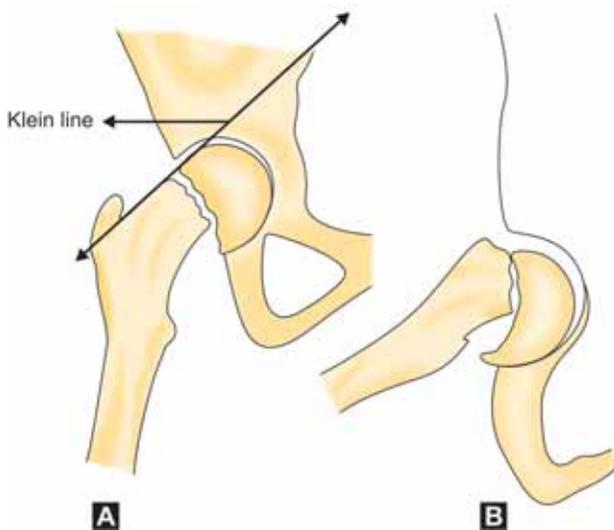
#### *Slipped Capital Femoral Epiphysis (SCFE)*

Slipped capital femoral epiphysis (SCFE) is a disorder in which there is disruption through the capital femoral physes. The term *SCFE* is actually a misnomer, because the epiphysis remains in normal position in the acetabulum, whereas the femur distal to the physes displaces anterolaterally and superiorly. SCFE typically occurs during adolescence, being found twice as often in boys than in girls. Additionally, obesity is also a factor in the disorder, with one half of the patients exceeding the 95th percentile of weight for their age. It also occurs in tall, thin, rapidly growing adolescents, however.

SCFE can be classified either in terms of duration of symptoms or the severity of the displacement. A newer

classification emerging is that “Stable” and “Unstable” slips. *The latter can present like a fracture neck of femur and can constitute a very acute emergency.*<sup>31</sup> If the symptoms have been present for less than 3 weeks, it is considered an acute slip, whereas when symptoms last longer than 3 weeks it is considered chronic. It is possible for a child with a chronic slip to experience an acute slippage, however, sometimes known as an “acute on chronic” slip. The slip is graded into mild, moderate and severe on “frog-lateral” view of hips.

Children with SCFE usually have a limp and hip pain that is often referred to the thigh, knee, or deep in the groin. Physical examination, usually shows loss of internal rotation of the affected hip, decreased flexion, and perhaps shortening of the affected limb. Diagnostically, the CBC and ESR are normal. Radiographic studies of children suspected of having SCFE should include AP pelvis with both hips, and frog-lateral view of both hips. On the AP view, a line drawn along the superior margin of the femoral neck cortex is useful for demonstrating subtle slips (Klein line). The line should intersect or fall within the epiphysis, usually by at least 20 percent. In patients with SCFE, the line passes along or outside the epiphysis (Fig. 66.15A). In subtle cases, the more remarkable finding will be an asymmetry from the normal hip. Because the slip in most cases of SCFE is usually posterior, the lateral view can actually reveal the slip better than AP view (Fig. 66.15B).



**Figs 66.15A and B:** Slipped capital femoral epiphysis: (A) AP view of the hip shows the Klein line not passing through epiphysis, but passing just superior to it. (B) Frog-lateral view shows the posterior displacement of the epiphysis (anterior displacement of femoral shaft). Use the opposite ‘normal’ hip for comparison

The physician making the diagnosis of SCFE should prescribe no weight bearing for the child and promptly refer him or her to an orthopedic surgeon. Studies have shown that surgical pinning *in situ* (rather than complete reduction and then pinning) provides the best results in terms of function and morbidity.<sup>31</sup> Bilateral SCFE can occur in 5 to 37 percent of children.<sup>32</sup> Thus, one must examine the opposite hip closely and inform the patient and his or her parents of the potential for this problem. Interestingly, subsequent slips can occur within 18 months after the first slip is diagnosed. Because of the possibility of sequential SCFE, patient should be followed closely for at least 1.5 years. The prognosis of SCFE is based on the chance of developing avascular necrosis or chondrolysis with the subsequent arthritis. These problems are less likely to occur when there has been a minimal amount of time of symptoms, is mild, and when the slip is mild is surgically fixed *in situ*, rather than attempted reduction then fixation.<sup>33</sup>

#### Cervical Spinal Instability

Certain non-traumatic conditions may lead to instability in cervical spine, and result in acute presentations in certain settings. Recognition and prompt action is necessary, in order to prevent neurological deficits, like quadriplegia or plegia.

#### ‘Grisel Syndrome’

This is a spontaneous atlanto-axial subluxation with inflammation of adjacent neck tissues that is commonly seen in children after upper respiratory infections. The children present with “cocked robin torticollis” (Fig. 66.16). The child resists acute attempts to move head because of pain. An orthopedic consultation should be sought.

One hypothesis is the hematogenous transport of peripharyngeal septic exudates to the upper cervical spine, through a direct connection between pharyngo-vertebral veins and the periodontal venous plexus and suboccipital epidural sinuses.<sup>34</sup> This causes atlanto-axial hyperemia and regional lymphadenitis, leading to spastic contractures of cervical muscles. This spasm, in presence of abnormally loose ligaments, could produce locking of the overlapping lateral joint edges of articular facets. This prevents their easy re-positioning and thus, is the cause of the atlanto-axial rotatory displacement. The predominance of this syndrome in childhood correlates with the predilection for the adenoids to be maximally hypertrophied and inflamed during this time.

Most of these displacements resolve spontaneously and never come to the attention of the physician. The



**Fig. 66.16:** *Torticollis/wry neck* in a 3-month-old infant. This can be due to 'osseous' and 'non-osseous' causes. 'Grisel syndrome' is an example of the latter

duration of symptoms and the 'wry-neck' deformity dictates the appropriate treatment, which may range from immobilization in a soft cervical collar and rest, to cervical traction or even posterior C1-C2 fusion, if necessary.<sup>35</sup>

#### *Juvenile Rheumatoid Arthritis*

Juvenile rheumatoid arthritis (JRA) is a chronic synovitis affecting the synovial joints that can affect the joints of cervical spine as well. The cervical spinal involvement occurs in the first two years of the onset and presents with stiffness. Pain and torticollis are rare. Neurological involvement is less commonly seen, than in an adult rheumatoid arthritis, probably because basilar invagination is so rare in JRA.<sup>36</sup> All patients should have flexion and extension lateral radiographs of cervical spine, which need to be repeated before any anesthetic. The most common radiographic feature in children with neck stiffness are the soft tissue calcification at the leading edge of C1, anterior erosion of odontoid process, and apophyseal joint ankylosis.<sup>37</sup> Treatment is generally non-surgical in conjunction with good rheumatologic care. A soft cervical collar may be applied till an orthopedic surgeon evaluates. Instability along with progressive neurological deficit requires a C1-C2 fusion.

#### *Down's Syndrome*

In these children, the cervical instabilities can develop both at occipito-atlantic and atlanto-axial levels. The

incidence of former has been reported to be high as 60 percent in children; and latter reported to be around 15-20 percent and is a gradual progressive lesion.<sup>38</sup>

Majority of these children are asymptomatic. When symptoms occur, they are usually pyramidal tract symptoms, such as gait abnormalities, hyperreflexia, and quadriparesis. Sudden catastrophic death is very rare.<sup>39</sup>

Trained personnel, who can pick out associated significant anomalies and also predict future neurological problems, must evaluate spinal radiographs, which need to be ordered when the child is examined in the emergency. Rest in form of a soft cervical collar may be given to the child, while awaiting the orthopedic surgeon.

#### CONCLUSION

The endeavor in this chapter has been not to cover and every acute orthopedic condition, which can present at the emergency room. The idea is to familiarize the emergency physician with the relatively common pediatric orthopedic emergencies, which would enable him/her to take adequate and appropriate initial measures, while awaiting the arrival of the specialist.

Undoubtedly trauma forms the majority of these emergencies. However, the emergency physician should also be aware of certain other non-traumatic conditions presenting as orthopedic emergencies.

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Ophthalmic disorders in children include a spectrum of diseases some of which present as acute sight-threatening and rarely life-threatening conditions, which have to be considered and treated as emergencies.

As expected, emergencies in children include diseases which are seen in adults. In addition, there are few conditions which are emergencies in children, but may not be considered so in adults such as neonatal conjunctivitis or 'ophthalmia neonatorum'. In clinical practice, particularly in developing countries or in remote rural areas where access to proper health care is restricted, a distinction must be made between true emergencies, i.e. conditions where immediate intervention and attention is required in every possible measure and conditions which are presented as emergencies by parents and caregivers reaching the emergency room outside working hours with a child suffering from a disorder which may be severe in nature, but may not really require intervention and care on a very urgent level. Correct judgment in this regard can be crucial in taking decisions regarding allocating precious and sometimes scarce material and manpower resources and can have a tremendous impact on the life of individuals and also play a role in averting potential litigious and medicolegal problems.

The approach to a child with an ocular emergency will of course depend on the age of the child and severity of the condition, but will equally importantly depend on the experience and expertise of the attendant physician be it a general practitioner, pediatrician, ophthalmologist or rural health guide. Care will have to be provided at the primary, secondary or tertiary level as the case may be and as far as possible, properly instituted measures at each step including prompt and correct referral when needed will go a long way in minimizing morbidity.

### Important Ocular Emergencies

- Similar to emergencies seen in adults
  - Trauma
    - Perforating or penetrating eye injuries
    - Thermal or chemical burns
    - Blunt trauma
  - Sight threatening infections
    - Corneal ulcer
    - Orbital cellulitis
    - Gonococcal ophthalmia neonatorum
  - Cavernous sinus thrombosis
  - Diseases encountered in childhood
    - Sight threatening congenital or developmental diseases
      - Congenital glaucoma
      - Retinopathy of prematurity
    - Sight threatening nutritional disorders
      - Keratomalacia
    - Life threatening diseases
      - Retinoblastoma
      - Neuroblastoma
      - Orbital metastasis from systemic malignancies

### Items in First Aid and Examination Kit

- Torch
- Magnifying loupe
- Ophthalmoscope
- Sterile cotton, gauze and bandages
- Broad-spectrum antibiotic eye drops and eye ointment (gentamycin, ciprofloxacin, ofloxacin, tobramycin)
- Fluorescein paper strips
- Litmus paper strips
- Sterile gloves
- Topical anesthetic eye drops (4% lignocaine or proparacaine)
- Colorful objects/toys/pictures of different sizes
- Visual acuity assessment charts or cards.

### Approach to Diagnosis and Management

A practical and sensible approach should be applied in approaching a child presenting with an ocular emergency. The nature and severity of the disease and the urgency of attention required must be quickly determined based on a quick history and preliminary

examination. More detailed history and examination can be undertaken once it is established that extra time spent in doing so is not going to be detrimental by delaying administration of appropriate therapy. For example a child with an acute chemical burn needs a different level and speed of care compared to a child with orbital cellulitis and cavernous sinus thrombosis which again will be different from a patient with a penetrating eye injury with a sharp object.

While one is listening to the parents or caregivers providing a history it is useful to simultaneously observe the condition of the child noticing the general health, the level of comfort, apparent state of visual acuity, etc.

While examining the child, one should first have a non-touch approach and depending on the age of the child and general condition, first gain his/her trust and confidence by a friendly and patient manner.<sup>1</sup> Distracting the child by asking apparently medically irrelevant, but questions the child is likely to be already conditioned to reply to such as 'Hello, I am so and so, what is your name?', 'What class do you study in?', 'Do you have a younger brother?' etc can be helpful while you attempt to examine the child. One must make a quick general assessment of the general physical health, observe if vision seems apparently normal or abnormal and then examine the eye guided by the history provided by the relatives. Preliminary examination with ambient room light and then with a torch without actually touching the child is recommended at first. In case, one feels the need to touch the child to open the eyelids or examine in more detail such as using a slit lamp, one must first inform the child and his/her parents what one is intending to do explaining that the procedure is non-invasive and will not hurt. Children have a great fear of pain and being hurt and their natural response to that is crying and trying to escape in which situations it becomes very difficult to examine the child and regaining their confidence can be a challenge.

The clinical examination must be completed quickly and efficiently and as thoroughly as possible. One should use the history as guidance to prepare an action plan for examination so that one can quickly establish the nature of the disease, the extent of involvement, the severity and complexity involved and estimate the extent of urgency in arranging for additional investigations if indicated and institute therapy as appropriate.

Extracautiousness must be exercised while examining the eye of a child after an ocular injury particularly if there is a likelihood of a penetrating wound and suspected perforating injury. Forcible examination in a child

struggling to get away is potentially dangerous in such situations as the eye shall be at considerable risk of further damage with extrusion or expulsion of the intraocular contents. Gentle retraction of the eyelids may be attempted avoiding excessive pressure on the globe applying countertraction against the bony orbital margins if required. In case these maneuvers meet with little success mild sedation or examination under general anesthesia may be required.

With this general outline on clinical approach to a child with an ocular emergency, one can supplement knowledge on how to examine a child in detail by referring to the chapter on pediatric eye diseases in Textbook of Pediatrics.<sup>2</sup>

### Specific Ocular Emergencies

While evaluating a child, the pediatrician should assess if the condition of the child can be broadly categorized into one of two categories, either medical or surgical. The referring pediatrician has an important role to play in preliminary assessment and prompt referral after initiating first aid therapy or other additional management before referral.

### Conditions More Commonly Seen in Neonates

**Ophthalmia Neonatorum:** Watering or discharge from the eyes soon after birth is abnormal, and should be treated as an emergency as potentially gonococcal infection can lead to a blinding keratitis if not treated promptly. A conjunctival smear should be prepared and examined after staining with Grams stain, a swab sent for culture and sensitivity, and prompt antibiotic treatment started. If Gram negative bacilli are identified, gonococcal ophthalmia neonatorum due to infection with *Neisseria gonorrhoea* is diagnosed and has to be treated with a single dose of injection ceftriaxone given intramuscularly and both the parents must be referred to a venereal diseases specialist to eliminate the primary source and reservoir of infection.

**Congenital corneal opacity:** Any opacity in the visual axis of a newborn, (e.g. cornea or lens) is an emergency since it may lead to progressive and irreversible amblyopia. Generalized corneal haze in the neonate may be seen in glaucoma. Later congenital glaucoma presents with watering, corneal haze, photophobia and buphthalmos.

**Congenital glaucoma:** The diagnosis is based on a high index of suspicion in a child with watering and or photophobia from birth or soon after birth with or without the presence of a cloudy cornea or enlarged



**Fig. 67.1:** A child presenting with bilateral hazy corneas since birth. Differential diagnosis includes congenital glaucoma and congenital hereditary endothelial dystrophy (CHED). Note the intense corneal clouding and increased corneal diameter suggesting the possibility of co-existing pathologies (For color version see plate 3)

eyeball (Fig. 67.1). If correctly diagnosed and treated early, irreversible blindness can be averted. Prompt referral to a tertiary care eye care center is mandatory.

**Retinopathy of prematurity:** ROP with threshold or plus disease is considered as a surgical ophthalmic emergency as laser therapy is indicated to prevent progression and blinding complications. The revised International Classification of Retinopathy of Prematurity<sup>3</sup> has recognized aggressive posterior retinopathy of prematurity (APROP) as an unusual form of ROP that rapidly progresses to a closed funnel of tractional retinal detachment within 1 or 2 weeks and therefore should be urgently referred to a vitreoretina specialist. Neonatal units should be aware that babies born before 32 weeks of gestation, weighing less than 1500 g at birth and were administered supplemental oxygen in the neonatal intensive care unit or suffered from septicemia are particularly at risk and must have their retinal screening test performed with papillary dilation. Should threshold ROP or plus disease be detected urgent laser therapy to the ischemic retina should be administered to avoid irreversibly progressive blinding complications.

#### *Conditions More Commonly Seen in Young Children*

**Keratomalacia:** Besides glaucoma, the other important emergency in the first 5 years of life is keratomalacia. Bilateral melting of the cornea (Fig. 67.2) occurs in nutritionally deficient children either due to inadequate breastfeeding or feeding with diluted cow's milk in the first 6 months of life or due to late weaning and a nutritionally imbalanced vitamin A deficient diet in



**Fig. 67.2:** A child with bilateral keratomalacia due to vitamin A deficiency (For color version see plate 3)

those over 6 months of age. Diarrhea, measles or other exanthematous or respiratory illnesses such as pneumonia may be precipitating factors leading to xerophthalmia and colliquative necrosis of the cornea. Treatment with oral vitamin A (parenteral if the child has uncontrolled gastrointestinal infection with excessive vomiting),<sup>4</sup> management of concurrent infections, dietary supplementation and supportive measures are required. The importance of health education of the mother regarding proper diet during the antenatal period and breastfeeding after birth is well established.

#### *Conditions More Commonly Seen in Older Children*

Refractive errors may be considered as an emergency, more so in young children, because refractive problems especially unilateral may lead to amblyopia and squint. In children, refraction under adequate cycloplegia is very important. Similarly, squint should not be ignored and requires early referral for complete investigation. Children do not grow out of squint.

Leukocoria, proptosis, red eye and injuries constitute other common emergencies in children.<sup>5</sup> Malingering and hysteric blindness may pose diagnostic problems in older children.

**Proptosis:** In a child presenting with proptosis or bulging of the eyeball, certain specific features should be looked for. The rapidity of onset, associated pain, fever, ocular bruit or pulsation, systemic signs and symptoms should be elicited in detail. The underlying etiology may be inflammatory (pseudotumor), infectious (orbital cellulitis), neoplastic (rhabdomyosarcoma (Fig. 67.3),



**Fig. 67.3:** Proptosis due to rhabdomyosarcoma  
(For color version see plate 3)

metastases, neuroblastoma, lymphangioma, capillary hemangioma, extraocular extension of retinoblastoma leukemia, lymphoma, neurofibroma), trauma (carotico-cavernous fistula, retrobulbar hemorrhage), or a congenital or vascular malformation.

The bulging of the eyeball may be associated with incomplete closure of the eyelids, leading to exposure keratopathy. This should be prevented by application of lubricating eye drops containing hydroxypropyl methylcellulose, or carboxymethyl cellulose and ointments at night or whenever the child sleeps. Lid taping or tarsorrhaphy may be indicated in severe cases or in cases where the child is comatose or unconscious, to prevent exposure keratitis and severe corneal ulcerations, which may result in blindness.

**Orbital cellulitis:** Orbital cellulitis is an ocular emergency, which can have severe systemic and ocular complications. A child with orbital cellulitis is usually toxic, febrile and typically presents with history of unilateral pain, redness, blurred vision and proptosis of recent onset. The critical signs are eyelid edema, erythema, conjunctival chemosis and injection and restricted ocular motility. It may occur due to direct extension of infection from paranasal sinuses, furuncle on the face, ear or throat infection, dental infection or as a complication of surgical or orbital trauma. Therefore, a detailed evaluation of other systems should be done to find the focus of infection.

The common causative organisms of orbital cellulitis in children are *H. influenzae*, *Staphylococcus aureus*,

*Streptococcus* and anaerobic bacteriae like *Bacteroides*. Diminution of vision in orbital cellulitis is usually due to optic nerve involvement, which reflects poorer prognosis; the other common cause is exposure keratopathy due to proptosis.

The patient should be promptly admitted for further management. Orbital ultrasonography can provide valuable information regarding extent of the disease. A contrast enhanced computed tomographic scan of the orbits, head and paranasal sinuses confirms the diagnosis and allows easier identification and extent of the abscess. The scan should be repeated in cases that do not show any signs of improvement after 48 to 72 hours of intravenous therapy. Blood cultures are useful in management but rarely positive after antibiotics have been started. A combination of broad spectrum antimicrobials is given intravenously to cover Gram positive, Gram negative and anerobic organisms for at least 72 hours, followed by oral antibiotics for 7-14 days, depending on the clinical response. The standard protocol of empirical treatment includes:

1. Injection vancomycin 40 mg/kg/day in 2-3 divided doses.
2. Injection ampicillin-sulbactam 300 mg/kg/day in 4 divided doses given along with above.
3. Injection metronidazole 30 mg/kg/day in 3 divided doses if dental infection is the source, patient is deteriorating rapidly or culture report reveals an anerobic organism.
4. Lubricant eyedrops and ointments are used for the prevention and management of exposure keratopathy.
5. Orbital abscesses and large subperiosteal collections should be drained surgically. If the focus of infection is in the paranasal sinus, then the pus should be drained by the otorhinolaryngologist, along with orbital drainage.

Intravenous antibiotics should be continued till the fever settles with resolution of symptoms and signs (minimum 1 week). Patients should be on constant follow up and parameters like visual acuity, proptosis, and limitation of ocular movements, exposure keratopathy, pupillary reactions, neck rigidity and mental status should be assessed on each visit.

**Leukocoria:** A white pupillary reflex or leukocoria is a characteristic feature of retinoblastoma. In children, leukocoria may also be seen with other congenital and acquired conditions such as toxocariasis (6 months-10 years), Coats' disease (in boys aged 0-18 years), retinal dysplasia, retinal vascular folds, persistent hyperplastic primary vitreous, retinal astrocytoma, cataract (Fig. 67.4), endophthalmitis, retinopathy of prematurity and familial exudative vitreoretinopathy.



**Fig. 67.4:** A child with unilateral developmental cataract (For color version see plate 3)

**Retinoblastoma** is the most common intraocular malignancy in children (Fig. 67.5) and appears as a white, nodular mass with calcification. It may have varied presentations such as esotropia, painful, red eye, cataract, poor vision, and orbital cellulitis, uveitis with hypopyon, high intraocular tension, hyphema, unilateral mydriasis and features of bilateral involvement and optic nerve extension with distant metastases. There may be positive family history in a small proportion (10%) of cases with bilateral involvement.

The primary goal of management of retinoblastoma is to save life. Salvage of the organ (eye) and function (vision) are the secondary and tertiary goals respectively. These children should be immediately referred for further investigations and management, because delay may adversely affect survival. The management of retinoblastoma needs a multidisciplinary team approach including an ocular oncologist, pediatric oncologist, radiation oncologist, radiation physicist, geneticist and an ophthalmic oncopathologist. The management is highly individualized and of late radical treatment modalities, e.g. enucleation and exenteration have been replaced by eye salvaging procedures like cryotherapy, laser photocoagulation, chemoreduction and lens-sparing radiotherapy.

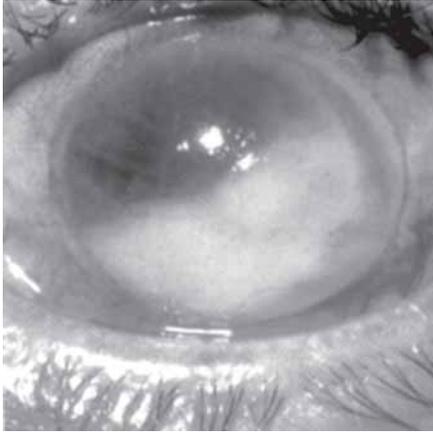
**Red eye:** A red eye is a common ocular problem and in children should be treated with care and sound judgement as the child may present to the emergency room late at night but the condition may not be so severe as may be the presentation. Red eye may be caused by simple trichiasis, floppy eyelid syndrome, lagophthalmos, blepharitis, dacryocystitis, conjunctivitis (bacterial, chemical, allergic, atopic, vernal), subconjunctival hemorrhage, foreign body, Steven Johnson



**Figs 67.5A and B:** Children presenting with leukocoria due to retinoblastoma (A) unilateral involvement and (B) bilateral involvement (For color version see plate 4)

syndrome, infectious keratitis, corneal abrasion, trauma, uveitis, phlyctenular conjunctivitis and carotico-cavernous fistula. Subconjunctival hemorrhage may be an alarming sign for the patient and the parents. The cause of the hemorrhage should be elicited, e.g. severe coughing (whooping cough), straining, minor local trauma, hemorrhagic conjunctivitis and rarely vitamin C deficiency. More serious conditions such as head injury, fractures and deep trauma must be ruled out.

**Infectious keratitis:** A corneal ulcer in a child usually presents with ciliary congestion, pain photophobia and occasionally iridocyclitis (Fig. 67.6). Associated trauma, foreign body, corneal xerosis, exposure keratopathy, neurotrophic keratitis should be ruled out. Examination under anesthesia may be required for obtaining corneal scrapings for culture and sensitivity. Empirical therapy



**Fig. 67.6:** Corneal ulcer in a child shows circumcorneal congestion and infiltration inferiorly (For color version see plate 4)

in the form of broad spectrum antibiotics (tobramycin and cefazolin) and topical atropine should be started immediately. Antiglaucoma therapy may be instituted in cases of raised intraocular pressure and impending perforation. Systemic antibiotics may be added depending on the severity of the ulcer and systemic condition of the child.

Viral keratitis may present as a typical dendritic ulcer with diminished corneal sensations and may be associated with herpes simplex eruptions elsewhere in the body. Treatment with topical antiviral medications and atropine is necessary. Stromal involvement with uveitis and secondary glaucoma has to be treated with systemic acyclovir, topical steroids, cycloplegics and anti-glaucoma therapy.

***Uveitis:*** Iridocyclitis in a child has a typical picture of a muddy inflamed iris, with miosis, ciliary congestion and pain with tenderness. The etiology may be difficult to establish even after thorough investigations, but early treatment is essential. Chronic iridocyclitis may complicate juvenile chronic arthritis in children and if left untreated may cause significant ocular impairment; hence these patients should be kept under close observation by an ophthalmologist. Topical atropine and steroid-antibiotic combinations, is the mainstay of treatment. Toxocariasis and toxoplasmosis should be kept as a differential diagnosis.

***Injuries:*** Any kind of injury in a child, be it chemical, mechanical or thermal is an ocular emergency.<sup>6</sup> The children should be immediately referred after receiving primary treatment. The pediatrician can give a single dose of intravenous antibiotic and tetanus toxoid. Moreover, the parents should be counseled that surgery under general anesthesia may be needed and the child

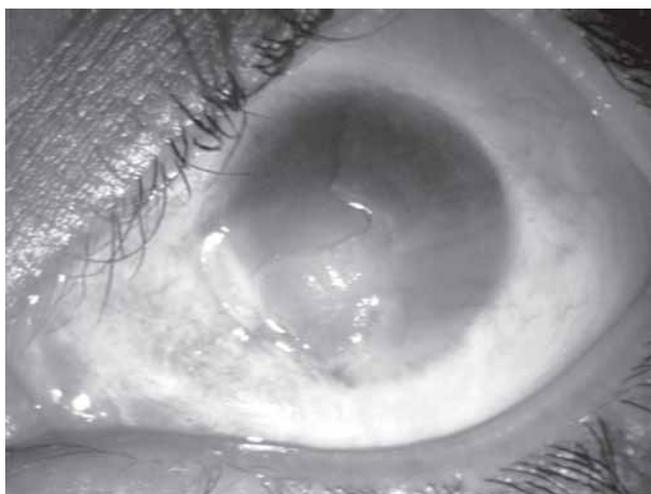


**Fig. 67.7:** Clinical picture of a case following *chuna* packet injury. Note the diffuse corneal opacity, limbal stem cell deficiency and a symblepharon at 4 O'clock (For color version see plate 4)

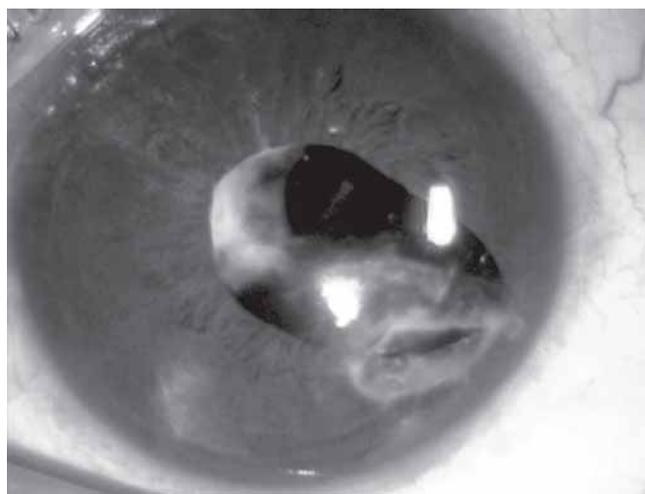
should be given light meals or sips of water, apple juice, clear soup till they reach the ophthalmologist.

***Chemical injuries*** need urgent attention and may be caused by alkalis or acids. '*Chuna*' packet injury is a common mode of chemical injury in our country (Fig. 67.7). Treatment should be instituted immediately even before testing vision. The primary care physician or the pediatrician should ensure prolonged and copious irrigation with saline or Ringer lactate till stabilization of pH occurs. Prompt referral to the ophthalmologist for further management should be done for sweeping of the fornices, removal of residual particulate matter, examination under anesthesia in smaller children and institution of early medical therapy. The child is managed with topical steroids such as prednisolone acetate (1%) every 6 hours; topical antibiotics such as ofloxacin (0.3%) every 6 hours; sodium ascorbate (10%) 4 hourly, sodium citrate (10%) 4 hourly and preservative-free tear substitutes every 2 hours; homatropine (2%) twice daily and oral vitamin C (500 mg) every 6 hours for 2 to 4 weeks. Antiglaucoma therapy including timolol maleate 0.5% drops and/or oral acetazolamide is prescribed in cases with raised intraocular pressure.

***Thermal burns:*** These are acute burns and are associated with oil splash injuries (Fig. 67.8) or firecracker injury. Thermal burns should be treated promptly and may be associated with lacerations and burns of the eyelid and the face. Explosive injuries by fireworks, crackers and bombs are thermochemical injuries and should be treated aggressively on the lines of chemical injuries as detailed above.



**Fig. 67.8:** A case with thermal injury showing an epithelial defect, circumcorneal congestion and diffuse corneal haze (For color version see plate 5)



**Fig. 67.9:** A child with penetrating ocular injury. The injury has healed with residual corneal opacity, astigmatism, irregular pupil and lenticular opacity (For color version see plate 5)

**Blunt injury:** Blunt ocular injuries characteristically result from trauma with a ball, stone, fist, stick, or fireworks, etc. and involve multiple intraocular structures at the site of trauma or at distant sites due to globe deformation. Blunt injuries are potentially dangerous and the extent of damage may often be predicted from the nature of the injury and the site of contact. Corneal perforation and edema may occur due to blunt trauma. Other manifestations of blunt trauma include blow out orbital fracture, hyphema, where the main aim is to reduce the intraocular pressure and prevent corneal blood staining; iridodialysis, lens opacity and displacement, vitreous hemorrhage, globe rupture, retinal breaks, giant tears, dialysis, detachment, choroidal tears, macular edema, optic nerve avulsion and traumatic optic neuropathy. The visual prognosis is guarded, as many more complication may take place with passage of time. Referral without delay is advocated after primary treatment.

**Penetrating trauma:** An injury caused by a sharp object in children (Fig. 67.9) may either be accidental or intentional and is more common in males. It is a surgical ocular emergency and demands urgent treatment. The prognosis in these cases depends on the type and site of injury, initial visual acuity, associated intraocular damage and quality of primary surgical repair. Introduction of infection should be prevented and delay in primary repair should be avoided. No topical medications should be applied in such cases, but the eye should be gently bandaged or protected with an eye shield before referral. It is imperative that

the eye should not be touched or manipulated. It is important to advise the patient to attempt not to strain, cough, blow their nose or bend over before seeing the specialist, which should be done at the earliest.

Successful patient outcome in pediatric ocular emergencies depends on proper recognition and evaluation as well as appropriate management and referral.<sup>7</sup> A comprehensive evaluation involving a concise history, general observation, pupil examination, and basic ocular tests lead to a firm diagnosis and thereby appropriate management and timely referral.

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Ear, nose and throat emergencies in children not only present to the ENT surgeon but may also present to the child specialist and the general practitioner. These group of doctors should be trained in not only diagnosing these conditions and also giving the primary treatment.

## EAR

### Foreign Body

Foreign bodies in the ear may be animate or inanimate. Animate foreign bodies like insects or cockroaches may be paralysed by keeping a wick immersed in ether or chloroform. Then the animal can be taken out using microcrocodile forceps.

Inanimate foreign bodies may be hygroscopic or non-hygroscopic. In case of a hygroscopic foreign body like a seed, the removal may be difficult as they tend to swell up. One must try to decongest the ear first by using a xylocaine adrenaline wick for sometime before attempting removal. In case the removal is not possible then an endaural or a post aural incision is required. Non-hygroscopic inanimate foreign bodies can be taken out easily. A dangerous inanimate foreign body is a mercury cell. One should be careful while removing it to avoid damage to the cell. In case the mercury leaks out copious irrigation with saline is needed.

### Ear Pain

It is a very common problem and one of the commonest causes of excessive crying in children. A thorough history taking and examination is required to determine the cause. The commonest cause of ear pain is acute suppurative otitis media. There is an associated history of preceding upper respiratory tract infection, often with fever. The ear drum may show congestion with or without bulge. Bulge suggests pus behind the drum. Relief of pain occurs if the drum bursts and starts discharging. Initial treatment is conservative and comprises antibiotics, decongestants (systemic and

topical) and steam inhalation. In case of persisting bulge, myringotomy may be required to drain the collected pus and promote early healing of the drum.

The other common cause of ear pain is otitis externa. Otitis externa may be generalized or localized (furunculosis). The treatment consists of antibiotics, analgesics and local packing of ichthamol glycerine which has a hygroscopic and antiseptic action.

Otomycosis (fungal infection) is another common cause of ear pain with or without itching. On examination white debris which looks like wet blotting paper is seen. In case of infection by *Aspergillus niger*, black spores may be seen. Treatment consists of cleaning of debris followed by local antifungal drops, e.g. 1 percent clotrimazole and systemic antihistaminic agents, e.g. syrup pheniramine maleate.

Wax impacted or otherwise is another common cause of pain in children. Wax can be removed using suction, syringing or by ear probe. Ceruminolytics are used to soften the wax before it is removed.

The other common causes of ear pain in children include trauma, foreign body, referred pain most commonly dental, neuralgic pain and herpes.

### Mastoid Abscess

A child may present with history of painful swelling behind the ear. There is likely to be associated history of fever and the diagnosis is likely to be a mastoid abscess. This may be a complication of acute suppurative otitis media (ASOM) or of unsafe variety of chronic suppurative otitis media (CSOM). In case of ASOM there is a history of ear pain with preceding URI. In unsafe (atticoantral) variety of CSOM there is history of foul smelling ear discharge which is scanty, continuous and purulent. Otoscopy may reveal marginal perforation, cholesteatoma or granulations. Pediatricians should learn to diagnose unsafe CSOM cases and refer these cases to ENT surgeons for surgical management as chances of developing complications are very high in these patients. Many a times these cases are often

just treated with ear drops for a long time without realizing the potential complications.

If a mastoid abscess has formed it needs to be treated with antibiotics and incision and drainage.

### Vertigo

Dizziness in children may be difficult to treat as the child may not be able to give a proper history. The diagnosis may go unrecognized in children. There must be a high index of suspicion to diagnose this condition. The common causes of vertigo in children are

- Congenital vestibular deficit
- Otitis media with effusion
- Meniere's disease
- Perilymph fistula
- Ototoxic drugs
- Benign paroxysmal vertigo of childhood
- Migraine
- Vestibular neuronitis
- Trauma
- Wax

The first important step is to attempt to find out the cause by proper history. The role of the parent is very important in eliciting the cause. The treatment consist of treating the cause and also giving symptomatic treatment in form of vestibular sedatives.

## NOSE

### Nasal Bleed

Nasal bleed or epistaxis can be another distressing emergency in children. The commonest cause is nasal picking and the commonest site is Little's area at the anteroinferior end of the septum where the Kisselbach's plexus of vessels is present. Bleeding is more common during the winter months because of dryness. Following are the common causes of bleeding in children

- Nasal picking
- Trauma
- Coagulation disorders like hemophilia
- Aplastic anemia
- Leukemias
- Purpura
- Angiofibroma
- Malignancies like rhabdomyosarcoma and olfactory neuroblastoma
- Osler Weber Rendu disease (hereditary hemorrhagic telengectasia).

The first aid treatment in case of nasal bleeding consists of making the patient sit up with both the nostrils pinched and breathing through the mouth for

10 minutes (Trotter's maneuver). Most of the times this is sufficient to control a minor bleed. If unabated the bleed from the Little's area can be controlled by using adrenaline – xylocaine soaked pack or by using chemical or electrocautery. If still bleeding continues, anterior nasal packing with liquid paraffin soaked gauze piece may have to be done. If this also fails then posterior nasal pack is required. Here Foley's catheter may be used. Normally the pack is not kept longer than 48 to 72 hours. If bleeding is not controlled then pack needs to be changed and a fresh pack put. Here Foley's catheter may be used. Maintaining of vitals is done during the course of all these procedures. If the above procedures also fail to control the bleed then one tries to localize the bleeding vessel using nasal endoscopy or angiography. The bleeding vessel may require to be ligated.

### Nasal Foreign Bodies

In a child presenting with persistent unilateral discharge blood stained or otherwise one needs to rule out a nasal foreign body. The history may not be forthcoming most of the times. The common nasal foreign bodies are rubber, beads, stones, maggots, leech, etc. Most of the times these foreign bodies are lodged in the inferior meatus. One should be careful while trying to remove them taking care not to push them into the airway. One can use an instrument like an eustachian tube catheter to remove the foreign body.

### Bilateral Choanal Atresia

This condition presents at birth as respiratory emergency. This is more so as the newborns are obligate nose breathers and the ability to breathe through the mouth does not occur until some months after birth. These children have normal oxygenation during crying but become cyanosed during intervening time. It is diagnosed by passing a red rubber catheter through each side of the nose. A more reliable methods is to keep a stethoscope whose bell has been removed in each nasal cavity and the air blast noted. A CT scan or a contrast is needed to confirm the diagnosis. Immediate management consists of inserting an airway. Feeding may be done through a nasogastric tube. A flanged nipple with one or two holes cut in it may put and may be strapped into the mouth with umbilical tapes around the ears. Definitive surgery may be done through transnasal, transpalatal, transseptal or transantral route. If the membrane is thin transnasal route may be used. Membrane may be perforated using an antral trocar or a Hager urethral dilator.

## THROAT

### Breathing Difficulty (Stridor)

The common causes of stridor in children are:

#### Congenital

- Vocal cord paralysis
- Congenital cysts
- Laryngomalacia
- Subglottic stenosis

#### Acquired

- Laryngotracheobronchitis
- Diphtheria
- Acute epiglottitis
- Foreign body
- Subglottic hemangioma
- Trauma
- Abductor cord paralysis
- Laryngotracheal stenosis
- Recurrent respiratory papillomatosis.

Acute laryngotracheobronchitis is a common cause of mild to moderate stridor in children. The management of acute laryngotracheobronchitis consists of administering oxygen and steam initially. If need be intravenous corticosteroids may be added. If stridor increases, endotracheal intubation needs to be done.

Diphtheria with laryngeal involvement is a more serious emergency. These patients require early airway management as they deteriorate very fast. It is advisable for them to undergo early tracheostomy. Intubation should be avoided so as to avoid displacing the membrane. IV administration of antidiphtheric serum and penicillin is necessary.

Acute epiglottitis is another emergency presenting with stridor. The most common causative organism is *H. influenzae* type B. The presentation is of an acutely ill child with stridor, dysphagia, muffled voice and drooling of saliva. If acute epiglottitis is suspected laryngeal examination should be avoided before the airway is secured. If endotracheal intubation is not possible by the anesthetist, airway should be secured by bronchoscopy before tracheostomy is done. Lateral X-ray of the neck illustrates the classical thumb sign showing the swollen epiglottis. In this eventuality the patient needs to be shifted to the pediatric ICU. Treatment with IV antibiotics should be immediately started.

A common and often misdiagnosed cause of stridor in children is bilateral abductor cord paralysis. The child may need to be examined using fiberoptic laryngoscope or under general anesthesia without the cords being paralyzed. Most of the cases need tracheostomy. A period of 12 to 18 months is required before attempting a definitive lateralization procedure on the vocal cords.

Laryngomalacia is the most common cause of congenital stridor. It is characterized by flaccidity of supraglottic structures. In majority of cases inspiratory stridor is the only symptom. The stridor is often intermittent appearing only when the child is feeding or crying or it may be more pronounced during sleep. Most of the times it is a self limiting condition and disappears by the age of 2 years.

Recurrent respiratory papillomatosis is another cause of stridor diagnosed on laryngeal examination. The first step is establishing the airway and if required emergency removal of the papillomas can be done using microlaryngeal surgery or carbon dioxide laser. Tracheostomy should be avoided as far as possible. Some empirical treatment in form of interferon and cis retinoic acid have been used. Injection cidofovir also gives satisfactory remission.

### Foreign Bodies

Foreign body ingestion is one of the common causes of accidental death in children less than 6 years of age. The history is of choking and coughing. Acute respiratory distress is rare but can be dangerous. The commonly inhaled foreign bodies include nuts, stone, bone, pin needle, bead, etc. If there is an endoscopic foreign body in the airway endoscopic removal under general anesthesia is required. If airway is compromised tracheostomy is required. Laryngeal foreign bodies are best removed with a direct laryngoscope while tracheal and bronchial foreign bodies are removed with a bronchoscope. Normally a ventilating bronchoscope with a Hopkin rod-lens system is used by pediatric endoscopists. These bronchoscopes are equipped with 2 side channels, one for ventilation and the other for suction and instrumentation. After removal of the foreign body a second bronchoscopy is done to see that no foreign body is left behind.

Foreign bodies such as meat bolus, fish bone and bone tend to get stuck at cricopharynx. These can be removed using hypopharyngoscope or pediatric esophagoscope.

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An emergency may be defined as an unforeseen circumstance that requires immediate action.<sup>1</sup> In dentistry pain, infection and maxillofacial injuries are the most common emergencies because of which the child may be brought to the pediatrician. The incidence of oral and dental emergencies in children is increasing due to numerous factors namely negligence on the part of parents about dental health, repeated falls against various objects, vehicular accidents and assault. The oral and dental emergencies may thus arise following trauma, pathology or surgery. The treating physician must apply the same basic principles to tackle the dental emergency as for routine medical emergency since oral cavity is an integral part of the body.

The commonly occurring oral and dental emergencies which are common in children where the pediatrician may be called to attend them, will be discussed broadly under four headings namely, odontogenic pain, oral infections, postoperative complications following dentoalveolar surgery and traumatic injuries of teeth and jaws.

### Odontalgia (Toothache)

The majority of children will be brought to a pediatrician with the complaint of a diffuse mouth pain which may not be localized to a specific tooth. Nelson and Neff documented that oral infection and toothaches accounted for 17 percent of all emergency department referrals. It is important to take a complete medical history from the parents and a thorough oral examination may be carried out for proper diagnosis of the cause of pain.

The most common cause of toothache is acute pulpitis (inflammation of pulp). The pulpitis may be caused by gross carious lesion or following trauma to the tooth exposing the pulp.<sup>1,2</sup> The treating pediatrician on intra-oral examination, will usually find carious tooth and swelling or inflammation of the surrounding soft tissues. The tooth involved may be tender on percussion. In addition there will be a history of pain caused by

extremes of temperature, sweets or pressure. In such a situation, a pellet saturated in oil of cloves may be placed in the carious cavity and analgesics and antibiotics may be prescribed. The child may also be referred to the dentist for a definitive treatment after acute symptoms have subsided. If the pain is following trauma to the tooth, it is first ascertained whether any part of the crown or root of the tooth is fractured and may be confirmed by taking dental radiographs. It is then managed endodontically or otherwise depending upon the presentation. The intention of the dentist is to save the deciduous teeth by all means so that the space required for permanent teeth is maintained. The premature removal of deciduous tooth may result in space loss and may contribute to malocclusion at a later stage.

### Oral Infections

#### *Dentoalveolar Abscess*

The dentoalveolar abscess is another common cause of pain in and around the mouth. This is a suppurative process involving the periapical region of a diseased/infected tooth. The frequency of dentoalveolar abscess is increasing in children due to high incidence of dental caries and is usually a sequel to pulpitis and pulp necrosis caused by carious exposure and bacterial invasion of the pulp. The other cause is severe blow or trauma to the tooth resulting in pulpal death because of severing of apical vessels and nerves.<sup>1</sup> The dead pulp becomes a bacterial medium resulting in bacteremia and then pulpal and periapical infections. This infection in a child's jaw spreads rapidly because of wide marrow spaces in the bone.<sup>2</sup> The long standing dentoalveolar infection can perforate the bony plate adjacent to the root of the involved tooth and then spreads into the subperiosteal area and to the surrounding soft tissues.

The signs and symptoms of dentoalveolar abscess are pain, tooth may be elongated and tender on percussion and mobile, swelling (may or may not be fluctuant), and finally child may have general symptoms, i.e. raised

body temperature, malaise and lymphadenopathy. In long standing case of dento-alveolar abscess there may be an intra- or extra-oral sinus present through which pus could be draining out. The periapical infections of teeth sometime develop into osteomyelitis of the bone involving medullary cavity and Haversian system. The clinical course of the disease depends on whether the inflammatory exudate spreads primarily into the intramedullary spaces of the cancellous bone or collects below the periosteum and soft tissue. Acute osteomyelitis of the mandible can be an emergency. However, two atypical forms occurs with some frequency in children. The first of these involving jaws of newborn infants results from acute inflammation of bone with spreading thrombosis of nutrient vessels. It presents with swelling and redness below the eye, and edema of eyelids. The alveolus and palate in the region of first primary molars may also be swollen. There may be a sinus formation after 2-3 days. It can be well managed with antibiotics. The second form of osteomyelitis, i.e Garre's osteomyelitis of the mandible is a non-suppurative infection and is characterized by thickening of periosteum overlying the affected bone resulting in hard swelling. It produces a persistent bony thickening. However, this variety of osteomyelitis occurs rarely in comparison to classical variety.

The first step in treatment is to identify the abscessed tooth by means of a clinical examination and appropriate dental radiographs. Antibiotic therapy, preferably penicillin, should be prescribed to prevent spread of infection. In addition to antibiotics, the child may be advised to take analgesics to control pain and asked to do warm oral saline rinses. If it is fluctuant and pointed, it should be incised and drained preferably intraorally. Once the acute phase subsides, the child may be advised to consult a dentist for further management.

#### *Ludwig Angina*

Ludwig angina is a life-threatening infection of the sublingual, submental and submandibular spaces.<sup>3</sup> It may occur following odontogenic infection, laceration of the floor of the mouth, fracture of the mandible and salivary gland infection. The patient usually presents with a pancervical brawny induration accompanied by fever, malaise and leukocytosis. The mandible appears fixed with the mouth half open and the tongue and the floor of the mouth are elevated. There is excessive drooling of saliva caused by the inability to swallow. The airway is compromised, producing a high pitched inspiratory stridor. The treatment mainly includes support of the airway, incision and drainage of a

fluctuant swelling, antibiotics and analgesics. In cases of severe respiratory distress, tracheostomy might have to be undertaken.

#### *Pericoronitis*

Pericoronitis is a localized form of gingival inflammation surrounding an erupting tooth. It is usually associated with erupting molars in the adolescents. This is due to accumulation of food debris between the gum and tooth, thereby allowing bacterial growth.<sup>1</sup> This condition is some times aggravated by the presence of an opposing tooth which traumatizes the tissue flap covering the unerupted tooth everytime the mouth is closed.<sup>1</sup> Depending on the degree of severity, the child may present with pain distal to the last erupted tooth in the dental arch and radiating pain to the ear, tender swelling, trismus, dysphagia, lymphadenopathy, fever and inability to close the jaws and a foul taste in the mouth.<sup>1</sup> Emergency treatment includes incision and drainage, (if swelling is fluctuant), antibiotics and analgesics. Warm oral saline rinses are also helpful. Grinding of the cusps of the opposing tooth if traumatizing, also provides immediate relief to the patient.

#### *Acute Herpetic Gingivostomatitis*

It is a systemic disease caused by the *Herpes simplex* virus. It is highly contagious. The virus is similar to *Herpes zoster* and chickenpox. The clinical presentation includes elevated temperature (usually 101 to 103°F), loss of appetite, general feeling of malaise and submaxillary lymphadenopathy. The gingiva displays a diffuse fiery red inflammation and after 4 or 5 days, small vesicular lesions appear and rupture creating small ulcerated areas covered with yellowish exudate.<sup>3</sup> The entire oral mucosa can be involved but the ulcers usually appear on the tongue, lips, palate and gingiva. The management includes making the child comfortable, controlling fever and managing dehydration. The parents should be reassured that the condition is self-limiting and will resolve within a few days. In addition, antiseptic mouthwashes and a bland diet should be prescribed.

#### *Acute Necrotizing Ulcerative Gingivitis (ANUG)*

This condition is also called as Vincent's infection or trench mouth.<sup>12</sup> It is characterized by the presence of fusiform bacillus and *Borrelia vincenti* spirochete, in large numbers.<sup>1,2</sup> It is most often found in adolescents and young adults and may occur in a relatively clean mouth. The acute necrotizing ulcerative gingivitis usually has a sudden onset with constant radiating and gnawing pain,

excessive salivation, a peculiar taste, bleeding from the gingival tissues, malaise and obvious fetid odor in the breath. The gingivae are very hyperemic and the interdental papilla is punched out. These lesions are frequently covered with a grey pseudomembrane and are painful and will bleed when the slightest pressure is applied. In more severe cases lymphadenopathy and elevated body temperature may also be present.

The predisposing factors associated with this disease are emotional stress, insufficient rest, poor nutrition, poor oral hygiene and heavy smoking.<sup>1</sup> The acute necrotizing ulcerative gingivitis must be differentiated from primary herpes gingivostomatitis. ANUG is usually seen in young and adults (15 to 35 years) while primary herpes gingivostomatitis is seen in children between 3 to 5 years.<sup>2</sup>

The first step in treatment is to remove pseudomembrane, gross deposits of calculus and food debris or other causes of local irritation if possible and then apply some antiseptics. The child should be advised to brush the teeth using super soft toothbrush without injuring the gums and hydrogen peroxide mouth rinses. Diluted hydrogen peroxide 1:1 with warm water, is vigorously swished and forced between the teeth as frequently as possible throughout the acute phase.<sup>2</sup> Antibiotic therapy is recommended only if the patient has an elevated temperature and lymphadenopathy. In addition, rest nutritious diet and a course of metronidazole are quite effective in controlling the condition.

### Postoperative Complications

The postoperative complications which may bring the child for an emergency treatment are hemorrhage and infections.

#### *Hemorrhage*

The majority of the bleeding problems are local in character and present little difficulty in management. However, on occasion it may become a serious problem. In the normal child, persistent hemorrhage from a tooth extraction is uncommon. A careful history should avert most unexpected episodes of postoperative bleeding. When the history or clinical findings suggest a bleeding problem, laboratory tests are indicated to establish or to rule out a hemorrhagic disorder.

The immediate treatment for the control of hemorrhage should include local means, i.e. making use in one form or another, of oral pressure pack. Clean the bleeding socket and ask the patient to bite on a gauge sponge for 30 min. If bleeding is not controlled, pack

the wound with gauge soaked in adrenaline and wait for 30 min. If still not controlled, apply little tincture ferri-perchloride over the bleeding area and ask the patient to bite on pressure pack. If unsuccessful, inject local anesthesia (2% lignocaine hydrochloride) and suture the buccal and lingual flaps of the wound and place the pressure pack. In the small child, or where cooperation is not forthcoming, the administration of a general anesthesia in order to place the suture accurately must be considered. Intubation is essential because of the risk of a sudden reflux of swallowed blood from the stomach. If bleeding is still not controlled, remove the suture, pack the socket with hemostatic agents such as gelfoam or oxycel and resuture the socket along with application of pressure. Application of cold pack is very helpful. Cold causes contraction of blood vessels.<sup>1</sup> Finally if we still fail to control the bleeding, investigate the patient for blood dyscrasias and treat accordingly by administration of whole blood or other components of blood.

#### *Infection*

The post-extraction infection is rare in children, but if present, is recognized by the presence of swelling, pain, erythematous and edematous socket edges trismus. The child may also complain of fever and a generalized malaise. Dental infection may also involve other structures and may result in Ludwig's angina or acute osteomyelitis.<sup>1</sup> The emergency treatment of dental infection consists of antibiotic therapy, analgesics and warm oral saline rinses.

#### *Dry Socket*

Dry socket or alveolitis or alveolar osteitis is a painful inflammation of the bone of the post-extraction dental socket caused by the disintegration of the clot or when the clot is washed out a tooth socket.<sup>1,2</sup> Any interference with the formation and preservation of the blood clot will contribute to this condition. With the loss of blood clot, the nerve endings in the bone become exposed to the oral cavity and this produces severe pain.<sup>1</sup> The emergency dental treatment is to relieve the patient of severe pain by application of local obtundent and an antiseptic to combat any localized infection that may be present. The most effective form of treatment is to dress the socket using sedatives such as the mixture of oil of cloves, zinc oxide and cotton wool. The dressing should be packed to the depth of the alveolus but applied loosely to cover all the exposed bone.<sup>1</sup> In addition, the patient may be prescribed analgesics and antibiotics.

## Traumatic Injuries of Teeth and Jaws

### *Dental Trauma*

Traumatic injuries of teeth constitute one of the main emergency situation that every pediatrician should be prepared to cope with at all times.<sup>2,4,7</sup> The incidence of injured anterior teeth in children varied from 4 to 13 percent in USA, England, Japan and New Zealand. It is important for the pediatrician to know which injuries can be managed without dental consultation and which needs emergency dental care.

Tooth fractures are usually caused by a blow to the tooth from a fall, sports and fight.<sup>5</sup>

The injuries to the teeth are associated with soft tissue lacerations of the mucosa of the lip or tongue or cheek. The management of injuries of the soft tissues of the oral cavity require the same emergency care procedures as used for other soft tissues injuries in the body. The simple soft tissue lacerations of the mucosa of the lip or tongue should be readily treated by suturing with 000 silk using a 3/8 or 1/2 circle 16 mm atraumatic round body needle.

Complications from dental injuries include color changes of teeth, infection, abscess formation, ankylosis, resorption of roots, loss of space in the dental arch, abnormal root development and loss of teeth. The early diagnosis and management can largely prevent these complications.

Berkowitz, et al categorized traumatic dental injuries into 2 groups, *viz.* injuries to the teeth including hard dental tissues and pulp, and injuries to the periodontal ligament and alveolar bone.<sup>8</sup> Andreason further categorized traumatic fractures of the teeth into complicated and uncomplicated fractures.<sup>9</sup>

Uncomplicated tooth fracture involves the enamel or dentin. Clinically, the tooth may have ragged edges and the center of the tooth may appear yellow because of the involvement of dentin. The child may complain of sensitivity to thermal or direct stimuli because of the proximity of the pulp. In this situation, the emergency treatment is aimed at protecting the pulp even though no frank exposure is present. The child may be referred to dentist within 24 hours for smoothening the sharp edges and for placing a dressing of calcium hydroxide over the exposed dentin to prevent conduction of thermal stimuli and pulp necrosis.<sup>2</sup> At a later date, the fractured tooth can be restored utilizing composite resin materials.

Complicated crown fracture involves the pulp of the tooth. In such fracture, in addition to sensitivity there is usually hemorrhage from the exposed dental pulp. Once the pulp is exposed it is very important to refer

the child to dentist immediately to prevent bacterial contamination of pulp and to provide subsequent pulp therapy and an artificial crown. The prognosis of such tooth depends upon the size of exposure and the time interval between the trauma and pulp therapy.

Crown root fracture usually appears as a split tooth and involves the enamel, dentin, cementum and the pulp.<sup>6</sup> The teeth usually involved are maxillary anterior teeth. In addition to hemorrhage at the gingival margin, the child may have a clinically displaced crown. The tooth may be mobile and extruded from the socket. The management of such fracture usually needs immediate referral to dentist for stabilization or extraction of the fracture segment in case of permanent tooth while deciduous tooth may be removed. Fracture of a root alone may be difficult to detect clinically. The looseness of the tooth and abnormal position in the dental arch are clues. Root fractures can often be successfully treated by appropriate positioning and splinting of the tooth where more than one-third of the root remains as a unit with crown.

Intraoral dental radiographs are very important diagnostic tools in evaluating all injuries involving fractures of the dentin, pulp or roots. With trauma to the deciduous anterior teeth, indirect damage to the follicle of permanent successor may take place leading to hypoplasia or dilaceration of permanent teeth.

### *Injuries to the Periodontal Structures*

Periodontal injuries involve the alveolar bone and the periodontal ligament. Periodontal ligament consists of slender elastic collagen fibers and holds the tooth in its socket. These get easily broken with trauma to the teeth. The protruded maxillary anterior teeth are more prone to this type of traumatic injuries. The affected teeth become abnormally mobile or get displaced. The patients usually complain of pain and increased sensitivity to thermal stimuli. The periodontal injuries may be further classified into five clinical types namely concussion, subluxation, intrusion, extrusion and avulsion.<sup>2</sup>

- a. Concussion causes minor damage to the periodontal ligament.<sup>5</sup> The tooth due to concussion becomes sensitive to percussion or pressure but is not displaced out of the tooth socket. Such injuries do not usually require immediate therapy.
- b. Subluxation produces excessive mobility of the tooth but no displacement within the dental arch. It is usually more damaging to the periodontal ligament. The tooth is usually tender on percussion. The child will often complain that his teeth feel unusual when he or she bites. Subluxated teeth usually require

immediate immobilization with an acrylic splint or periodontal wiring and long term follow-up by the dentist.<sup>2,6</sup>

- c. Intrusion is usually common in primary teeth but has been seen in permanent dentition also. Intruded teeth are pushed up into the socket and tooth may appear avulsed. In addition, compression fracture of the alveolar socket may be present. In such cases immediate dental consultation, treatment, and a close follow-up are necessary.
- d. Extrusion occurs with vertical displacement of tooth out of the alveolar socket into an abnormal position. It is associated with the fracture of the labial wall of the alveolar socket. The anterior maxillary teeth are usually involved. The extruded primary teeth are usually extracted with 24 hours while the permanent teeth must be realigned and immobilized as soon as possible by the dentist. The delay in repositioning of the involved tooth can result in stabilization of tooth in an ectopic position.<sup>6</sup>
- e. Avulsion means a tooth which has been completely knocked out. Such injuries are common at the age of 7-10 years. The avulsed primary teeth are usually left out due to the close proximity of the permanent tooth to the socket. The treatment of avulsed permanent tooth require immediate dental consultation for rapid reimplantation and careful handling of the tooth. The best prognosis exists if the tooth is reimplanted in less than ½ hour post-avulsion.<sup>10</sup> Since time is of great importance in replanting teeth, the first contact with the patient on telephone should advise the patient or the parent to hold the avulsed tooth by the crown and then gently rinse the tooth and not scrub the crown or root and push the tooth gently into the socket into its normal position. If immediate replantation is not possible, it is advised to place the tooth under the child's tongue so that it remains moist in saliva. Cold milk from a refrigerator or an iced isotonic saline or saliva is the best medium for storage and to maintain the periodontal ligament vitality.<sup>2</sup> The patient is further instructed to contact the dentist for reimplantation and immobilization in the dental office.

Dental follow-up of such reimplanted teeth is necessary to prevent future ankylosis and resorption of the roots. Meanwhile an antibiotic should be given in standard dose alongwith tetanus toxoid. A primary tooth is generally not implanted because of the many difficulties in management and the danger to the developing permanent tooth bud. If the child is 2 years old or younger, quick replantation may be attempted because the immaturity of the primary roots aids in

reattachment. This should be done very soon after the accident because success decreases rapidly with time. The replanted teeth may be stabilized for a few days with surgical paste such as zinc oxide impression paste or periodontal pack or with wiring.

### Maxillofacial Injuries

The incidence of facial injuries in children is rather low than the adults particularly during the first five years of life and the most common facial bone fractured is the mandible.<sup>2,11</sup> The etiology of facial injuries is varied and includes accidents in or about the home, vehicular accidents and assault.<sup>2</sup> The facial injuries in children vary from a small abrasion to a substantial laceration or even a fracture. The severity of injury increases with the advancement of age. Primary consideration in patient with facial injuries should be protection of the patient's life and thus initial attention in emergency must be directed at maintenance of airway for respiration, control of hemorrhage, shock and neurologic assessment.<sup>2,11,13</sup>

- a. *Maintenance of airway:* The most common cause of airway obstruction in a child with facial injuries is the accumulation of blood in the oral cavity and pharynx. A fractured mandible may cause the tongue to fall posteriorly and create obstruction. A broken tooth aspirated by a child can also block the airway. In such situations the mouth should be gently suctioned and any foreign body in the form of broken tooth lying in the mouth should be removed. If avulsed teeth had been inhaled, it may be removed by bronchoscopy. The falling of tongue posteriorly due to fracture of mandible can be controlled by passing a 2/0 black silk suture through the tip of the tongue and then pulling it outward or by tying suture to the child's shirt button. If the mandible is displaced backward it should be pulled gently forward by bilateral digital pressure at the angles of mandible. The airway may also be at risk from swelling of the soft tissues under the tongue and in the laryngeal region, in particular after an attempt at strangulation.<sup>14</sup> If larger vessels are ruptured in the neck or floor or mouth, a hematoma may cause a similar embarrassment. To avoid aspiration of blood, the child may be placed on right or left side and oral airway may be inserted if required. If still there is evidence of laryngeal obstruction, there should be no hesitation in performing tracheostomy in a child with a fractured mandible or maxilla who is unconscious or who is showing signs of increasing respiratory distress.<sup>1</sup>
- b. *Control of hemorrhage:* The hemorrhage is best controlled initially by oral pressure pack and later on by ligating any blood vessels that are easily visualized.

- c. *Management of shock:* Because of the child's small blood volume, the loss of apparently insignificant amount of blood may produce hypovolemia. When hypovolemic shock is present, it is essential to restore the circulating blood volume by blood transfusion.<sup>11</sup>
- d. Finally if needed the child may be given tetanus toxoid prophylactically.<sup>2</sup>

### Diagnosis

The history, clinical examination and radiographs are very important to confirm the diagnosis of facial fractures. The common signs and symptoms of fractures of mandible and maxilla are pain, swelling, crepitus, disturbance in occlusion, difficulty in opening and closing the mouth, tenderness on palpation, abnormal mobility, trismus, impaired function, anterior open bite, subconjunctival hemorrhage, facial deformity and fetid odor.

The next step is gentle palpation in diagnosis of facial fractures. It should be done in a order beginning from forehead to mandible. The forehead and supra-orbital rims are palpated for any depression or step off deformity. The diagnosis of fracture of zygoma in the early stage becomes difficult because of overlying edema. Once the edema subsides, a dimple over the course of zygomatic arch is pathognomic of a fracture.<sup>13</sup> The maxillary fracture is diagnosed by placing the thumb and forefinger of one hand on the left posterior quadrant of maxilla and rocking gently from side to side and followed by the same procedure on the right posterior quadrant and then on the anterior teeth.<sup>13</sup> If a complete fracture is present the entire maxilla will move.

To diagnose the fracture of mandible, the forefinger of each hand are placed 4 teeth apart on the mandibular teeth with the thumb below the jaw and alternate up and down motion is made with each hand. The fracture will allow movement between the fingers and a peculiar grating sound (crepitus) will be heard.<sup>13</sup>

The mandibular condyle is palpated on the side of face with the help of forefinger by placing it in the external auditory meatus and asking the patient to open and close the mouth. The unfractured condyle will leave the glenoid fossae when the mouth is opened otherwise not.<sup>13</sup>

### Radiographs

The Waters' view (occipitomeatal) is the most useful X-ray to diagnose fracture of maxilla and a submental view for fracture of zygoma.<sup>2</sup> The posteroanterior view along with lateral oblique views of the right and left

mandible can help in confirming the diagnosis of fracture of mandible.<sup>2</sup> The panorex view usually shows the mandible in its entirety and is also very good view to see the condylar regions bilaterally and the temporomandibular joints.<sup>2</sup>

### Treatment

The repair of the soft tissue wound on the face may be done in the same way as for any other soft tissue lacerations on the body. Facial fractures in the emergency are a diagnostic rather than a treatment problem. Final treatment of facial fractures is rarely done in the emergency and once the diagnosis has been established, the specialist should be contacted for further management of facial fractures.<sup>2</sup> However, some sort of temporary fixation should be placed to keep the patient comfortable and to keep the fragments in as good position as possible. A barrel bandage is the most simple form of fixation which should be tied as a first aid measure.<sup>13</sup> General anesthesia is indicated for the more significant facial injuries in children. Simple lacerations of the face can be repaired in the emergency room with local infiltration anesthesia, with or without sedation. The choice of anesthetic is influenced by the patient's age and his ability to cooperate, the individual laceration, the need for specialized equipment, and the availability of anesthetist trained in pediatric anesthesiology. The choice of local anesthetic has some importance in the case of facial injuries. Because of the rich vascularity of the face, the addition of a vasoconstrictor to the local anesthetic has a great benefit for wound exploration and hemostasis. Two percent lignocaine which contains 1:200,000 epinephrine is usually recommended as a local anesthetic agent.

### Dislocation of the Temporomandibular Joint

It occurs when the capsule and temporomandibular ligament are sufficiently loosened to allow the condyle to move to a point anterior to the articular eminence during opening.<sup>2</sup> Dislocation can be unilateral or bilateral and often occurs when the mouth is widely opened during yawning or following a long dental treatment session.<sup>2</sup>

The dislocation is reduced by standing in front of the patient and pushing downward and backward the mandible by applying pressure on the occlusal surfaces of the lower posterior teeth with the help of thumbs wrapped in gauze. This will cause a net posterior positioning of the mandible which will jump the condyles back into the glenoid fossa.

A dental emergency kit containing instruments and medicines should be maintained in the emergency

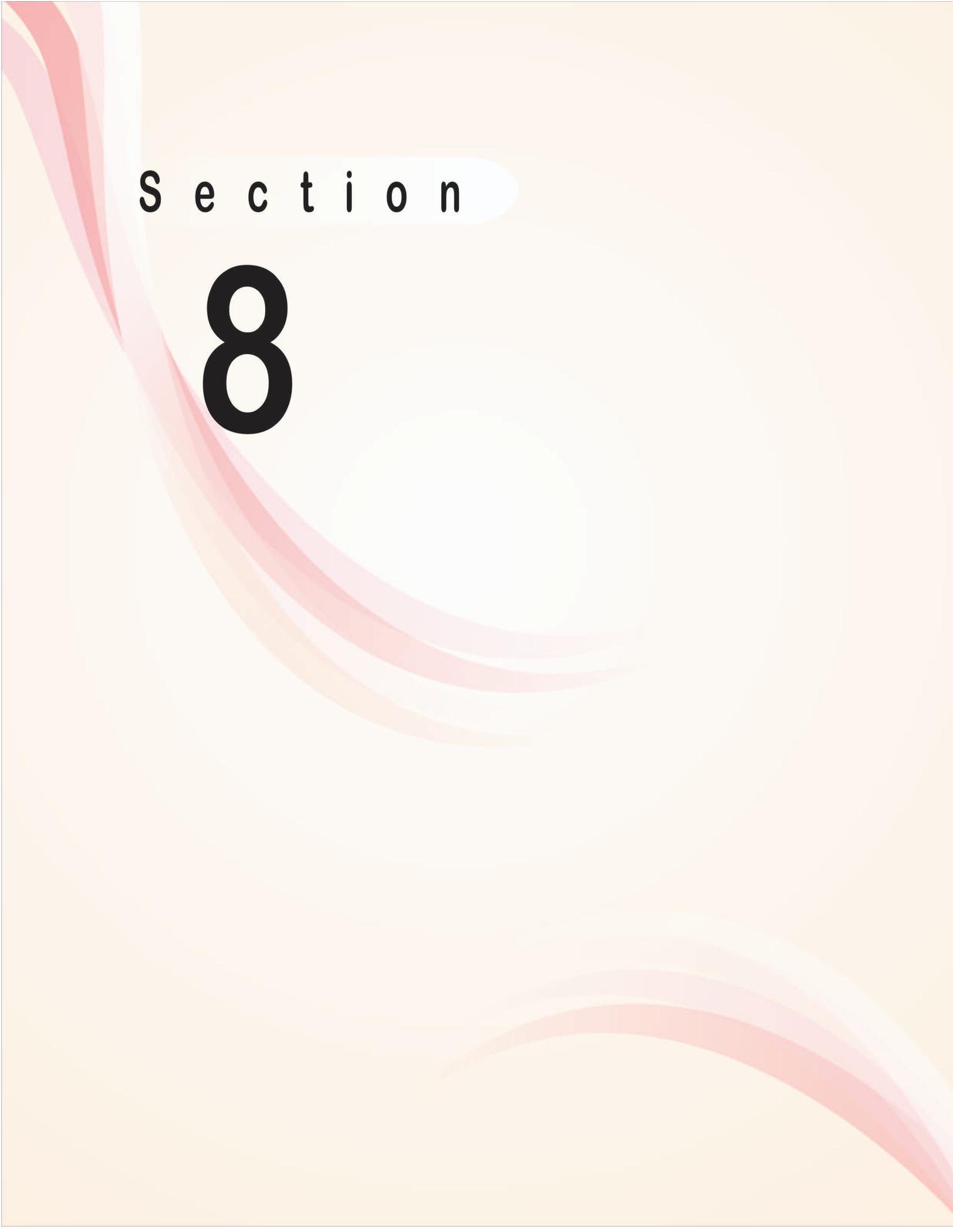
**Table 69.1: Dental emergency kit**

<i>Instruments</i>	<i>Medicine</i>
1. Mouth mirror	1. Oil of cloves
2. Probe (Explorer)	2. Pyorine (Gum paint)
3. Tweezer	3. Mercurochrome 1 percent in aqua
4. Dental extraction forceps	4. Tincture ferri-perchloride
5. Cement spatula	5. Powder zinc oxide
6. Glass slab	6. Ethyl chloride spray
7. Artery forceps	7. Two percent lidocaine with 1:200,000 epinephrine
8. Stainless steel wire 26 gauze	
9. Wire cutter	
10. Suture needle and '000' silk thread	

department to effectively deal with the dental emergencies in children (Table 69.1).

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S e c t i o n

8



# Procedures in Emergency Room

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## 70.1 Sedation, Analgesia, Anesthesia

Anil Sachdev

### INTRODUCTION

The treatment and reduction of pain is a basic human right for all, regardless of age.<sup>1</sup> Unfortunately, children frequently receive no treatment or inadequate treatment for pain and painful procedures, with newborn and critically ill children being especially vulnerable. This is because of the conventional “wisdom” that children neither respond to nor remember painful experiences to the same degree that adults do, which is simply untrue. Infact, all of the nerve pathways essential for the transmission and perception of pain are present and functioning by 24 weeks of gestation.<sup>2</sup>

Painful diagnostic or therapeutic procedures are often necessary during emergency care of children who already have painful and frightening injuries and illnesses. There are many reasons why effective analgesia, analgesia and sedation are not common place in the emergency department. The explanations for less use of analgesia or sedation include lack of consensus about optimal safe effective methods, medications, patient monitoring, lack of physician familiarity with local anesthetic techniques and dosing, insufficient time to carry out sedation and belief that children have only short-term memory of pain.

In India, the past decade has seen what may be considered a revolution in the recognition and treatment of pain and anxiety in children. Advantages of safe and effective management of pain and anxiety in the emergency department include reduction of psychological trauma and its sequelae, reduction of stress for the pediatricians and parents and a better success rate for the procedures.

Due to diversity in population no ‘cookbook’ is available for the method and medication to be used for a particular procedure.<sup>3</sup> What we must rely on is a broad understanding of the pharmacokinetics and physiological effects of group of diverse agents.

### Neurophysiology of Pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The American Pain Society (APS) in its Policy Statement on chronic pain in children defines pain as “the result of a dynamic integration of biological processes, psychological factors and social/cultural context considered within a developmental trajectory.”<sup>4</sup> This type of pain includes persistent (ongoing) and recurrent (episodic) pain with possible fluctuations in severity, quality, regularity, and predictability.

The basic mechanism of pain perception has four components, transduction, transmission, perception and modulation.<sup>5</sup> Noxious mechanical, thermal or chemical stimuli excite afferent nerve fibers that transmit information about the potential injurious stimuli from the periphery to the dorsal horn of the spinal cord. The pain impulse is transmitted via A-delta (large, myelinated) and C (small, unmyelinated) fibers. The tissue injury causes release of inflammatory mediators, (e.g. bradykinin, prostaglandins, cytokines, catecholamines, substance P) that sensitize the A and C fibers and recruit other neurons resulting in hyperalgesia. This nociceptive sensory input reaches the second order neurons in spinothalamic, spinoreticular and spino-mesoencephalic tracts and is then widely distributed throughout the brain. As there is no single pain center, the perception and modulation occurs within a distributive neuromatrix.

Pain can occur in single or multiple body regions and can involve single or multiple organ systems. According to the above definitions, tissue damage does not need to be present in order for the child to experience pain. Therefore, as a profession, we no longer refer to pain as “real” or “psychosomatic.” Pain is now categorized as

“structural pain,” “pain associated with tissue damage,” or “functional pain,” “pathological pain not associated with ongoing tissue damage”. Two children undergoing the same surgical procedure may respond in a completely different manner, depending on their age, gender, previous pain experiences, and coping skills.

Pain perception is a highly subjective experience. Any procedure by its very nature causes pain, and the stress of being in an unfamiliar environment and awakening to changes in physical functioning can compound this sensation. The clinician has a unique challenge when attempting to predict pain intensity and duration. Failure to assess the patient’s pain symptoms and behaviors, as well as to act on them, can result in unrelieved pain and suffering. Infants and young children may not be able to conceptualize or articulate either the intensity and/or the quality of their pain. Therefore, reliable tools for analyzing pain behaviors are necessary. Lack of pain assessment may result from multiple misunderstandings or misconceptions regarding pain in children.<sup>6</sup> Thus the biggest barrier to adequate treatment continues to be poor pain assessment and lack of knowledge on how to treat pain.

### Principles of Sedation and Analgesia

In choosing a technique for sedating an infant or child, it is first essential to identify clearly the goals of the sedation plan and to differentiate between sedation and analgesia. Not all procedures or clinical situations demand both, and there is commonly a greater need for one or the other. To optimize the therapy, physicians first must understand the requirements of the procedure or clinical scenario in addition to the needs and physiologic condition of the patient.

Sedation is the administration of agents to depress the state of consciousness. It may vary from *conscious sedation*, in which the patient is awake and responds verbally to commands and questions, to general anesthesia, in which the patient is completely unconscious.<sup>7</sup>

Sedation is, rather, a continuum, and a child may pass from a state of conscious sedation to deep sedation to general anesthesia with unexpected ease and rapidity. A dose of medication that causes one child to be sedated but responsive may produce unconsciousness and an impaired reflexive ability to protect the airway in another child. The drugs chosen and the underlying condition of the patient may make this transition more or less likely, but individual variations in drug response are not always predictable. Physicians, therefore, always must be prepared for the common possibility that the patient may pass into a greater

depth of sedation than initially anticipated and be able to manage the consequences. The goals of sedation are: anxiolysis, co-operation, amnesia, immobility and lack of awareness.

### PRE-EVALUATION

Any patient who is to undergo sedation must have a medical evaluation to determine what underlying conditions, if any, will affect the choice of the sedation prescription and plan. The major issues that must be addressed relate to four general areas: (a) airway and respiratory system, (b) cardiovascular status (including hydration and adequacy of intravascular filling), (c) factors affecting drug metabolism and disposition, and (d) nothing-by-mouth (NPO) status and risk for aspiration.

### ASSESSMENT TOOLS

#### Pain Assessment Tools

Although assessing pain is a simple task, it is one that is infrequently performed. Clinicians continue to estimate the presence or absence and amount of pain that a child is experiencing based on their own perceptions. This subjective data can result in inaccurate documentation of pain scores and failure to implement appropriate pain management practices. There are a myriad of pediatric pain tools available that demonstrate good reliability and validity, are user friendly, and time efficient. The neonatal pain, agitation, and sedation scale (NPASS) is used for premature infants up to 44 weeks post conception.<sup>8</sup> The FLACC is a behavioral pain assessment tool that evaluates the infant/toddler’s facial expression, leg movement, activity, cry, and ability to be consoled.<sup>9</sup> The Wong-Baker FACES pain rating scale is used for developmentally appropriate 3 year olds and older and is probably the most widely known and well received of all pain tools used for young children who can conceptualize that an event can have an escalation in intensity.<sup>10</sup>

#### Sedation Scores

Although pain assessment is the first step in evaluating pain, a sedation level assessment is equally important and should be done to assist the clinician in analyzing whether or not pain medications need to be withheld or titrated down. When a child is receiving opioids, a sedation assessment should be performed with every pain assessment, including the post-intervention assessment. The most commonly used procedural sedation assessment tool is the University of Michigan Sedation

Scale.<sup>11</sup> The COMFORT scale<sup>12</sup> is another commonly used PICU pain and sedation tool that utilizes both behaviors and physiologic parameters. Other scoring systems, such as the Sedation-Agitation Scale, also eliminate the use of physiologic parameters and visually assess the level of the patient's comfort, grading it from 1 (nonarouseable) to 7 (dangerous agitation such as pulling at the endotracheal tube).<sup>13</sup> A commonly used sedation scale in the adult ICU population is the Ramsay sedation score.

## MONITORING

All patients receiving sedatives must have basic monitoring using pulse oximetry, heart rate, blood pressure, and a means of assessing adequacy of ventilation.<sup>14</sup> Blood pressure should be measured at intervals of no longer than 5 minutes and more frequently during bolus doses of drugs likely to affect cardiac output and vascular resistance.

Paramount to the safe conduct of sedation is the presence of an independent monitoring clinician whose roles are to monitor the patient and attend to the airway, administer drugs, and record clinical data and events.<sup>14</sup> Physicians who are preoccupied with performing a procedure cannot be expected to detect effectively the early warning signs that a complication may be developing. The early detection of adverse events and prompt intervention are the only ways to avert catastrophic consequences.

The potential risks of sedation include airway obstruction, hypoventilation, apnea, and cardiopulmonary impairment.

## Fasting Guidelines for Conscious or Deep Sedation

Fasting<sup>15</sup> guidelines are the same as for any anesthetic regardless of how 'light' the sedative technique be (Table 70.1.1).

## Is an Intravenous Catheter Necessary?

Needle phobia is universal among children. Previously healthy children who present for painful procedures will not have pre-existing IV access. It would be difficult to manage a child during a painful procedure without IV access. Intravenous access is important for any emergency drugs to be administered, for fluid administration, if there is any hypotension and to administer sedative or analgesics intravenously. If EMLA (eutectic mixture of local anesthetic) is available it can be applied an hour before the procedure for better success of IV access.

**Table 70.1.1: Fasting guidelines**

Age	Solids and non-clear liquids (including milk)	Clear liquids (hours)
> 36 months	6-8	2-3
6 to 36 months	6	2-3
< 6 months	4-6	2

**Table 70.1.2: Characteristic of an ideal sedative**

Rapid onset
Predictable duration
No active metabolites
Rapid recovery
Multiple routes of delivery
Easy to titrate
Minimal cardiopulmonary effects
Not altered by renal or hepatic disease
No drug interactions
Wide therapeutic index

## Sedative or Analgesic Best for Children Undergoing Painful Procedures?

This is the most difficult to answer as there are no definitive techniques for a given procedure. The ultimate choice depends on pediatrician's preferences and comfort, and the answers to the following question; (i) Is the procedure painful? e.g. lumbar puncture, bone marrow aspiration; (ii) What is the duration of the procedure?; (iii) Does the child need to be motionless (EEG, CT scan, MRI); and (iv) Is the child outpatient or inpatient?

The character of an ideal sedative or analgesic are depicted in the Table 70.1.2

Whatever the indication for sedation and analgesia, the general recommendations should be followed religiously as shown in Table 70.1.3.

## SPECIFIC DRUGS

### Benzodiazepines

Benzodiazepines are sedatives, anxiolytic, anticonvulsant but *not analgesic*. The biggest advantage of these drugs are their *amnesic* property. Of all the drugs benzodiazepines have best anterograde and retrograde amnesia. Of the benzodiazepines, midazolam is a preferred agent for sedation in the emergency room because it is water soluble, has shorter duration and quicker onset of action than diazepam and lorazepam. Because of pain during intravenous, erratic absorption intramuscular injection and long duration of action,

**Table 70.1.3: General recommendation for sedation and analgesia**

- Assess the child and beware of 'Full Stomach' in emergency situation
- NPO guidelines
- Obtain consent
- Establish the venous access
- Check airway and resuscitative equipment including suction apparatus
- Monitor heart rate and oxygen saturation
- All the medications to be diluted and labeled and injected at a very slow rate. After administration of each drug flush the line
- After injecting one drug before injecting another drug, wait at least for 15 to 20 seconds. Watch the respiration.
- In the midazolam + fentanyl combination, inject midazolam first
- Administer Atropine/Glycopyrrolate, then midazolam and finally ketamine when using this combination
- Document before and after sedation
- The pediatrician should be trained in pediatric advanced life support

diazepam is not a suitable sedative in the emergency department. Midazolam has minimal hemodynamic effects and is metabolized by liver and excreted by the kidneys. Intravenous flumazenil can reverse midazolam sedation at a dose of 0.01 mg/kg/dose up to a maximum of 0.04 mg/kg. The recommended dosage of midazolam for various routes is given in Table 70.1.4.

When a combination of midazolam and narcotic is contemplated the dosage of narcotic and midazolam

must be individualized and administered by titration rather than by fixed dosage schedule.

### Trichlofos Sodium

Trichlofos sodium has been used for rendering children immobile during painless procedures to keep the child motionless, like ophthalmological examinations, echocardiogram, EEG, CT scan and MRI scan. Despite the safe records and absence of respiratory depression in sedated children, it is advisable to have continuous pulse oximetry monitoring during the procedure. A combination of trichlofos and paracetamol can be used if a mild analgesic effect also is required. The dose is 50 to 100 mg/kg and the onset of action is in 30 to 40 minutes and duration of action is 90 to 120 minutes.

### Pethidine/Promethazine/Chlorpromazine

The combination of pethidine (2 mg/kg), promethazine (1 mg/kg), and chlorpromazine (1 mg/kg) called 'lytic cocktail' has been used for many years for sedation in children especially for cardiac catheterization. Due to availability of better drugs and significant episodes of hypotension, apnea, prolonged recovery and dystonic reactions, the above combination is no longer recommended.

### Morphine

Morphine is the gold standard narcotic agent by which other narcotic analgesics are compared. Although a very good analgesic, its main disadvantages are histamine release (not suitable for reactive airway disease children), long duration of action and possible hypotension especially in hypovolemic children. Its metabolite Morphine-6-glucuronide is also a potent narcotic. Morphine causes much more nausea and vomiting than other opiates. Though, it is an excellent analgesic for postoperative analgesia, it is not an ideal agent for emergency room procedures due to its longer duration of action. The recommended dosage for various routes is given in Table 70.1.4.

### Fentanyl

Fentanyl<sup>17</sup> is a potent synthetic opiate agonist and is 100 times more potent than morphine. Its faster onset of action, short duration and potent analgesic effect make this drug narcotic of choice for wide variety of painful procedures in the emergency room. It should be given in a dose of 1-3 µg/kg. Fentanyl has an onset of action within 2-3 min and the duration of action is 45-60 min. If fentanyl is given fast, it might cause

**Table 70.1.4: Route and dosages**

Route	Dose (mg/kg)	Onset (Min)	Duration (Min)
Midazolam			
Oral	0.5-0.7	15-20	45-90 min
Per rectum	0.25-0.5	10-30	60-90 min
Intranasal	0.2-0.5	5-15	45 to 60 min
Intramuscular	0.05-0.15	10-20	60-120 min
Intravenous	0.05-0.15	2-3	30-60 min
Morphine			
Subcutaneous	0.1-0.15	10	4-5 hr
Intramuscular	0.1-0.15	10	4-5 hr
Intravenous	0.1-0.15	2-5	4 hr
Ketamine			
Oral	6-10	10-30	1-2 hr
Intramuscular	3-5	2-10	60-90 min
Intravenous	1-2	0.5-1	10-30 min

respiratory depression and apnea. Fentanyl causes mild decrease in the heart rate and peculiar effect to chest wall rigidity, which may impair ventilation. Naloxone will reverse the adverse effects of fentanyl. The combination of fentanyl and midazolam is very good for severe painful procedures but one should be cautious of respiratory depression or even arrest due to its synergistic effect. The newer drugs, ultrashort acting alfentanil and sufentanil, have not entered the Indian market yet.

### Ketamine

Ketamine<sup>17</sup> was introduced as an intravenous anesthetic agent. It produces dissociative anesthesia, profound analgesia and sedation while maintaining spontaneous respiratory effort. Though it was introduced as an anesthetic agent it is being used widely for many procedure related pains by the non-anesthesiologist because its potent analgesic effect occurs even when the laryngeal and pharyngeal reflexes are preserved. Because of its bronchodilatory effect it is a very good analgesic agent for asthmatic children. It increases heart rate and blood pressure. The unpleasant hallucinations seen often in adult occur less frequently in children. Since ketamine increases salivation it is mandatory to administer antisialogogue (glycopyrrolate or atropine) before injecting ketamine. No reversal agent for ketamine exists. Ketamine should never be taken lightly and resuscitation equipment and drugs should be ready when it is administered. The recommended dosage for various routes is given in Table 70.1.5. Premedication with atropine or glycopyrrolate (causes less tachycardia) 0.01 to 0.02 mg/kg IV or IM.

### Propofol

Propofol which was used initially as a general anesthetic, due to its short half-life is now widely used for short-term sedation. The recommended dosage is 1-4 mg/kg intravenously; the onset of action is within 60 sec and the duration of action lasts for 10-15 min. Though long-term (> 48 h) sedation with propofol may cause severe metabolic acidosis, it is being recom-

mended for procedures like CT scan, MRI, intercostal drainage insertion and central venous line placements. Its main advantage is immediate and smooth recovery. Propofol, a lipid emulsion, is very painful during IV injection. The pain can be alleviated by prior administration of 0.5 mg/kg of lignocaine or mixing it with propofol solution itself. If propofol is to be given in a small doses it is advisable to dilute with 5 percent dextrose. This agent is associated with some drawbacks like apnea, hypotension, and airway obstruction. So it is mandatory that a pediatrician should be well trained in airway management.

### Non-narcotic Analgesics

Weak analgesics like paracetamol and nonsteroidal anti-inflammatory drugs are the most commonly used drugs in general pediatric practice and sometimes in postoperative analgesia. Though, they are very useful in mild pain, they are not suitable for the procedure related pain in the emergency room.

### Local Anesthetics

Local anesthetic<sup>18</sup> agents are sodium channel blockers preventing depolarization of the nerve. To act at the sodium channel, local anesthetics must first enter the cell in non-ionized form and then act inside the cell. Local anesthetics are weak bases, so at physiological pH they exist primarily in the ionized state. In certain local conditions like infection and inflammation, a state of relative tissue acidosis exists and the local anesthetic is not effective. Adding epinephrine to the local anesthetics causes vasoconstriction, decreases rate of absorption and thereby prolongs the duration of the block and reduces the toxicity. Epinephrine containing local anesthetics should never be used in areas supplied by end arteries such as finger, toes, penis and the tip of the nose.

The two drugs, which are commonly used, are lignocaine and bupivacaine. Lignocaine has quicker onset and shorter duration of action and bupivacaine has slower onset and longer duration of action. Toxicity includes tinnitus, anaphylaxis, convulsions, cardiac arrhythmias and cardiovascular collapse. The arrhythmias are more common with bupivacaine than lignocaine and it is difficult to treat these drug induced rhythm disturbances.

The general guidelines for using local anesthetic agents include:

1. Use smallest possible needle (24 or 25G) to raise the wheal. First inject subcutaneously and then raise the intradermal wheal to prevent pain.

**Table 70.1.5: Dosage of some local anesthetics**

Drug	Dose (mg/kg)	Onset (min)	Duration (min)
Lignocaine (plain)	4	3-6	60-90
Lignocaine (adrenaline)	7	5-10	90-120
Bupivacaine	2.5	10-15	180-240

2. All resuscitative equipments and drugs should be ready to manage possible overdosage and toxicity.
3. It is always safer to have intravenous line in place.
4. To prevent intravascular injection, always aspirate before injecting the local anesthetic.

Infiltration of local anesthesia as an adjunct to sedative drugs is very useful in the following situations: (i) Lumbar puncture; (ii) Suturing small lacerated wounds; (iii) Central venous line placement; (iv) Arterial line placement; (v) Intercostal drainage tube insertion (vi) Bone marrow aspiration and biopsy; and (vii) Liver and kidney biopsy.

### EMLA

EMLA is an eutectic mixture of local anesthetic cream, which is a mixture of lignocaine, and prilocaine in water based cream, which provides analgesia even in intact skin. It should be applied at least 60 minutes before the procedure. There are some reports of methemoglobinemia after its application in children less than 6 months of age due to the presence of prilocaine. Its main usage is for intravenous placement but it can be used for lumbar puncture and circumcision.

### Local Anesthetics

The dosage of some local anesthetics is given in Table 70.1.5.

### Digital Nerve Block

Of all the regional nerve blocks, the most useful block to be learnt by the pediatrician is digital nerve block. The paired digital nerves enter the digits medially and laterally. Inject 1 to 2 ml of local anesthetic in the web space on either side of the finger or the toe. The usual approach is to enter from the dorsal surface where it is less painful. Epinephrine containing local anesthetic should never be used. It is very useful for suturing finger injuries, removal of warts and foreign body removal.

### Synergism

If two drugs of different mechanisms of action are combined, one may potentiate the other one and reduce the dose requirement of each of them for optimal usage. But at the same time, it may carry the increased risk of respiratory depression.

#### *Example 1: Midazolam and Fentanyl*<sup>6</sup>

Combining sedative and analgesic will be very effective for many procedures like lumbar puncture, wound

suturing, closed fracture reduction and immobilization. The main advantages of midazolam is amnesia with mild muscle relaxation. Both the drugs should be diluted and injected slowly and titrated to the desired effect without exceeding the upper dose limit of each drug for that particular child. When these combinations are given, it is mandatory to monitor the patient by pulse oximetry. The pediatrician administering these combinations must be skilled in airway management and resuscitation.

*Example 2: Atropine or Glycopyrrolate (0.02 mg/kg), Midazolam (0.05 mg/kg), Ketamine (0.5 to 1 mg/kg); All Intravenous.*

It is a good combination for painful procedures like wound suturing and fracture reduction. This cocktail effect is not reversible and airway reflexes may not be maintained.

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## 70.2 Pulse Oximetry

Dhiren Gupta

Measurement of PaO<sub>2</sub> has been the standard method for evaluating oxygenation in the clinical setting. Pulse oximetry is now a widely available technology that provides an easy, noninvasive, and reliable method to monitor oxygenation. Pulse oximetry has become the standard of care in the intensive care unit and is quickly becoming routine in the, and other clinical settings. When arterial oxyhemoglobin saturation, it is referred to as SaO<sub>2</sub> [SaO<sub>2</sub> = HbO<sub>2</sub>/(HbO<sub>2</sub> + Hb)] and when it is measured by pulse oximetry, it is referred to as SpO<sub>2</sub>.

### Principle of Pulse Oximetry

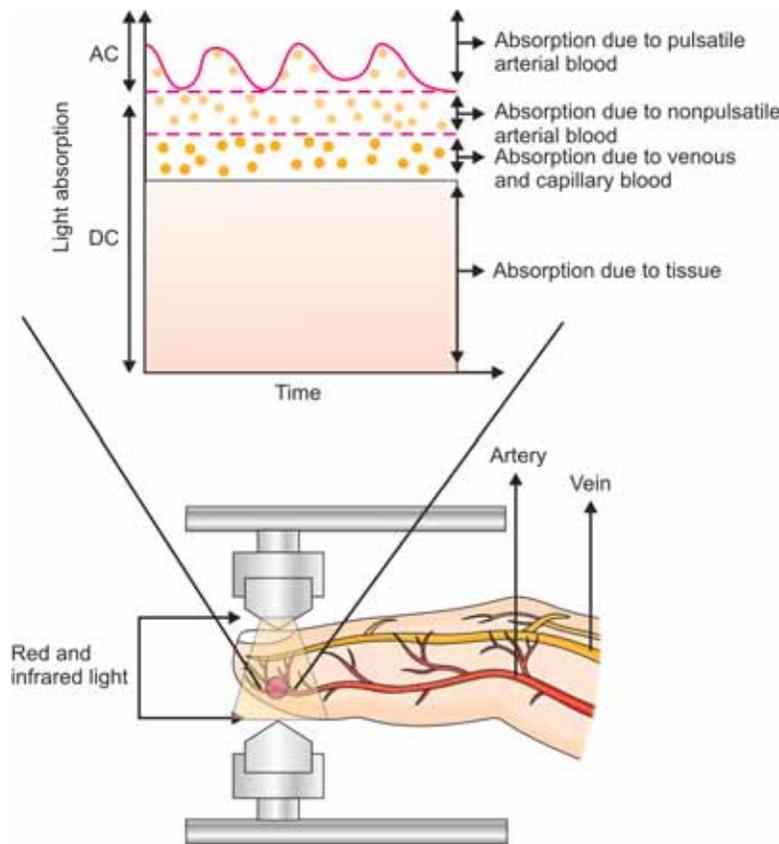
Measurement in conventional pulse oximetry is accomplished through the application of the Lambert-Beer law, which describes the relationship between a colored substance, the length of the path on which light can pass through it, and the corresponding light absorption by that substance. The principle of pulse oximetry is shown schematically in Figure 70.2.1. The light passing through tissue is absorbed by tissue and by venous and arterial blood. The ratio is calculated at two wavelengths of light, usually around 660 nm (red) and 940 nm (infrared). The tissue, blood, and bone absorb much of the emitted light, but some passes all the way through and is measured by a light-sensitive photodiode that is placed opposite of the LEDs. During the cardiac cycle, the pulsating arterial blood that fills the vascular beds during systole causes changes in light absorption. In addition, the absorption of both red and infrared light is affected differently by the amount of oxygen bound to hemoglobin in the blood. Therefore, reduced hemoglobin and oxyhemoglobin can be distinguished from one another in the pulsating arterial blood based on their differences in red and infrared light absorption respectively.

Pulse oximeter has two components—Absolute value of SpO<sub>2</sub> and plethysmography analysis. Simultaneous

analysis of both are required for correct interpretation of pulse oximetry reading. Normal arterial oxygen saturation is considered to range between 97% and 99%. The pulse oximeter uses empirical calibration curves developed from studies of healthy volunteers to calculate SpO<sub>2</sub>.<sup>2</sup> The partial pressure of oxygen dissolved in the plasma is measured as the PaO<sub>2</sub>. The oxygen dissociation curve (Fig. 70.2.2) shows the relation between SpO<sub>2</sub> and PaO<sub>2</sub>. A SpO<sub>2</sub> greater than 95% correlates to the normal range of PaO<sub>2</sub>, which is 80 to 100 mm Hg. A PaO<sub>2</sub> of 60 mm Hg or less correlates to a SpO<sub>2</sub> of less than 90% as per the dissociation curve. A change in temperature and pH also causes a shift in this relation. As pH increases (alkalosis) or temperature decreases (hypothermia), the shift is to the left as hemoglobin binds more tightly with oxygen delaying its release to tissues. Acidosis (low pH) and fever shift the curve to the right, as the hemoglobin molecule loosens its affinity for oxygen, making it easier to be released to the tissues.

### Trouble Shooting and Clinical Limitation of Conventional SpO<sub>2</sub> Monitoring

All clinical monitoring parameters have their limitations, and conventional SpO<sub>2</sub> is no exception. It is the responsibility of the clinicians using the technology to understand the limits of the technology and to make the appropriate adjustments and assumptions in order to properly interpret monitoring data. SpO<sub>2</sub> is not directly measured; it is a calculated value using algorithms that are based on certain assumptions that make it an approximation of the actual oxygen saturation (SaO<sub>2</sub>) and not an absolute value. Excessive motion artifact is one of the biggest disadvantages of conventional pulse oximetry and occurs when a patient's movements cause the SpO<sub>2</sub> monitor to incorrectly interpret patient movement as a



**Fig. 70.2.1:** Principle of pulse oximetry. Light passing through tissue containing blood is absorbed by tissue and by arterial, capillary, and venous blood. Red and infrared light pass through the patient's blood, and the amount of light received by the detector on the other side indicates the amount of oxygen that is bound to the hemoglobin. (Oxygen attaches to the heme portion of hemoglobin molecules in the red blood cells. Each hemoglobin molecule can carry up to four oxygen molecules.) Oxygenated hemoglobin (oxyhemoglobin, or  $\text{HbO}_2$ ) absorbs more infrared light than red light, while deoxygenated hemoglobin (Hb) absorbs more red light than infrared light. By comparing the amounts of red and infrared light received, the instrument can calculate the  $\text{SpO}_2$ . Usually, only the arterial blood is pulsatile. Light absorption may therefore be split into a pulsatile component (AC) and a constant or nonpulsatile component (DC)

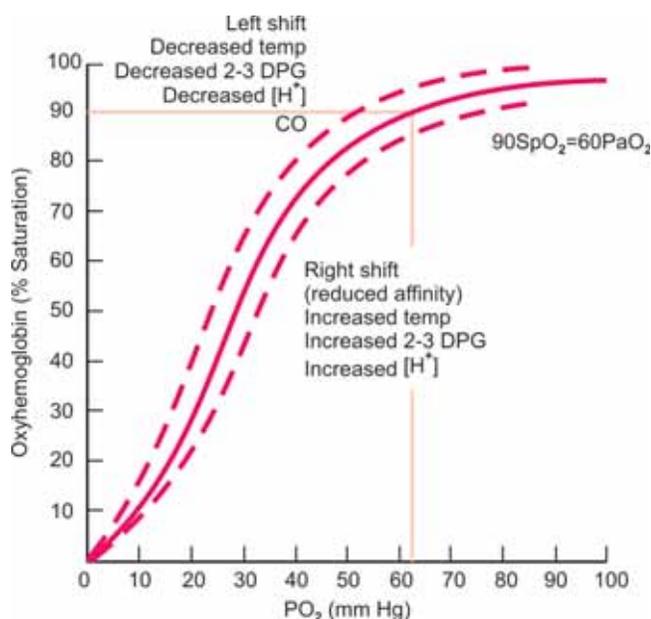
pulse. The resultant increase in false alarms and erroneous measurements can have the effect over time of desensitizing clinicians to the alarms and increasing the chance of missing a significant true alarm.<sup>3</sup> In fact, evidence indicates that most of the low oxygen saturation alarms provided by pulse oximetry are false. This is one of the greatest disadvantages of conventional pulse oximetry. There can be various factors which can lead to erroneous readings (Table 70.2.1).

### Interpretation and Trouble Shooting

Readings of 90% or less may indicate that the patient needs supplemental oxygen and further tests as confirmation of hypoxia.

It is important to remember that pulse oximeters measure and calculate the oxygen saturation of the hemoglobin in arterial blood, not the actual oxygen content of the blood; therefore, they do not provide a measure of actual tissue oxygenation or how well the patient is ventilated. Be cautious interpreting readings when there has been a sudden change in  $\text{SpO}_2$ . One example would be a sudden decrease from 97%  $\text{SpO}_2$  to 85%  $\text{SpO}_2$ ; this is physiologically impossible. Evaluate this information in conjunction with the patient's clinical condition and the above-listed limitations.

Oxygen saturation values below 70% obtained by pulse oximetry are unreliable. Any time hypoxia is suspected, but not confirmed with pulse oximetry,



**Fig. 70.2.2:** The oxygen dissociation curve is a graph that shows the percent saturation of hemoglobin at various partial pressures of oxygen

ABGs should be performed<sup>4</sup> even when the pulse oximeter reads the  $SpO_2$  as normal, the patient could have undetected carbon dioxide retention. Therefore, it is important not to rely on the information from pulse oximeters alone in the assessment and diagnosis of hypoxemia.

### Interpretation of Photoplethysmography

Photoplethysmography (PPG) which actually reflects the arterial pulse waveform pattern. The pulse waveform is derived from the infrared signal, which is influenced mainly, but not exclusively, by arterial blood. Each pulse then appears as a peak simultaneous to the arterial pulse pressure curve displayed from a radial artery. PPG can be obtained from transmissive absorption (as at the finger tip) or reflective (as on the forehead). The shape of the PPG waveform differs from subject to subject and varies with the location and the manner in which the pulse oximeter is attached. The height of pulse component of the PPG is proportional to the pulse pressure.

**State of blood vessel:** A conventional pulse oximeter monitors the perfusion of blood to the dermis and subcutaneous tissue of the skin. Thus, PPG of the pulse oximeter has been proposed as a method of monitoring macrocirculation and microcirculation. Oximeters have been shown to be useful in detecting systolic blood

pressure.<sup>5</sup> On the contrary, some works proposed this method to assess the patency of arterial grafts, the viability of bowel and the early detection of radial artery occlusion owing to arterial lines. The signal of pulse oximetry curves, however, may be lost in the presence of cardiac output less than 2.4 l/min/m<sup>2</sup> and very high mean systemic vascular resistance index. In patients with severe tricuspid regurgitation, the measured curve may be not related to systolic pressure as venous flow becomes pulsatile. In one report, the PPG amplitude has been shown to increase following arterial vasodilatation, which enhances the respiratory variation of the waveform.

**Prediction of fluid responsiveness (Fig. 70.2.3):** By reflecting the pulsatile changes in absorption of light between the beam source and the photodetector of the pulse oximeter, the 'pulse' wave is assumed to be the result of the beat-to-beat changes in stroke volume transmitted to the peripheral circulation. In this regard, analysis of the respiratory variation in the plethysmographic signal measured from pulse oximetry has been proposed for a long time as a technique to assess hemodynamic monitoring in pediatrics patients and blood volume status in mechanically ventilated patients.

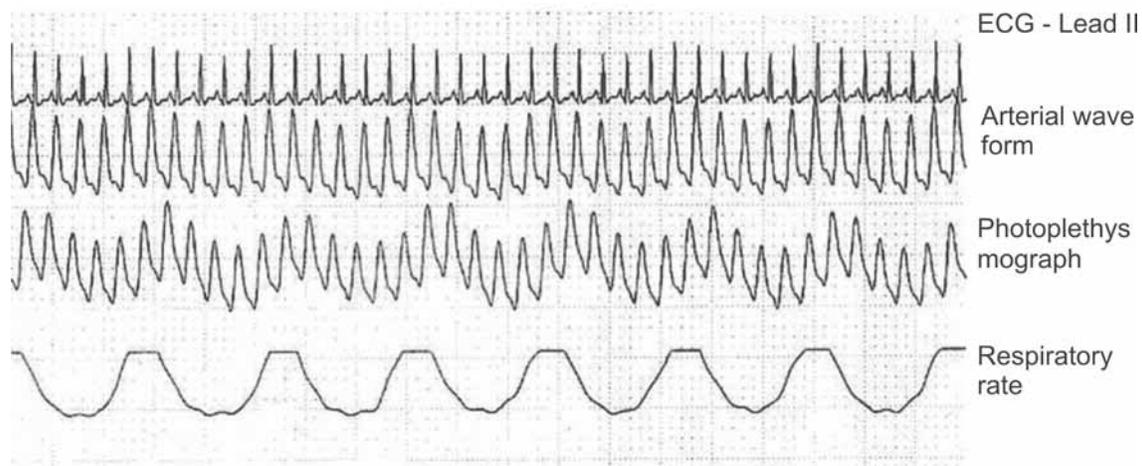
Solus-Biguenet et al<sup>6</sup> were the first to demonstrate that respiratory change in the plethysmographic waveforms and it was a useful method to predict fluid responsiveness. Using the Finapres, these authors demonstrated that pulse photoplethysmographic waveform (PPV final) predicted fluid responsiveness in patients undergoing major hepatic surgery.<sup>6</sup> Similarly, a series of 22 hypotensive patients showed that percentage change over a single respiratory cycle of pulse plethysmography [DELTA]PV<sub>PLT</sub> values lower than the threshold value of 15% poorly predicted volume responsiveness, whereas all [DELTA]PV<sub>PLT</sub> values above 15% were associated with a positive response to fluid challenge. Mandatory conditions to allow the use of heart-lung interaction indices are regular cardiac rhythm, tidal volume greater than 8 ml/kg and deep sedation of mechanically ventilated patients.<sup>7</sup> Thus, these results cannot be extrapolated to patients experiencing spontaneous breathing activity.

### New Developments

In 2005, Masimo Corp. announced the development of their 'Rainbow Technology' Rad-57 pulse oximeter. This device uses eight wavelengths of light to measure  $SpO_2$  as well as  $SpCO$  (pulse oximeter estimate of COHb%) and  $SpMet$  (pulse oximeter estimate of MetHb%). The handheld, battery-powered Rad-57 was later followed

**Table 70.2.1: Artifacts in pulse oximetry**

Factor	Effect
Carboxyhemoglobin (COHb)	Slight reduction of the assessment of SaO <sub>2</sub> by pulse oximetry (SpO <sub>2</sub> ) (i.e., overestimates fraction of Hb available for O <sub>2</sub> transport)
Methemoglobin (MetHb)	At high levels of MetHb, SpO <sub>2</sub> approaches 85%, independent of actual oxygen saturation (SaO <sub>2</sub> )
Sulfhemoglobin	Not reported (affects co-oximetry by producing a falsely high reading of MetHb)
Hemoglobin F	No significant effect
Hemoglobin H	No significant effect
Indigocarmine	Transient decrease
Indocyanine green	Transient decrease
Isosulfan blue (patent blue V)	No significant effect at low dose; prolonged reduction in SpO <sub>2</sub> at high dose
Methylene blue	Transient, marked decrease in SpO <sub>2</sub> , lasting up to several minutes; possible secondary effects due to effects on hemodynamics
Anemia	If SaO <sub>2</sub> normal: no effect; during hypoxemia, at Hb values less than 14.5 g/dL: progressive underestimation of actual SaO <sub>2</sub>
Polycythemia	No significant effect
Acrylic fingernails	No significant effect
Ambient light interference	Bright light, particularly if flicker frequency is close to a harmonic of light-emitting diode switching frequency, can falsely elevate SpO <sub>2</sub> reading.
Blood flow	Reduced amplitude of pulsations can hinder obtaining a reading or cause a falsely low reading.
Henna	Red henna: no effect; black henna: may block light sufficiently to preclude measurement
Jaundice	No effect. Multi-wavelength laboratory oximeters may register a falsely low SaO <sub>2</sub> and a falsely high COHb and MetHb.
Motion	Movement, especially shivering, may depress SpO <sub>2</sub> reading.
Nail polish	Slight decrease in SpO <sub>2</sub> reading, with greatest effect using blue nail polish, or no change
Sensor contact	"Optical shunting" of light from source to detector directly or by reflection from skin results in falsely low SpO <sub>2</sub> reading.
Tape	Transparent tape between sensor and skin has little effect. Falsely low SpO <sub>2</sub> has been reported when smeared adhesive is in the optical path.
Vasodilatation	Slight decrease
Venous pulsation (e.g., tricuspid insufficiency)	Artifactual decrease in SpO <sub>2</sub>



**Fig. 70.2.3:** Simultaneous recording of ECG, systemic arterial pressure, plethysmographic 'pulse' (PLETH) and respiration (transthoracic impedance) curves in a mechanically ventilated patient with large respiratory change in pulse plethysmography. Greater change reflects fluid responsiveness

by a bench-top version, the Radical-7. In March 2008, Masimo Corp. released another innovation in multiwavelength pulse oximetry: the noninvasive measurement of Hb total. This measurement can be done with same machine is now available in India.

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## 70.3 Non-Invasive Blood Pressure Measurement

Dhiren Gupta

Measurement of blood pressure should be routine in the emergency department. For more than 20 years, noninvasive blood pressure (NIBP) monitors have been widely used in operating rooms and critical care units to closely monitor blood pressure in patients of all ages. Despite the widespread use of automated blood pressure monitors, clinicians continue to debate over the accuracy and reliability of automated NIBP devices compared to other methods of blood pressure determination.

### Why Measure Arterial Blood Pressure?

**Organ blood flow = (arterial pressure – venous pressure)/resistance**

Regrettably, tissue perfusion (i.e., organ blood flow) cannot be directly measured in clinical practice. In the absence of a measurement of actual blood flow to individual organs, and assuming constant venous pressure and constant resistance, measurement of arterial blood pressure gives a reasonable estimate of the adequacy of tissue perfusion. However, physiology helps our limited capacity. Under normal circumstances, organ blood flow is strictly maintained within normal range by autoregulation, i.e. during wide changes of arterial blood pressure, blood flow remains constant through constriction or dilation of the afferent vessels. Unfortunately, in pathological conditions, (hypertension, trauma, sepsis, etc.) autoregulation can be significantly impaired and flow may become directly dependent on perfusion pressure. Most physicians currently use the maximal (systolic) and minimal

(diastolic) arterial pressure to assess cardiovascular status because these two pressures are easily measurable using a sphygmomanometer.

Studies have increased clinical interest in also analyzing other pressures, especially pulse pressure (PP) and mean arterial pressure (MAP). In this article we will focus on the non-invasive blood pressure measurement. Before discussing various techniques of blood pressure measurement we will describe the importance of various blood pressures.

### Practical Information from Various Blood Pressures

#### *Practical Information of Mean Arterial Pressure*

Autoregulation of the MAP is a key feature of the cardiovascular system. Acute decreases in MAP are counteracted by the sympathetically mediated tachycardia, increases in stroke volume (mediated via positive inotropic effect and venoconstriction) and arterial systemic vasoconstriction. In critically ill patients, especially those with sepsis or who are receiving sedative drugs, these compensatory mechanisms can be either impaired or overwhelmed.

The constancy of MAP from aorta to periphery large arteries explains why MAP is considered the driving pressure for perfusion of most vital organs.<sup>1</sup> As a result, when MAP falls below the lower limit of autoregulation, regional blood flow becomes linearly dependent on MAP. In some pathological settings, MAP overestimates the true perfusion pressure because of marked increases in extravascular pressure at the

outflow level in specific vascular areas (intracranial hypertension, abdominal compartment syndrome) or because of marked increases in systemic venous pressure (right heart failure). There is no universally accepted MAP threshold that provides assurance that blood flow is independent of arterial pressure in most vital organs. Indeed, the critical level of MAP probably differs among organs and depends on numerous factors, including age, previous history of hypertension, neurovegetative state and vasoactive therapy. Thus, there is no single 'magic value' for therapeutic MAP goals in shock states but increasing MAP higher than lowest normal value does not result in improved tissue oxygenation and regional perfusion.<sup>2,3</sup> For e.g., if lowest mean blood pressure of a 1 year old child is 50 mm Hg and while managing shock if you have achieved other end points of shock (pulse rate, capillary refill time, urine output) then do not try to raise MAP beyond this limit.

*Formula that Approximates the MAP for Age in both Males and Females<sup>4</sup>*

MAP (5th percentile at 50th height percentile)

$$= 1.5 \times \text{age in years} + 40$$

MAP (50th percentile at 50th height percentile)

$$= 1.5 \times \text{age in years} + 55 \text{ (Target in shock)}$$

*Practical Information of Systolic and Diastolic Arterial Pressures*

The various patterns of arterial pulse observed with ageing<sup>5</sup> and in chronic hypertensive states<sup>6</sup> may help us to understand the hemodynamic correlates of SAP and DAP. Increases in the tone of distal muscular arteries is the landmark of systolic/diastolic hypertension, with increased MAP and essentially unchanged pulse pressure because of congruent increases in SAP and DAP. This pattern is typically observed in the early stages of essential hypertension in young or middle-aged individuals. Alternatively, increased stiffness of proximal elastic arteries is the landmark of systolic hypertension, with increased PP, increased SAP and decreased DAP. Increased SAP contributes to left ventricular pressure overload and increased oxygen demand, whereas decreased DAP can potentially compromise coronary perfusion and oxygen supply. This pattern is typically observed at the late stages of essential hypertension in elderly individuals.<sup>7</sup>

In clinical practice, differences in mean DAP values are believed to reflect mainly changes in vascular tone, with lower DAP corresponding to decreased vascular tone. As discussed above, and for a given MAP,

increased arterial stiffness also tends to be associated with lower DAP (and higher SAP as well).

*Practical Information of Pulse Pressure*

It is widely accepted that peripheral PP at rest depends mainly on SV and arterial stiffness (1/compliance). In this regard, in older individuals increased arterial stiffness leads to increased PP, and this results in systolic hypertension associated with decreased DAP. On the other hand, in patients with cardiogenic or hypovolemic shock, decreased SV results in a lower PP. The paradoxical finding of a low PP in the elderly and in patients with hypertension or atherosclerosis strongly suggests that SV is markedly low because arterial stiffness is expected to be increased in these patients.

It is likely that the monitoring of short-term PP changes in critically ill patients may provide valuable, indirect information on concomitant SV changes. Change in pulse pressure can also guide inotropes and fluid management in shock. In this regard, increases in PP induced by passive leg raising are linearly related to concomitant SV changes in mechanically ventilated patients.

Despite the limitations of peripheral blood pressure measurement, maintaining a reasonable value of arterial pressure is associated with signs of adequate organ function in most critically ill patients. The following suggestions may enhance the effectiveness of arterial blood pressure monitoring.

- The mean arterial pressure (MAP) is the best physiological estimate of perfusion pressure and is less subject to measurement variability than the systolic pressure.
- A MAP  $\geq 70$  mm Hg (in adult or age  $\times 1.5 + 55$  for  $> 1$  year old) is a reasonable target for most patients. At times (chronic hypertension, cerebral edema, spinal cord ischemia, abdominal compartmental syndrome etc.), higher values are necessary.
- Optimal blood flow through vital organs is first achieved by maintaining an adequate circulating volume. An increase in blood pressure achieved using vasoconstrictor agents in hypovolemic patients does not provide adequate organ perfusion and can be deleterious.

### How to Measure Blood Pressure?

The basis of any physiological measurement is the biological signal, which is first sensed and transduced or converted from one form of energy to another. The signal is then conditioned, processed, and amplified. Subsequently, it is displayed, recorded, or transmitted

(in some ambulatory monitoring situations). Blood pressure sensors often detect mechanical signals, such as blood pressure waves; convert them into electric signals for further processing or transmission. They work on a variety of principles, for example, resistance, inductance, and capacitance. For accurate and reliable measurements a sensor should have good sensitivity, linearity, and stability. There are two methods for blood pressure measurement-Direct (intra-arterial) and indirect. In this article we will focus on non-invasive blood pressure measurement.

### Indirect Blood Pressure Measurement

Indirect measurement is often called noninvasive measurement because the body is not entered in the process. The upper arm, containing the brachial artery, is the most common site for indirect measurement because of its closeness to the heart and convenience of measurement, although many other sites may have been used, such as forearm or radial artery, finger, etc. Distal sites such as the wrist, although convenient to use, may give much higher systolic pressure than brachial or central sites as a result of the phenomena of impedance mismatch and reflective waves.<sup>8,9</sup> An occlusive cuff is normally placed over the upper arm and is inflated to a pressure greater than the systolic blood pressure. The cuff is then gradually deflated, while a detector system simultaneously employed determines the point at which the blood flow is restored to the limb. The detector system does not need to be a sophisticated electronic device. It may be as simple as manual palpation of the radial pulse. The most commonly used indirect methods are auscultation and oscillometry, each is described below. Automatic, noninvasive measurement has become a popular and, if applied to appropriate clinical situations, is an accurate method of determining BP. Advantages include (1) more time for staff to attend to other tasks; (2) timed repetition of BP measurements; (3) continuous display of the systolic pressure; and (4) a display of other several parameters (e.g., systolic, diastolic, and mean BP; pulse rate), depending on the machinery. Noninvasive machines use a detection system based on auscultatory, oscillometric, or Doppler principles. Automatic oscillometric devices determine BP by electronically determining the pulse amplitude. This method and Doppler are the most accurate of the indirect methods.

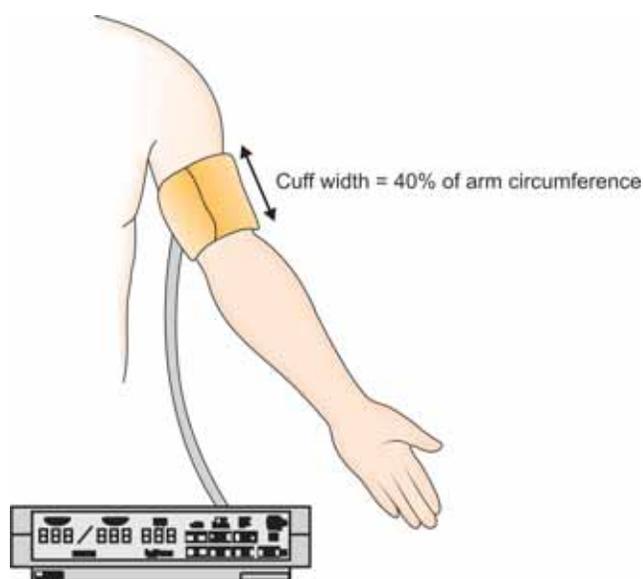
### Auscultatory Method

The auscultatory method most commonly employs a mercury column, an occlusive cuff, and a stethoscope.

**Table 70.3.1: Various cuff sizes**

Extremity circumference* (cm)	Cuff name
5-7.5	Newborn
7.5-13	Infant
13-20	Child
17-25	Small adult
24-32	Adult
32-42	Wide/large adult
42-50	Thigh

\*Determined as middle of upper arm of middle of upper thigh



**Fig. 70.3.1:** Cuff size-Using a cuff that is too small will lead to falsely high readings, and using a cuff that is too large will lead to falsely low readings. The cuff width selected should equal 40% of the arm circumference. Bladder width should be 80-100% of arm circumference

When measuring blood pressure in babies and children it is important to select the appropriate sized blood pressure cuff (Table 70.3.1). The cuff width selected should equal 40% of the arm circumference (Fig. 70.3.1). The stethoscope is placed over the blood vessel for auscultation of the Korotkoff sounds, which defines both SP and DP. The Korotkoff sounds are mainly generated by the pulse wave propagating through the brachial artery. The Korotkoff sounds consist of five distinct phases. The onset of Phase I Korotkoff sounds (first appearance of clear, repetitive, tapping sounds) signifies SP and the onset of Phase V Korotkoff sounds (sounds disappear completely) often defines DP. Observers may differ greatly in their interpretation of

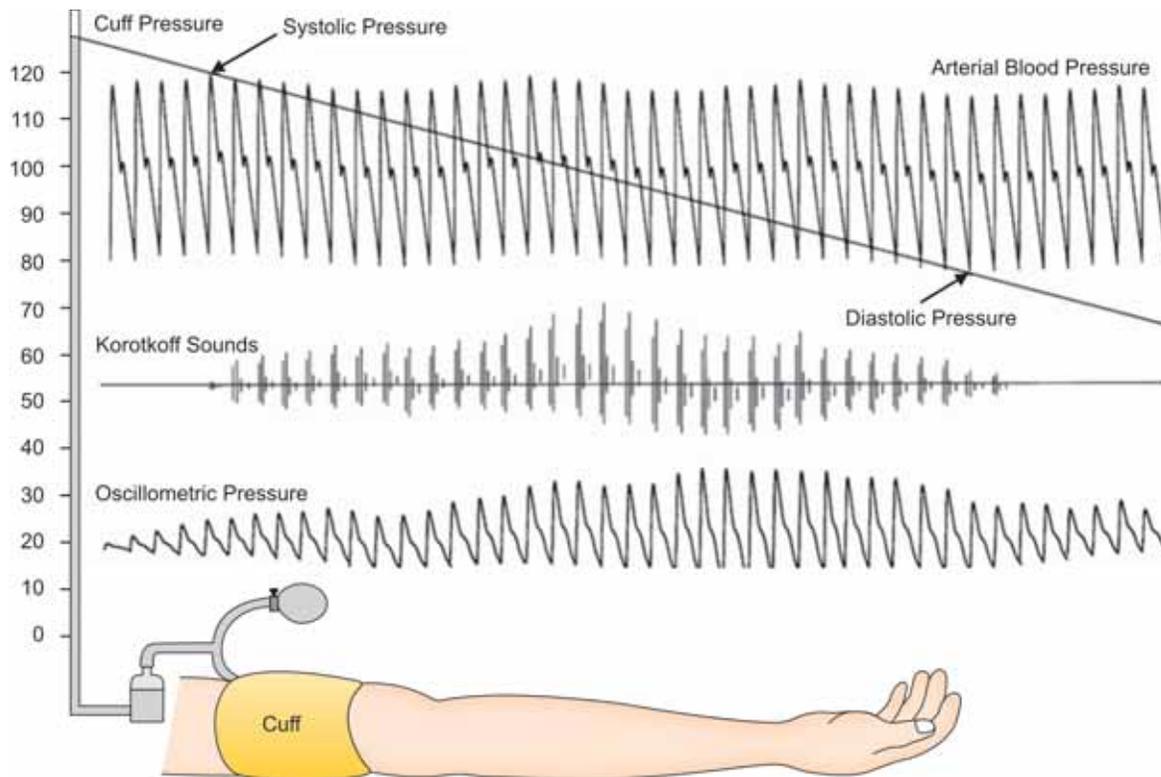


Fig. 70.3.2: Indirect blood pressure measurements: oscillometric measurement and auscultatory measurement

the Korotkoff sounds. Simple mechanical error can occur in the form of air leaks or obstruction in the cuff, coupling tubing, or Bourdon gage. This technology is improved by improvement in instrumentation include sensors using plethysmographic principles, pulse-wave velocity sensors, and audible as well as ultrasonic microphones. The readings by auscultation do not always correspond to those of intra-arterial pressure. The differences are more pronounced in certain special occasions such as shock.

### Oscillometric Method

In recent years, electronic pressure and pulse monitors based on oscillometry have become popular for their simplicity of use and reliability.<sup>10</sup> The principle of blood pressure measurement using the oscillometric technique is dependent on the transmission of intra-arterial pulsation to the occluding cuff surrounding the limb. An approach using this technique could start with a cuff placed around the upper arm and rapidly inflated to about 30 mm Hg above the systolic blood pressure, occluding blood flow in the brachial artery. The pressure in the cuff is measured by a sensor. The pressure is then gradually decreased, often in steps,

such as 5 to 8 mm Hg. The oscillometric signal is detected and processed at each step of pressure. The cuff pressure can also be deflated linearly in a similar fashion as the conventional auscultatory method.

Figure 70.3.2 illustrates the principle of oscillometric measurement along with auscultatory measurement. Arterial pressure oscillations are superimposed on the cuff pressure when the blood vessel is no longer fully occluded. Separation of the superimposed oscillations from the cuff pressure is accomplished by filters that extract the corresponding signals. Signal sampling is carried out at a rate determined by the pulse or heart rate.<sup>10</sup>

The oscillation amplitudes are most often used with an empirical algorithm to estimate SP and DP. Unlike the Korotkoff sounds, the pressure oscillations are detectable throughout the whole measurement, even at cuff pressures higher than SP or lower than DP. Since many oscillometric devices use empirically fixed algorithms, variance of measurement can be large across a wide range of blood pressures.<sup>11</sup> Significantly, however, MP is determined by the lowest cuff pressure of maximum oscillations.<sup>12</sup> and has been strongly supported by many clinical validations.

### Limitations

The shortcomings of noninvasive BP techniques are the same shortcomings of any cuff measurement technique, including patients with obese arms, uncooperative moving patients, and patients with very high or very low BP. Even with these limitations, automatic machines are more accurate, precise, and reliable than auscultation in patients with very low or very high BP, primarily because the sensing devices are more sensitive than the human ear. The cycle length of the inflation-deflation sequence of the older machines was exceedingly long and led to frequent failure. Newer machines have rectified this problem.

The most accurate method of measuring BP is with an intra-arterial catheter transduced to an electronic display. The ability to identify beat-to-beat variability, respiratory variation, and longer trends is unsurpassed by any other currently available technology. In addition, the placement of the arterial catheter enables frequent sampling of arterial blood without additional arterial punctures. Arterial line pressure monitoring is used increasingly in emergency departments, particularly because lack of ICU bed availability mandates longer stays in the emergency department for critically ill patients. The risk of arterial injury or thrombosis related to arterial line insertion is low but real and can result in vascular compromise. Traditional methods of noninvasive BP measurement are often inadequate in the following situations, and invasive monitoring should be considered.

1. Exceedingly high (>250 mm Hg systolic) or low (< 80 mm Hg systolic) BPs. Although the invasive method also is less accurate at these extremes than in the physiologic range, the error is significantly less.
2. Many clinicians believe that any patient receiving sodium nitroprusside should have continuous invasive monitoring because of rapid fluctuations in blood pressure, although this is unsupported in the literature.
3. In a patient who is rapidly going into shock, the best chance to insert an arterial line may be in the emergency department while the arterial pulse is still palpable, although this should not be allowed to delay transfer to a more appropriate location for definitive care.
4. Anatomic indications for invasive monitoring include patients who are critically ill and either have

no limb or no have suitable limb (e.g., too obese) to undertake conventional measurement.

5. Frequent arterial sampling is required. The requirement in such cases is for vascular access rather than the monitoring modality per se. Patients who are ill enough to require frequent arterial sampling usually benefit from continuous arterial BP monitoring.

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## 70.4 Intramuscular Injections

Daljit Singh, Puneet A Pooni

Although the predominant route of administration of drugs in ER is intravenous, circumstances may necessitate intramuscular (IM) injections. It must be borne in mind that the IM route should be avoided in seriously ill children with poor peripheral perfusion which results in erratic absorption.

The size of syringe and needle depends on the size of the child, amount of muscle tissue, volume of medication and its viscosity. For younger children 25-26 gauge needle 1.25-2.5 cm in length attached to a 1-2 ml syringe is usually appropriate.

The viscosity of medication or size of the older child may necessitate use of 23-25 gauge, 2.5 cm needle. The relationship of pain with length of needle is unclear. While some providers believe that a shorter needle causes less pain and discomfort, it was observed that infants at 16 weeks who received intramuscular injections with a 2.5 cm, 23 or 25 gauge needle experienced fewer local reactions (such as erythema, inflammation or tenderness) than those who were given the same injection with a 1.6 cm, 25 gauge needle.

### Sites of IM Injections

The choice of IM site depends on patient's age, drug volume and nature of drug. Absorption rates vary among different muscle areas. The selected site must have healthy muscle with no local discomfort or infection, good circulation and must not have major blood vessels and nerves in the proximity.

**Birth to 2 years:** Vastus lateralis on the anterolateral aspect of the middle one-third of thigh between greater trochanter and knee should be used.

**Older children:** Apart from vastus lateralis, the deltoid muscle below the acromian process and above the level of the armpit is acceptable. The ventrogluteal site is located in the triangle formed between anterior iliac spine, iliac crest and greater trochanter of the femur, and it is easily accessible in all positions. The site should not be used until the child has been walking in order to develop the muscle mass.

The dorsogluteal site at the upper outer quadrant of gluteal region is not recommended in children unless no other muscle are is available for IM injections, as it is dangerously close to the sciatic nerve and often has abundant subcutaneous tissue.

### Procedure

The IM route takes effect more quickly than subcutaneous (SC) and a larger volume of drug, up to 3 ml, can be administered into a muscle. The deltoid muscle, however, should receive no more than 2 ml. Meticulous attention should be directed towards the following aspects:

1. Check the label on the drug and the dosage. The medication should be at room temperature.
2. Wash your hands with soap and water.
3. Prepare the vial/ampoule for withdrawal of the drug, maintaining asepsis.
4. Assemble the disposable needle and syringe without touching the connecting area or the uncapped needle.
5. Withdraw the medication into the syringe. In case of vials, this is facilitated by draining air into the syringe to the required volume and pushing in into the vial held upside down.
6. If any large air spaces are noted, expel the air by tapping the syringe while needle is pointing upright and adjusting the plunger.
7. Have someone available to restrain the child as necessary. Clean the selected site with an alcohol swab. Use a circular motion moving outward from the site of the injection to a distance of about 5 cm in diameter. The antiseptic should be dry before needle is inserted to prevent carrying in of the solution.
8. Hold the syringe between thumb and fingers, stretch the skin over the injection site with the other hand and insert the needle in a dart-like manner at a 90-degree angle to the desired length. It helps to mask the pain stimulation by grasping the site before injecting. The plunger should not be depressed while needle is being inserted, as the solution thus injected may cause irritation to the tissues along the needle track.
9. Pull back the plunger to verify that a vein has not been entered. In the unlikely event of blood being withdrawn, remove the needle, apply pressure on the area with a gauze, and reinject at a different site.
10. If no blood returns, inject the medication at a slow and even rate. Faster injection produces high pressure pain in the muscle.

11. Withdraw the needle quickly and smoothly at the same angle, while applying counteraction with a dry gauze.
12. With gauze in place massage the area in a circular movement to distribute the medication, promote absorption and reduce pain.
13. Apply gentle pressure with dry sterile gauze in case of any bleeding.
14. Discard the syringe and needle in the appropriate container.
15. Observe the patient for 15 to 30 minutes for any adverse effects.

**Complications:** Failure to comply with the guidelines to choose a safe site may result in injury to the nerve leading to possible temporary paralysis and extreme pain. Administration errors may cause inadvertent IV injection or bone injury.

## 70.5 Intravenous Infusion

Daljit Singh, Puneet A Pooni

The intravenous route is commonly used in emergency room (ER) for infusion of fluids and administration of drugs. The choice of fluid, additives, volume and rate of infusion are determined according to the clinical requirements. Fluid overload and underhydration must be scrupulously avoided.

After setting up the IV line, the next step is to regulate the flow of fluid. The required rate in ml/h needs to be converted into drops per minute. A standard IV set is appropriate for administering large volume of fluids as in diarrhea with dehydration; occasionally more than one IV line is required. The drop rate (drops per minute) is calculated by the formula:

$$\text{Drop rate} = \frac{\text{Volume of solution (ml)} \times \text{Drop factor}}{\text{Time (min)}}$$

Drop factor (drops/ml) varies with the type of set and the viscosity of the fluid. For most crystalloid solutions, the drop factor for a standard IV set is 16 drops/ml. Infusion of 120 ml over 1 hour would come to  $120/60 \times 16 = 32$  drops per min. Drop rate can also be calculated by the formula:

$$\frac{\text{Drops/ml}}{60} \times \text{Amount to be infused/hour}$$

However, in many emergency room situations small accurate amounts may be required, and use of a microdrop chamber is necessary. A simple guideline using a microchamber is that number of drops per minute is the same as the ml volume to be infused in one hour as can be noted by placing the figure 60 drops/ml in the above formula.

### Precautions During Infusion

Maintenance of the IV access during infusion requires careful attention. To prevent infiltration of fluid,

immobilization of the limb is necessary using tape and splints, as flexion of the extremity at the site of venipuncture and excessive movements easily dislodge the needle tip from the thin veins. If the local area becomes edematous the infusion must be discontinued. If there is no edema but infusion has stopped, patency may be checked by noting return of blood flow through the needle on lowering the bottle below the injection site.

Blockage of the needle or tubing with blood may occur if the rate is too slow and may also be caused by kink in the tubing, or closed clamp or valve. A smaller vein or needle is more likely to get blocked. Flow rate may be increased by manipulation like increasing the height of the fluid column or restoring lost patency of the needle by flushing with a heparinized solution.

It is also important to protect the child from infection due to IV infusion by maintaining asepsis at the injection site and the connecting points especially during administration of drugs, and by changing the tubing every 48 hours.

When infusion pumps are used, the IV sites must be checked every 1/2 hourly for infiltration and the progress of infusion should be verified at least every hour to rule out mechanical or electrical failures.

### Intravenous Infusion of Drugs

Several types of intravenous drug delivery methods and systems are available that may or may not be accurate for delivering IV medication.

For intravenous drug therapy it is essential that not only the correct dose and volume is used but also that the desired concentration of the drug reaches the site where it can be most effective. The rate of drug delivery and absorption must be consistent. Depending upon the site selected for introduction into the intravenous system, there can be delay in the drug initially reaching

the child and a mistiming of peak and trough blood levels obtained. When IV set are changed, there may be some loss of drug with the discarded equipment which must be taken into consideration.

For continuous infusion of drugs in a small volume of fluid, e.g. inotropic agents, precision-control syringe infusion pump is very useful in the emergency room, although mechanical flow rate infusion pumps for controlled continuous infusion of fluids are generally

not used in this setting. The syringe is filled with fixed volume of fluid, say 50 ml, along with calculated dose of drug and is set at required rate in ml/hour, connected to the IV line through a 3-way connector. An infusion rate of 1 µg/kg/min is achieved by setting the pump at 1 ml/h and adding 'x' mg of drug in 50 ml fluid, where 'x' is 3 x wt (kg). Adjustment in the flow rate may be made by varying the ml/h infusion or amount of drug added.

## 70.6 Vascular Access

M Jayashree

Vascular access is an essential step in the management of nearly every hospitalized child, especially in an emergency situation like cardiopulmonary arrest, burns, prolonged life-threatening status epilepticus and shock due to trauma, dehydration or sepsis. There is no more exasperating situation than the inability to establish intravenous (IV) access in a critically ill child, yet this predicament often confronts physicians. Venous and arterial vascular access can be divided into several categories. Peripheral venous access is obtained by placing a short needle or cannula in a subcutaneous vein of an extremity, the head, neck or torso.<sup>1</sup> Central venous access is gained by inserting a long cannula either through a subcutaneous vein or directly into a deep vein and then advancing that cannula into the superior or inferior vena cava, the right atrium or the pulmonary artery.<sup>2</sup> Intraosseous access is achieved by introducing a metal trocar into the marrow cavity of a long bone, usually tibia.<sup>3</sup> In the neonate, access to the aorta or the right atrium can be obtained by cannulation of the umbilical vessels. Access to a vessel can be gained through percutaneous puncture, cut down or a combination of both.

The safest and most effective vascular access is obtained by carefully matching the child's size, therapeutic needs and length of required treatment with the most appropriate device and technique.

This article will be an overview of the various access routes, the device, insertion techniques their indications and contraindications.

### CANNULATION OF PERIPHERAL VEINS

Peripheral venous access is obtained by placing a short needle or cannula in a subcutaneous vein of an extremity or the head, neck or torso.<sup>1</sup> This type of vascular access is the commonest used in children and

associated with very few complications. This standard technique may however, fail in situations of cardiopulmonary arrest and shock, where in the small veins collapse, and cannulation becomes difficult.

### Devices

Types of venous cannulas used in infants and children are butterfly needles, over the needle catheters, and through the needle catheters.

**Butterflies:** Also known as scalp vein needles, these vary in size from 19 to 25 gauge; are useful for drawing blood and for a very short-term vascular access. Because motion can lead to vessel perforation, by the sharp tip of the needle, butterflies are not well suited for the extremities, and hence placement in a vein close to a flexor surface is contraindicated.

**Over the needle catheters:** These short cannulas are thin walled, semi flexible tubes, now the mainstay of every day vascular access and shown to be the first choice in any patient. Ranging in size from 14 to 26 gauge, they are suitable for both veins and arteries. Availability, versatility, low cost and limited endothelial irritation make these cannulas very popular. They are however, not indicated for long-term use.

### Sites for Peripheral Venous Cannulation

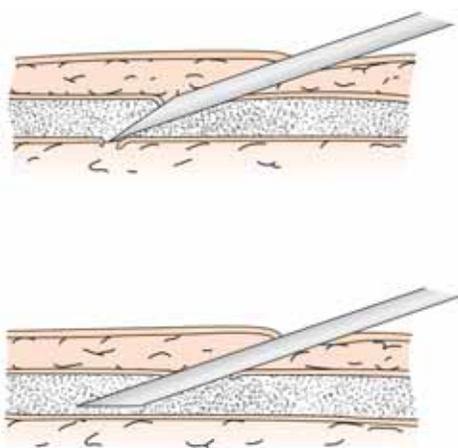
1. **Upper extremity:** The most commonly employed access site in children is the dorsum of the hand. The elbow offers reliable access through the basilic vein, but flexion often leads to catheter kinking and extravasation. Unless it is unavoidable, the dominant upper extremity should not be used for vascular access.
2. **Lower extremity:** Veins of the dorsal aspect of the foot tend to be more difficult to cannulate than those

on the hand. The saphenous vein at the level of the ankle is a remarkably constant traditional access site. Cannulas in the feet restrict mobility and are best restricted to use in infants.

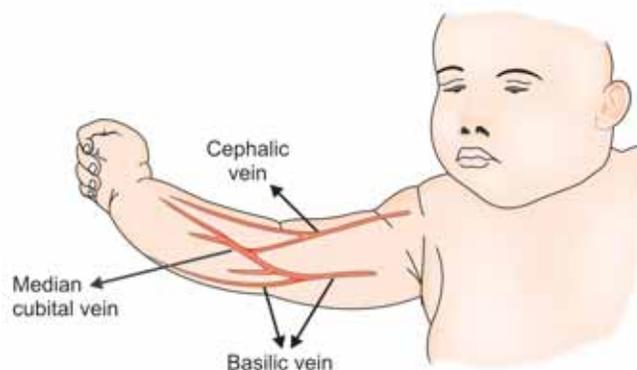
3. **Scalp:** The flat surfaces of either side of the head are reliable sources of vascular access in newborns and infants. The cosmetic drawback of head shaving as well as parents' perception of "needle in head" make this a less desirable access in children.

### Technique for Upper or Lower Extremity Peripheral Venous Cannulation Using an Over the Needle Catheter (Figs 70.6.1A and B)

- a. Universal precautions for asepsis should be followed (hand washing, cleansing of the area).
- b. Immobilize extremity, locate and stretch the vein.
- c. Apply tourniquet proximal to the vein.
- d. Flush the needle/catheter to be used, leaving some fluid in the lumen.
- e. Puncture the skin slightly distal and lateral to the site of the vein selected using an 18 or 20 gauge needle to facilitate entry of the catheter through the skin.
- f. Insert the cannula through the puncture site, bevel downwards and prick the vein until blood flows freely.
- g. Once it is sure that cannula is in the vein, advance the catheter over the needle into the vein, remove the needle.
- h. Remove tourniquet.
- i. Strap the catheter firmly in place.



**Fig. 70.6.1A:** Top, When the venipuncture is performed with the needle point bevel up, the needle point pierces the deep wall of the vessel before blood return is apparent. Bottom, with the needle point inserted bevel down, the point of the needle enters the mid-lumen of the tiny vein



**Fig. 70.6.1B:** Veins of the upper extremity

**Contraindications:** Peripheral lines should be avoided in an extremity that has significant burns, traumatic injury, or cutaneous infection. In a patient with neck or upper chest trauma, the ipsilateral arm should not be used as the integrity of the proximal veins cannot be assessed. Similarly in cases with massive abdominal trauma the lines should be started in the upper extremities rather than the lower extremities.

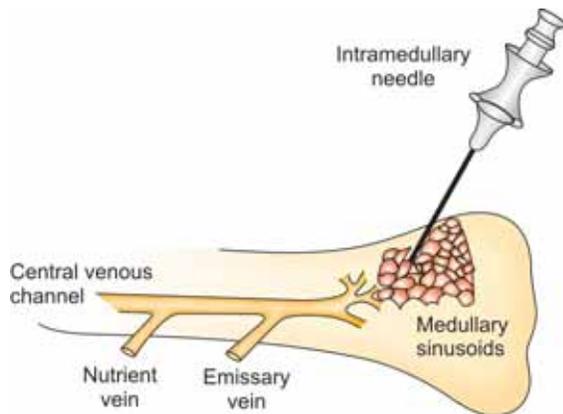
### Intraosseous Cannulation

Rapid intravenous (IV) catheterization is vital but difficult during pediatric resuscitations. As small peripheral vessels often collapse because of shock. Alternative approaches to emergent venous access such as central line placement or venous cut down take significant amount of time especially in young children.<sup>4,5</sup> The technique of intraosseous (IO) infusion offers hope for rapid vascular access in critically ill children.

**History:** This technique is not a new one and was originally described in 1922 by Drinker et al and Doan. There was widespread use of this technique in the 1940's and 1950's especially among pediatric patients. The advent of better IV technology relegated intraosseous infusion to relative obscurity until the 1980's. Recently there has been a renewed interest in pediatric literature suggesting the use of intraosseous infusion in situation where conventional IV access is difficult.<sup>3,6</sup>

IO needle placement is increasingly documented for emergent venous access in patient ages ranging from premature infants to adults.<sup>7-10</sup> IO placement was faster than peripheral venous access in a prospective study of dehydrated children randomized to either IO or peripheral venous access.<sup>11</sup>

**Physiology:** The medullary cavity of the marrow is composed of a spongy network of venous sinusoids



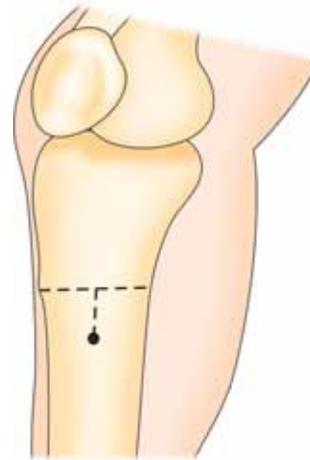
**Fig. 70.6.2:** The intramedullary venous system demonstrates position of intraosseous needle in the medullary sinusoids

that drain into a central venous canal. Blood then exits the venous canal by nutrient and emissary vein into the circulation (Fig. 70.6.2). Fluids or drugs injected into the medullary space rarely diffuse more than a few centimeters before entering the venous circulation. An anatomical advantage of the marrow space is that it functions as a rigid vein and does not collapse in presence of hypovolemia and peripheral circulatory shock. This method is, however, limited for younger children, because of the physiologic replacement of red marrow by less vascular yellow marrow at approximately 5-6 years of age.

**Method/Technique:** Several sites are available for intraosseous infusion. The proximal tibia is generally agreed to be the optimal site for infusion in children. A point is selected in the midline on the medial flat surface of the anterior tibia 1 to 3 cm below the tibial tuberosity (Fig. 70.6.3). The needle is directed at an angle of 60 to 90°, away from the growth plate to avoid inadvertent injury to this structure and is advanced with a boring or screwing motion. The distal tibia is also an excellent site, recently said to be superior to the proximal tibia because of ease and reliability of needle placement. The cortex and the overlying tissue are both thin. This site may be used in children and adults, whereas the proximal tibia is limited to children and infants.

Although used in the past, the sternum and ileum are considered less suitable sites for insertion. Insertion into the sternum can be dangerous, particularly during chest compression and there is a substantial risk of mediastinal puncture.

Entry into the marrow space is confirmed by noting a lack of resistance, needle standing upright without



**Fig. 70.6.3:** Insertion site in the proximal tibia. The tibial tuberosity and medial border of the tibia are palpated. Halfway between these points and 1 or 2 cm distally, the needle is inserted pointing away from the joint space, in a caudal direction

support, aspirating marrow and ease with which the fluids can be infused. The insertion site should be observed for extravasation. After conventional vascular access is established, the intraosseous infusion should be discontinued.

**Complications:** Complications due to intraosseous infusion are an infrequent occurrence. The most common complications are subcutaneous and subperiosteal infiltration of fluid or leakage from the puncture site.<sup>12</sup> Localized cellulitis and formation of subcutaneous abscesses have been reported to occur in 0.7 percent of cases.<sup>13</sup> Of more potential concern is the risk of osteomyelitis, which has been reported to the tune of 0.6 percent, especially in cases when the catheter remained *in situ* for prolonged period or in patients who had received hypertonic infusions.<sup>14</sup> No lasting negative effects have been seen on bone, the growth plate and marrow elements. The possibility of fat embolism also exists, but has not been documented since the marrow in children is relatively fat free.

Few deaths have been related to sternal puncture complicated by mediastinitis, hydrothorax or injury to heart and great vessels. These can be avoided if tibia or femur is used rather than sternum.<sup>15</sup>

#### Indications and Contraindications

This procedure should be limited to emergencies in which intravenous access cannot be obtained or in

which the time required to establish IV access may significantly alter the chances of survival. Cardiac arrest is the most common indication; others include shock, extensive burns and major trauma. Blood products, fluid and a wide variety of pharmacologic agents have been administered through the marrow cavity. Before injection, hypertonic and alkaline solutions should be diluted. Drugs should be given in the same dose as with intravenous route; fluids are given at the same rate.

There are a few absolute contraindications to the use of intraosseous infusion. These include the presence of osteogenesis imperfecta or osteopetrosis and an ipsilateral fractured extremity because of risk of extravasations. The risk of infectious complication is increased when the needle is introduced through an area affected by cellulitis or an infected burn.

### Cannulation of Central Veins

Central venous cannulation enables delivery of the infusate directly into the central circulation and delivery of medication at or near the site of action. Central venous cannulation allows secure IV access in critically ill children who may require large-volume fluid infusions, and essential for the infusion of vasoactive drugs such as epinephrine and norepinephrine. A

central venous catheter is not only essential for monitoring CVP, which is an indirect measurement of cardiac preload, but also provides access for blood sampling for measurement of mixed venous saturation (SvO<sub>2</sub>). The monitoring of trends in mixed venous saturation enables trending of cardiac output in the absence of other continuous tissue cardiac output devices. They are also placed in children receiving chemotherapy, parenteral nutrition and prolonged antibiotic therapy. Many factors should be considered before placement of a central venous catheter like purpose of the catheter, length of therapy and age and size of patient. The indications and complications of different sites central venous catheters are presented in Table 70.6.1.

#### Sites for Central Venous Cannulation

1. **Subclavian vein:** The subclavian vein continues to be the preferred site for central vascular access in both adults and children. The feasibility and relative safety of this route have been extensively demonstrated even in the smallest of children.<sup>2,16</sup> The principal drawbacks to this route are the need for immobilization during insertion and its complications like pneumothorax, hemothorax, infection, thrombosis and cardiac tamponade.

**Table 70.6.1: Indications, contraindications and complications of venous catheters**

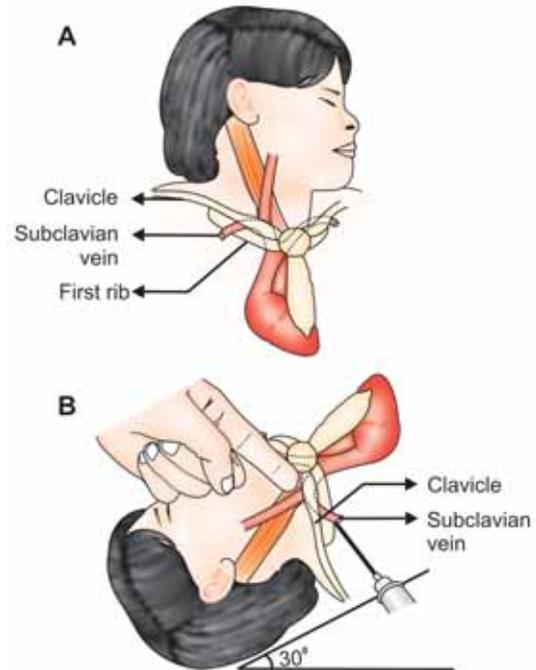
Site	Indication	Contraindication	Complication
Basilic	Drug and fluid Thrombophlebitis, cellulitis administration	Poor site for long-term monitoring Local musculoskeletal trauma	
Femoral vein	Administration of large volume Preferred site for Swan- Ganz catheter insertion in young children Drug administration	None	Retroperitoneal hemorrhage Laceration of vessel Inferior vena cava thrombus Infection
Internal jugular vein	Administration of large fluid volumes Long-term monitoring or pacing Temporary pacemaker placement	CPR Coagulopathies Cervical spine injury	Pneumothorax Hemothorax Carotid artery puncture Nerve injury Horner's syndrome Air embolism
Subclavian vein	Administration of large fluid volumes Long-term monitoring Parenteral nutrition	Chest wall deformity scoliosis PEEP Severe agitation	Pneumothorax Hemothorax Subclavian artery puncture Air embolism Brachial plexus injury Sepsis

2. **Jugular vein:** This is an alternative to the above mentioned route. However, the complication rates are higher and the catheter is more difficult to secure. External jugular vein is visible and superficial but the disadvantage of compromise of airway during the process of insertion makes it a less popular route. Internal jugular vein on the other hand is more difficult to cannulate and carries a high-risk of bleeding and other complications.<sup>17</sup>
3. **Femoral vein:** Catheterization of the femoral vein as well as femoral artery is employed successfully in the acute care setting, particularly in the immobile child. This route is not desirable outside the intensive care unit and for long-term access in a mobile patient.

### Technique for Central Venous Access (Subclavian line) Seldinger Technique

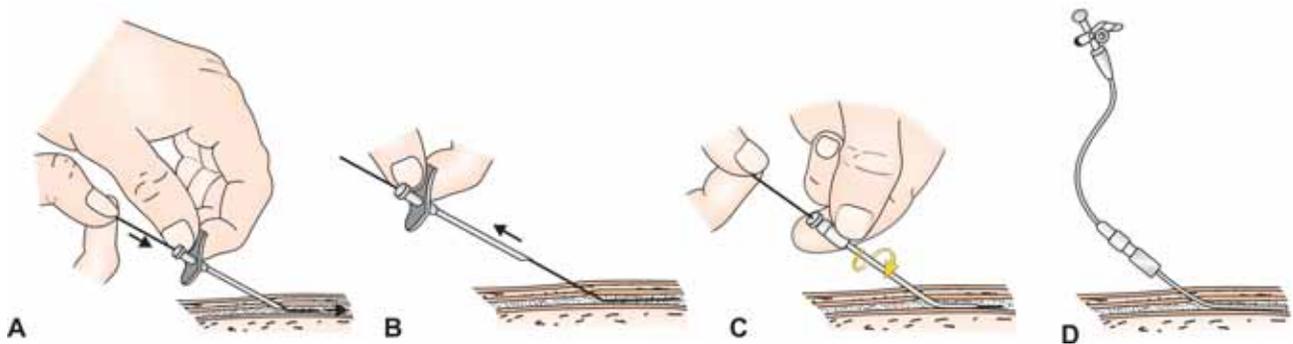
The Seldinger technique has withstood the test of time as the preferred approach to all central venous catheterizations. It basically involves the percutaneous placement of a catheter over a guide wire. ECG monitoring is essential during central line placement because of the risk of inducing dysrhythmias when wires or catheters enter the heart.

- Infraclavicular subclavian vein cannulation is the preferred method for central vascular access in infants and children (Figs 70.6.4A and B and 70.6.5A to D).
- Universal precautions of asepsis should be followed.
  - Hyperextend the patient's neck to open the costoclavicular angles.



**Figs 70.6.4A and B:** Subclavian vein. (A) Anatomy; (B) Technique

- Put the child in 30° head down (Trendelenburg position) and also turn away the head from the side to be punctured. The right side is preferred.
- Identify the junction of the middle and medial thirds of the clavicle.
- Anesthetize the skin with 1 percent lignocaine.



**Figs 70.6.5A to D:** Modified Seldinger technique for catheter placement. The needle is inserted into the target vessel, and the flexible end of the guidewire is passed freely into the vessel (A). The needle is then removed, leaving the guidewire in place (B). The catheter is advanced with a twisting motion into the vessel (C). Finally, the wire is removed and the catheter connected to an appropriate flow or monitoring device (D). Reproduced from Schwartz AJ, Cote CJ, Jobes DR, Ellison N. Scientific Exhibit. Central venous catheterization in pediatrics

- f. Flush the needle catheter and syringe with sterile saline.
- g. After locating landmarks specific to the proposed site of cannulation, prick a small hole in the skin with an 18 gauge needle.
- h. Then use a thin needle (18 gauge) and introduce through the skin prick, advancing towards a fingertip placed in the suprasternal notch. Simultaneously apply negative pressure to the syringe attached to the needle. Once free flow of blood is noticed, disconnect the syringe and insert an appropriate sized flexible guide wire through the needle into the vessel.
- i. Once the guide wire passes beyond the tip of the needle, remove the needle, simultaneously advancing the guide wire to the junction of superior vena cava and right atrium.
- j. After the needle is pulled entirely from the wire, a dilator is threaded over the guide wire through the skin, into the vessel and then removed.
- k. Then an appropriate sized catheter is advanced over the wire into the vessel up to the junction of superior vena cava and right atrium.
- l. The guide wire is then removed and the catheter is aspirated and flushed to ensure patency.
- m. The position of the catheter is checked radiographically. The catheter is then sutured to the skin.
- n. Strap with sterile dressing.

### Arterial Access

Arterial blood sampling is necessary in the evaluation and management of critically ill children. Repeated access to arterial blood is best accomplished by catheterization of an artery that can enable both continuous monitoring of blood pressure and blood sampling in a critically ill child.

While cannulating an artery, sufficient collateral blood should flow to the distal tissues perfused by the vessel to allow these tissues to remain viable should the catheter become thrombosed.

Vasospasm and thrombosis are the principal causes of arterial catheter failure. The addition of heparin (1 U/mL) and papaverine (a smooth muscle relaxant; 30 mg/250 mL) to the catheter infusion solution (0.9% or 0.45% NaCl) decreases the incidence of catheter failure.<sup>18</sup> If arterial cannulation leads to thrombosis and early signs of circulatory compromise to an extremity, current guidelines recommend immediate catheter removal and systemic heparinization with unfractionated heparin.<sup>18</sup> Approximately 70% of catheter-related arterial thromboses will resolve with these measures. However, thrombolytic therapy with tissue plasminogen activator may be added, if perfusion does not

improve in 24 hours. If all medical management fails, balloon thrombectomy via an arteriotomy can be employed to prevent limb loss.

**Complications:** The most serious complication of arterial puncture is permanent damage to the artery interrupting the arterial supply to the concerned distal extremity. Localized or generalized infection, air or particulate embolization, tissue necrosis, ischemia and growth failure of the affected limb are some of the other complications seen with arterial lines.<sup>19</sup> With the development of modern transcatheter monitoring techniques, the need for direct arterial access in children is decreasing.

### Indications for an Arterial Line

These includes: (i) frequent monitoring of blood gases, (ii) continuous display of systemic arterial blood pressure, and (iii) as a withdrawal site for exchange transfusion.

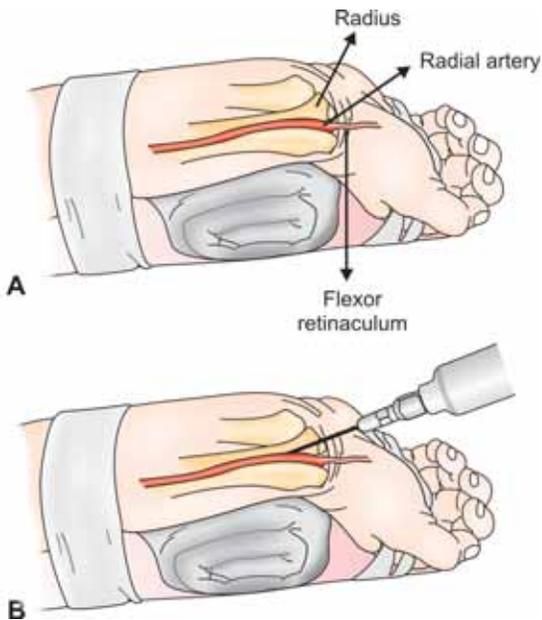
### Sites for Arterial Access

The radial artery is the preferred site for both percutaneous and cut down cannulation in the upper extremities.<sup>20</sup> Similarly in the lower extremities the dorsalis pedis, the posterior tibial and the femoral artery are suitable for arterial cannulation. The insertion of long catheters in the still patent umbilical vessels has been one of the mainstays of neonatal monitoring. Though axillary artery cannulation in children has a reduced risk of ischemia due to good collateral supply, it carries a risk of cerebral embolism due to flushing close to the aortic arch and a potential risk of brachial plexus injury. Femoral catheters carry a risk of vascular problems or ischemia of the leg, as well as concern regarding fecal contamination and infection. Catheterization of the femoral vein and artery in the same leg may increase the risk of limb ischemia, especially in low-flow states or when potent vasoconstrictors are used.

Temporal arteries should not be cannulated because of the possibility of embolization to the central nervous system.

### Technique

The main source of blood flow for the fingers is the superficial palmar arch. In most (88%) people this arch is predominantly supplied by the ulnar artery. Approximately 12 percent of normal adult patients demonstrate radial artery dominant palmar arch flow. Collateral circulation of the hand may be evaluated using modified Allen's test or by Doppler flow method. The



**Figs 70.6.6A and B:** Radial artery  
(A) anatomy and (B) cannulation

hand circulation should be closely monitored following radial artery cannulation. If any evidence of hand ischemia is observed, the catheter should be removed immediately.

#### *Steps of Arterial Cannulation (Figs 70.6.6A and B)*

Universal aseptic precautions should be taken as for any cannulation.

1. Dorsiflex the hand at the wrist to 45°. Maintain dorsiflexion with a roll of gauze placed behind the wrist.
2. Locate the radial pulse.
3. Make a skin break using the tip of a 20 gauge needle.
4. Puncture the anterior wall of the artery with the cannula. Advance the catheter slowly until blood appears in the needle. Lower the needle carefully to a 10° angle. Advance the catheter slowly over the needle into the lumen of the artery and remove the needle gently.
5. Securely tape the catheter in place.
6. Use 1-5 U/ml of heparinized saline to maintain the patency of the catheter.
7. Label the arterial line to prevent administration of drugs through the catheter.

#### *Indications for Removal of an Arterial Catheter*

1. The patient is stable and no longer requires frequent blood sampling or continuous arterial blood pressure monitoring.
2. The catheter is blocked.

3. Signs of infection are present at the catheter site.
4. Signs of vascular compromise are present in the area distal to the catheter.

#### **FACTORS THAT INCREASE THE RISK OF ARTERIAL CATHETER THROMBOSIS**

- Larger catheter-to-vessel ratio.
- Prolonged cannulation.
- Multiple cannulation attempts.
- Presence of peripheral vascular disease.
- Venous and arterial femoral catheterization in single extremity.
- Younger age.
- Thrombogenic conditions.

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## 70.7 Venous Cut Down

Anil Sachdev

Venous access is essential in the management of pediatric patients. Though venous cut down has become less frequent in the present era because of availability of a variety of devices which can be inserted without a cut down, it is a procedure which should be known to the personnel dealing with pediatric emergencies.

### Access Sites

The usual access sites are:

1. Long saphenous vein at ankle.
2. Median cephalic vein at elbow.
3. Basilic vein at elbow.
4. External jugular vein.

### Procedure

The procedure is being described for the cut down of long saphenous vein. After checking the equipment (Table 70.7.1) and localization of the vein (superior and anterior to the medial malleolus), the part is cleaned and draped. The local site is infiltrated with lidocaine. One cm incision is made at the upper border of medial malleolus extending from front to backwards. After dissecting the superficial planes, the vein is separated from the surrounding tissue by blunt dissection. If the cut down is done at the upper end of the thigh for saphenous vein, then the nerve is to be separated from the vein, the vein is muscular, round and pink while the nerve is flat and string like. After identifying the vein, two stay sutures are taken surrounding the vein with silk, one above and the other one below the site for puncture and the suture is not tied over the vein but the ends of the sutures are held with artery forceps. If a cannula is to be inserted, it is inserted like any other peripheral cannula after stretching the lower stay suture.

**Table 70.7.1: The equipment list for cut down**

- Surgical cap and mask
- Sterile gloves
- Protective eyewear
- Povidone-iodine solution
- Lidocaine without epinephrine
- Sterile drapes
- Needles
- Syringes
- Bandages tape
- Surgical blade
- Artery forceps
- Needle holder
- Plain forceps
- Suture material-silk
- Catheter for insertion

If a thicker catheter is passed, a small V shaped nick is made in the vein and the catheter is inserted directly under vision. Connecting to an IV infusion checks flow through the catheter. The proximal suture is tied over the catheter and the distal suture is tied if the vein has been cut. It is optional to tie it in cases where an angiocath has been inserted in the vein. Then the catheter is stitched to the skin and the wound is closed by interrupted sutures after securing proper hemostasis. The wound is then covered by sterile dressing.

### Complications

The possible complications of the procedure include:

1. Hemorrhage.
2. Complete cut through the vein.
3. Accidental arterial puncture.
4. Extravasation.
5. Infection.

## 70.8 Lumbar Puncture

Varinder Singh, Shishir Bhatnagar

Lumbar puncture (LP) is a very common procedure done in pediatric emergency as well as other inpatient services. The procedure is done to collect the cerebrospinal fluid for various pediatric diseases. The common indications are for the diagnosis and confirmation of possible etiology of meningitis, for supportive evidence in encephalitis, for diagnosis of sub-arachnoid hemorrhages (for example in hemorrhagic disease of newborn), myelopathies with specific CSF changes (for example Guillain-Barre syndrome-albuminocytological dissociation), and to look for meningeal involvement in patients with acute leukemias. It is also used for intrathecal administration of drugs, for example, specific immunoglobulin in cases of tetanus, chemotherapeutic agents in patients of acute leukemia, etc.

### Technique

The LP is performed with a 21G or 22G, 1 1/2 inch long ordinary disposable needle in children. Disposable LP needles especially meant for the purpose can also be used, particularly in adolescent or obese children where in the length of the standard disposable needle may not be adequate. The lumbar tap or puncture can be done with patient in sitting or lying position. The patient is put in lateral decubitus position, with the knees drawn up against the abdomen and head flexed. The sitting position is preferred in very small children where flexion of the thoracic spine may lead to apnea causing sudden death. The back is arched dorsally with maximal flexion of the spine to provide maximum width of intervertebral space. The LP is done through the space between third and fourth lumbar vertebra or fourth and fifth lumbar

vertebra. The line joining the iliac crests identifies the space between third and fourth lumbar vertebra as it intersects at the aforesaid space. The patient is positioned as above. A large area of the back starting from below the ribcage till the sacrum and till the lateral aspects of the flanks is cleaned, using chlorhexidine (Savlon), 10 percent povidone iodine and 70 percent alcohol in that order. The cleaning is started from above downwards and from center outwards. The area is draped with sterile towels and drapes. It may be prudent to use the drapes conservatively among infants and younger children so as to be able to monitor the infant during the procedure. The correct level is checked by palpating through the drape without contaminating the gloves. The needle (with stylet if a LP needle is used) is introduced in midline into the selected space with the bevel of the needle pointing upwards and 10°-15° cephalad. As the needle passes through the dura, a sudden loss of resistance is felt. The needle is advanced slightly more and the stylet if present is removed. The CSF usually immediately starts trickling. If the CSF fails to come out then the needle is slightly rotated. If the CSF still fails to come out then remove the needle and reintroduce in the same space or a space above or below the selected level. About 1-2 ml of CSF is collected in three different vials for biochemical, culture-sensitivity and cytological examination. In case of therapeutic LP equal volume of CSF is replaced by the drug to be injected. The needle is taken out quickly and the site is sealed with tincture benzoin. The patient is kept in bed for few hours in head low position.

The procedure may not be done if there is frank papilledema or severe bleeding tendency.

## 70.9 Abdominal Paracentesis

Varinder Singh, Shishir Bhatnagar

Abdominal paracentesis or ascitic tap is the puncture of the abdominal wall with a needle for aspiration of peritoneal cavity fluid. It is commonly performed to confirm etiology of ascites or to relieve respiratory embarrassment due to tense ascites. Any long sterile needle may be adequate for this. The puncture is made on the umbilico-iliospinal line in right or left lumbar fossa, lateral to the lateral border of the rectus muscle

when the patient is lying supine or if the patient is in semi Fowler or cardiac position, place the needle midway between the umbilicus and pubis. It is always prudent to clean and sterilize a wider area around the puncture site with standard technique. The patient may be sedated prior to paracentesis. A wide bore (18-20G) needle is inserted attached to a syringe at the desired site horizontally into the abdominal wall and then the

direction is changed to put needle into the abdominal cavity through a zig-zag tract. A continuous negative pressure draws the fluid into the catheter or syringe, moment the abdominal cavity is reached. If upon entering the cavity, air is drawn then withdraw the needle immediately. Repeat the procedure with sterile equipment till free fluid comes out. The required amount of fluid is drawn and the needle is removed. The puncture site is sealed with tincture benzoin.

While performing the tap for therapeutic measures, one should never remove a large amount of fluid too rapidly because hypovolemia and hypotension may occur due to rapid fluid shifts. Also puncture around scars from previous surgeries should be avoided as there may be localized bowel adhesion in these areas increasing the chances of entering a viscus.

## 70.10 Pericardiocentesis

Anil Sachdev

Pericardial space is potential space in which a small amount of fluid is present normally. However, in certain conditions, the amount increases and leads to pericardial effusion or get filled with air especially in children on mechanical ventilation (Fig. 70.10.1). Large collection of fluid or air in the pericardial space may lead to tamponade. Pericardiocentesis is the technique of aspiration of fluid or air from the pericardial space. It is either done therapeutically as a life saving measure in cases of cardiac tamponade in emergency especially in trauma patients or post cardiac surgery cases or as a diagnostic procedure in cases of pericardial effusion (mainly to differentiate between tuberculous and pyogenic etiologies).

### Procedure

Pericardiocentesis is a procedure fraught with high-risk but when done by an expert in controlled settings, it is a life-saving measure. It is ideally carried out in the

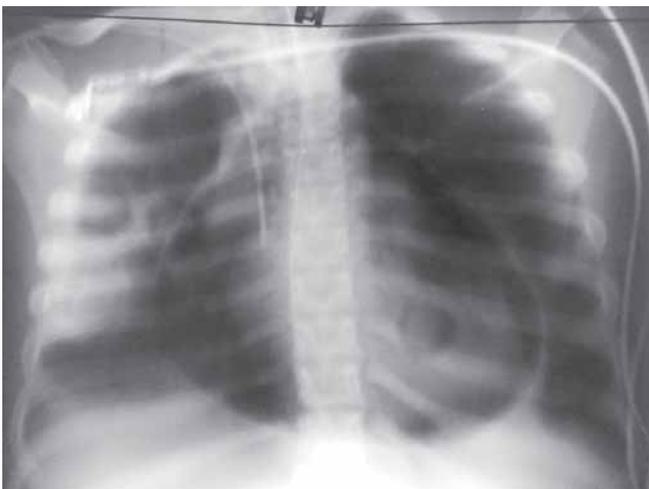


Fig. 70.10.1: Pneumopericardium

ICU setting or in the operating room, but can be performed anywhere in case of tamponade. After taking a proper consent and securing an intravenous line, the patient is given sedation (best omitted in emergency tapping). The patient is positioned with a 45-60° anti-Trendelenburgh tilt of the bed or in supine position. The patient is attached to multiparameter monitor for continuous monitoring of ECG, SpO<sub>2</sub>, heart rate, blood pressure and ETCO<sub>2</sub> if patient is intubated. The airway management and resuscitation equipment including defibrillator should be immediately available. Pericardiocentesis should be performed under real-time echocardiographic guidance. If this modality is not available, prior echocardiographic imaging should be done to localize and size assessment of the fluid. In life saving situation, procedure should be completed even in the absence of bedside echocardiography. Some operators prefer an ECG lead attached to aspirating needle to detect epicardial contact. If the needle touches the epicardium, ST segment elevation becomes evident on the ECG monitor. Taking complete aseptic precautions, the part is painted and draped. Xylocaine is infiltrated at the site of puncture. The space can be approached between the left costal margin and xiphoid, near cardiac apex, 5th or 6th intercostal space at left sternal margin or 4th intercostal space at right sternal margin (Fig. 70.10.2). The equipment requirement is summarized in Table 70.10.1.

The aspiration needle is attached to a 20-30 cc syringe with a three way and the needle is advanced through the skin at an angle of 45° to skin and directed towards the left nipple or the tip of scapula. The needle is advanced while maintaining negative pressure with syringe till the time fluid is obtained. The contact with ventricular wall is indicated by ECG changes like ST segment changes and T wave inversion, QRS widening or premature ventricular contraction. If such changes



**Fig. 70.10.2:** Positioning of the needle for bedside pericardiocentesis in PICU (For color version see plate 5)

occur, operator should withdraw needle little. If ECG does not revert to normal, needle should be withdrawn completely. If pericardiocentesis is being performed for tamponade, the fluid withdrawal is associated with relief of symptoms, decrease in CVP and increase in intra-arterial blood pressure. If there is blood in the pericardial tap, a rough difference about the source of the blood can be made by the fact that pericardial blood does not clot while the blood from the ventricle clots. But this is not universally accepted. Also the hematocrit of the aspirated fluid can be compared with patient's to differentiate. If the amount of fluid is large, a small catheter may be left in the pericardial space using Seldinger's technique to drain recurrent effusions or bleeding. The position of the catheter is confirmed by

**Table 70.10.1: Equipment requirement for pericardiocentesis**

1. Surgical cap and mask
2. Sterile gloves
3. Protective eyewear
4. Povidone-iodine solution
5. Lidocaine without epinephrine
6. Sterile drapes
7. Needles  
20 G, Infant-2.5 cm, Child-3-5 cm, 18-20 G 7.5 cm Adolescent
- Over-the-needle IV catheter
- Over-the-guide wire single lumen 18-20G central line, Pig tail catheter (For continues drainage)
8. Syringes
9. Spinal needle
10. Sterile ECG lead with alligator clip
11. ECG machine
12. Laboratory tube
13. Emergency equipment ready

chest roentgenogram. The collected fluid is sent for relevant investigations.

### Risk and Complications

1. Laceration of ventricular epicardium or myocardium or coronary vessels. Patient with previous cardiac surgery has higher chances of injury.
2. Lethal arrhythmias like ventricular fibrillation or tachycardia.
3. Pleural or intra-abdominal laceration causing pneumothorax, pneumoperitoneum.
4. Rupture of diaphragm.
5. Esophageal or bowel perforation causing mediastinitis, or peritonitis.
6. Local infection.

## 70.11 Thoracocentesis/Pleural Tap

Varinder Singh, Shishir Bhatnagar

Pleural tap is another common bedside procedure done either to confirm the etiology of pleural effusion, or to relieve cardiorespiratory embarrassment due to a massive collection of fluid in the pleural cavity. The tap is performed in 7th-9th intercostal spaces in scapular or posterior axillary line, on the affected side. Select the interspace to be tapped on the basis of the dullness to percussion and the level of effusion on the erect chest X-ray. The tap is performed one interspace below the spot where tactile fremitus is lost and

percussion becomes significantly dull. The space is approached from superior border of the rib to avoid damage to the neurovascular bundle that lies in the lower margin of the rib in a groove. Ideally the patient should be sitting on the side of the bed or on a stool, leaning forwards resting hands on a table in front of him, and the assistant in front to support the patient. If the patient is too sick and unable to assume this position, the procedure may performed with the patient lying laterally on the side of the pleural

effusion with his back near the edge of the bed or else the head of the bed can be maximally elevated.

The site of the tap is identified and marked. The part is cleaned and draped as for any surgical procedure. It is vital to anesthetize the skin, periosteum and the parietal pleura with 1-2 percent xylocaine. A wide bore needle or 19G intravenous catheter is attached to a 3-way stopcock and syringe. The needle is pushed directly into the desired interspace above superior edge of the rib steadily until a pop is felt upon entering the

pleural space. The needle is advanced a little further and stylet removed. If air bubbles are obtained on attempt to aspirate, withdraw the needle slowly under constant aspiration as the pleural space may have been passed through without detection during insertion. If no fluid is still obtained then a space above or below the puncture site is tried. Minimal fluid sometimes may only be aspirated under sonographic guidance. At the end of the procedure the needle or catheter is removed and the puncture site sealed with tincture benzoin.

## 70.12 Tube Thoracotomy and Needle Decompression

Varinder Singh, Shishir Bhatnagar

This is one of the common minor surgical procedures apart from venous cut down which requires to be done in any pediatric emergency. The common indications for tube thoracotomy or “chest tube placement” are pneumothorax, pyo-pneumothorax, empyema thoracis and hemothorax. The best site for tube insertion depends on the localization of the fluid and presence of air. In case of pneumothorax, the preferred site is the second intercostal space, anteriorly in the mid clavicular line. For empyema, the chest tube is preferably placed in the third to fifth intercostal space in the mid-axillary line, avoiding breast tissue. The child is positioned supine or with the affected side up. After cleaning with savlon povidone iodine and 70 percent alcohol, and draping, the puncture site is anesthetized with 1-2 percent xylocaine. A 0.5-1.0 cm incision is made directly over the desired interspace. A small curved hemostat is inserted to bluntly dissect a tract over the superior margin of the lower rib forming the space, through the intercostal muscles and into the pleural cavity. In older children, a trocar and cannula can be used. There are various types of chest tubes available. Commonly used are the red rubber Malecot catheter or the Disposable Portex.<sup>TM</sup> Chest drain which has several holes at the distal end. If a Malecot tube is being used then a clamp is placed 0.5-1 cm from tip of the appropriately sized catheter and the two are passed through the previously punctured space into pleural cavity. The tube is angled anteriorly and superiorly and the catheter is inserted into the thoracic cavity. The other end of the catheter is kept clamped to avoid any sucking in of the air. After placement, the Malecot may be pulled out gently till some resistance is felt due to the bulb abutting the thoracic wall. The tube is then secured to the chest wall with sutures. The tube is attached to an underwater seal and the clamp removed. In a well placed catheter, the

water column moves freely in the tube with each inspiration. The under water seal bottle or bag must always be kept below the level of the chest of the patient in order to prevent any retrograde flow.

The procedure is usually followed by check X-ray after few hours to assess the placement of tube and also to look for any early benefits of the procedure. In case a Portex tube is being used then ensure that all the holes at the inserted end are in the pleural cavity as any drainage hole left in the thoracic wall or outside can cause subcutaneous emphysema and loss of the water seal. This means that many infants or small children may need to have larger lengths of the tube placed inside to prevent leakage. This can affect lung expansion or cause increased pain.

Often in cases of tension pneumothorax, when the child is gasping or very hypoxic an immediate intervention may be required which may preclude arranging appropriate tube. In such a situation an emergency needle decompression of the chest may be done. An ordinary sterile disposable needle or aspiration needle is tightly attached to an intravenous tubing. The opposite end of the intravenous tube is placed under saline in a sterile bottle. The patient is usually sick and lying supine. In this position, the air commonly rises up to collect around the second intercostal space. After cleaning, the second intercostal space is infiltrated with 1-2 percent xylocaine in the mid clavicular line. The needle is pushed perpendicularly into the space till a loss of resistance is felt. If a tension pneumothorax is present, a gush of air usually follows which can be seen as large amount of bubbles appearing at the other end dipped in saline. In a way this method is both diagnostic and therapeutic intervention of patients with tension pneumothorax. The needle may be stabilized with help of adhesive tape till proper tube thoracotomy is arranged.

## 70.13 Cervical Spine Stabilization in Trauma

Sukhmeet Singh

Prompt assessment and intervention are essential for successful treatment of childhood trauma.<sup>1</sup> Whenever head and neck injury is suspected, the cervical spine must be completely immobilized when the airway is opened.

### Immobilization during Transportation

The victim must be transported in neutral position without moving head or neck. It requires 3-5 persons to lift the victim in a straight line.

#### *First Aid for Spine Stabilization in Injured Victims*

The First aid providers should use manual spine stabilization (i.e. stabilization with hands rather than devices) and should avoid using immobilizing devices. Rescuers should use the head tilt–chin lift to open the airway (Immobilization devices can interfere with opening the airway, and there is no evidence that first aid providers can use devices correctly. Even the jaw thrust can move the injured spine, so it is no longer recommended for the first aid rescuer). If you suspect a spine injury, it is best not to move the victim. If you are alone and must leave the unresponsive victim to get help, extend one of the victim's arms above the head. Then roll the victim's body to that side so that the victim's head rests on the extended arm. Bend the legs to stabilize the victim.

### Opening Up Airway

Open airway with jaw thrust method. Head tilt and chin lift method is contraindicated in trauma cases because it may worsen existing cervical spine injury. Care must be taken to ensure that neck is maintained in neutral position (Fig. 70.13.1), traction on or movement of neck must be avoided. This is best accomplished using the combined jaw thrust/spinal-stabilization maneuver.

- Place 2 or 3 fingers under each side of the lower jaw at its angle and lift jaw upwards and outwards.
- After opening airway, an oral airway may be used.

### Neutral Position for Head and Neck

The prominent occiput of the child predisposes the neck to slight flexion when placed on a completely flat surface.

- Place a thin layer of firm padding under the child's torso to elevate it up to 2 cm, allowing the head to assume a neutral position.

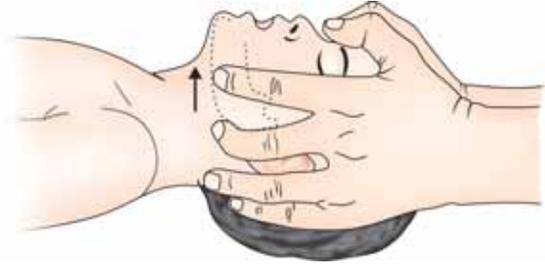


Fig. 70.13.1: Positioning of the neck

- If available, use pediatric spine boards with shallow head wells.
- A semirigid extrication collar should be applied, but it must fit perfectly which does not allow any movement.
- Optimal immobilization of the cervical spine is achieved with long spinal board commercial head immobilizers, foam blocks or linen rolls, (Fig. 70.13.2) and tape in addition to collar.



Fig. 70.13.2: Immobilization by rolls

### Rescue Breathing

After opening of airway with jaw thrust maneuver, if the victim is not breathing then give rescue breathing.

- It can be accomplished easily by 2 rescuers. One rescuer opens up the airway with jaw thrust and second rescuer gives mouth-to-mouth breathing
- It is difficult for one rescuer to perform these two maneuvers simultaneously. It can be done by maintaining jaw thrust and closing nose with cheek and giving mouth-to-mouth breathing.

### Endotracheal Intubation

If child is properly immobilized on a spinal board and a semirigid collar is in place, endotracheal intubation



Fig. 70.13.3: Performing endotracheal intubation

can occasionally be accomplished by one person. But if there is any doubt about the effectiveness of cervical spine immobilization, one rescuer must stabilize the neck while the second rescuer performs the endotracheal intubation (Fig. 70.13.3).

#### REFERENCE

1. Chameides L, Hazinski MF. Pediatrics advanced life support. American Heart Association, 1997.

## 70.14 Heimlich Maneuver

Sukhmeet Singh

The Heimlich maneuver (subdiaphragmatic abdominal thrusts) is recommended for the relief of complete upper airway obstruction. These thrusts increase intrathoracic pressure, creating an artificial cough that forces air and may force foreign bodies out of the airway.

### Foreign Body Airway Obstruction (FBAO)

More than 90 percent of deaths from FBAO in pediatric age group occur in children younger than 5 years; 65 percent of the victims are infants. It should be suspected in infants and children who demonstrate the sudden onset of respiratory distress associated with coughing, gagging, stridor or wheezing. These symptoms may also be caused by infections such as epiglottitis and croup. Infection should be suspected if child has fever, accompanied by congestion, hoarseness, drooling, lethargy or limpness. These children should be taken immediately to an emergency facility. Time should not be wasted in a futile and probably dangerous attempt to relieve this form of obstruction.

### Indication

Attempts to clear the airway should be considered when FBAO is witnessed or strongly suspected or when the airway remains obstructed (no chest expansion) during attempts to provide rescue breathing to the unconscious, non-breathing infant or child.<sup>1,2</sup> If FBAO is witnessed or strongly suspected, the child should be encouraged to continue spontaneous coughing and breathing efforts as long as the cough is forceful. Relief

of obstruction should be attempted only if signs of complete airway obstruction are observed, which are ineffective cough (loss of sound) increased respiratory difficulty accompanied by stridor, development of cyanosis, and loss of consciousness.

Never intervene if victim is able to speak even in whisper, is coughing effectively or wheezing. Your attempt to help dislodge the object at this time may cause the partial obstruction to become complete obstruction.

### First Aid in Choking

Terms used to distinguish choking victims who require intervention (e.g. abdominal thrusts or back slaps and chest thrusts) from those who do not have been simplified to refer only to signs of mild versus severe airway obstruction. Rescuers should act if they observe signs of severe airway obstruction: poor air exchange and increased breathing difficulty, a silent cough, cyanosis, or inability to speak or breathe. Rescuers should ask 1 question: "Are you choking?" If the victim nods yes, help is needed.

### Procedure

Perform the following steps to relieve airway obstruction in the conscious victim:

- Stand behind the victim, arms directly under the victim's axilla encircling the victim's torso (Fig. 70.14.1).
- Place the thumb side of one fist against the victim's abdomen in the midline slightly above the navel and well below the tip of the xiphoid process.



**Fig. 70.14.1:** Position for performing the Heimlich maneuver in a child

- Grasp the fist with the other hand and exert a series of quick upward thrusts. Do not touch the xiphoid process or lower margins of the rib cage because force applied to these structures may damage internal organs.
  - Each thrust should be a separate, distinct movement, intended to relieve the obstruction.
- Continue abdominal thrusts until the foreign body is expelled or the patient loses consciousness.

### Procedure in Infants

Back blows and chest thrusts are recommended for infants.

Heimlich maneuver is not recommended for infants because of risk of injuries to stomach, diaphragm, esophagus and liver. For these reasons use of *back blows* and *chest thrusts* are recommended for infants (Fig. 70.14.2).

#### Back Blows

- Hold the infant face down, resting on the forearm, Support the infant's head by firmly holding the jaw. Rest your forearm on your thigh. The infant's head should be lower than trunk.
- Deliver up to 5 back blows forcefully between the infant's shoulder blades, using the heel of the hand.



**Fig. 70.14.2:** Position for the procedure in infants

#### Chest Thrusts

- Place your free hand on the infants's back, holding the infant's head. One hand supports the head and neck, jaw and chest while the other hand supports the back.
  - Turn the infant while the head and neck is carefully supported, and hold the infant in the supine position, draped on thigh. The infant's head should remain lower than trunk.
  - Give up to 5 quick downward chest thrusts in the same location and manner as chest compressions two fingers placed on the lower half of the sternum, approximately one finger's breath below the nipples.
- 5 back blows and 5 chest thrusts should be repeated until the object is expelled or the infant loses consciousness.

#### If you are Choking and Alone (Fig. 70.14.3)

- Use your fist to perform the Heimlich maneuver.
- Try other methods that will apply upward force into your abdomen. Lean forward and press into the edge of a table, kitchen sink or back of chair.



**Fig. 70.14.3:** Procedure to be adopted when one is choking and alone

#### *If Victim Loses Consciousness*

If the victim becomes unresponsive, all rescuers are instructed to activate the emergency response number at the appropriate time and provide CPR. Every time the rescuer opens the airway (with a head tilt–chin lift) to deliver rescue breaths, the rescuer should look in the mouth and remove an object if one is seen. The tongue jaw lift is no longer taught, and blind finger sweeps should not be performed. Some studies showed that chest compressions performed during CPR increased intrathoracic pressure as high as or higher than abdominal thrusts. Blind finger sweeps may result in injury to the victim's mouth and throat or to the rescuer's finger with no evidence of effectiveness.

#### *If Victim Loses Consciousness*

- Open the airway using Tongue Jaw Lift Method and if you see the obstructing object, remove it with a finger sweep.
- Attempt rescue breathing: If chest fails to rise, reposition the head and reattempt rescue breathing again.
- If the airway remains obstructed in the unconscious victim, repeat the Heimlich maneuver in lying down position.

#### *Heimlich Maneuver in Victim who is Unconscious or who Becomes Unconscious*

- Place the victim supine. Kneel beside the victim or straddle the victim's hips (Fig. 70.14.4).



**Fig. 70.14.4:** Procedure in an unconscious patient

- Place the heel of one hand on the child's abdomen in the midline slightly above the navel and well below the rib cage and xiphoid process. Place the other hand on top of the first.
- Press both hands into abdomen with a quick upward thrust. Each thrust is directed upward in the midline and should not be directed to other side of abdomen.

Perform a series of 5 thrusts. If unsuccessful, open airway with tongue jaw lift and remove foreign body if you see it. Attempt rescue breathing. If unsuccessful, repeat Heimlich maneuver for 5 times.

#### *Heimlich Maneuver in Victim who is Unconscious or who Becomes Unconscious*

- Actiate the EMS
- Open up the airway, remove the object if you see it.
- Begin CPR.

Everytime you open up the airway to give breath, open the victim's mouth wide and look for the object. If you see the object, remove it with your fingers. If you do not see the object, keep doing CPR.

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1. Emergency Cardiac Care Committee and Subcommittees. American Heart Association Guidelines for Cardio-pulmonary resuscitation and emergency cardiac care, V,VI,VII. JAMA,1992;268:2251-81.
2. Chameides L, Hazinski MF. Pediatrics advanced life support. American Heart Association 1997.

## 70.15 Insertion of Nasogastric Tube

Daljit Singh, Puneet A Pooni

### Insertion of Nasogastric Tube

Nasogastric (NG) tubes allow substances to be introduced or removed from the digestive tract. In the ER the common indication for inserting a NG tube is for decompression of the stomach in cases with paralytic ileus, intestinal obstruction, poisoning or coma. The same tube may be retained for administration of drugs and feeding subsequently.

The materials required for the procedure include appropriate size NG tube, syringe (5 to 10 ml), bowl of water, stethoscope, and adhesive tape.

**Size of NG tube:** The size of the tube varies with age/weight (Table 70.15.1).

**Insertion of tube:** In conscious patients, NG tube insertion is unpleasant and painful, necessitating a gentle approach. Using good technique during insertion can minimize patient discomfort. In adults, preapplication of topical lidocaine has been observed to reduce pain, but in children procedure is routinely done without analgesia or topical anesthesia. Skill and experience is required for proper insertion and fixation of the tube especially in small infants. The steps of procedure include:

1. Hands should be properly washed after assembling the materials.
2. For right handed operator, standing on the patients right side is convenient and *vice versa*.
3. Soft tubes made of polyurethane silicon rubber are generally preferred. Insertion length is measured from tip of the nose to external auditory meatus and further to xiphisternum. This distance may be marked with a piece of tape.
4. The tube should be lubricated by dipping it in water or by applying water-soluble lubricant to the tube. Oil, gels or petroleum jelly should not be used because of the risk of aspiration and clogging of the tube.

**Table 70.15.1: Recommended size of tube**

Age	Weight (Kg)	NG tube (Fr)
<1 mo	<3.5	6-8
1-6 mo	3.5-7	8-10
1-3 yr	10-12	10-12
3-6 yr	14-21	12
6-8 yr	21-27	12-14
>8 yr	>27	14-16

5. After slightly extending the neck of the child, tip of the tube is inserted into the nostril, guiding it toward the nasopharynx. No force should be used and if the tube is stuck or resistance is encountered, it should be slightly withdrawn and reinserted maintaining a medial and downward direction. As the tip of the tube reaches the nasopharynx, the head is flexed to facilitate the desired length to be gently pushed in.
6. The tube should be immediately withdrawn if cyanosis or respiratory distress occurs, indicating that it may have entered the laryngeal opening.
7. The tube should be fixed properly with adhesive tape, being careful not to block the nostril. While using adhesive tape it is important to ensure that it is not twirled around the tube or loosely applied allowing inadvertent movement of the tube. The tape should be applied longitudinally over the nose and folded along the adjacent portion of the tube, thereby firmly fixing it.
8. The gastric contents should be aspirated and inspected to verify correct placement of tube. Gastric pH is 0-4. The placement can be confirmed by injecting air and auscultating over the epigastric area for gurgling sound. The amount of air injected may range from 0.5 ml in preterm neonates to 5 ml in older children. If in doubt the throat should be inspected, as the tube may have curled in the oropharynx. The final confirmation is obtained on X-ray.
9. The end of the tube should be occluded with adapter or stopper. The position of the tube should be reconfirmed before any intervention involving the tube for example NG feeding or drug administration. If continuous aspiration is required, the end of the tube needs to be connected to a container with an extension tube.

### Removing the Tube

While removing the tube it should be pinched with thumb and forefinger or gentle suction should be applied with syringe.

### Complications

Patient may have reflex bradycardia, apnea, aspiration of gastric contents and occasionally bleeding due to ulceration of the naso-oropharyngeal and gastric mucosa.

## 70.16 Urinary Bladder Catheterization

DK Gupta

The indications for this procedure include: (i) Monitoring urine output and hydration; (ii) To relieve bladder outlet obstruction, e.g. posterior urethral valves; (iii) As clean intermittent catheterization (CIC) for neurogenic bladder; (iv) For collecting urine sample.

### Procedure

Urethral catheterization requires strict aseptic conditions and selection of proper size of catheter. The perineum and the genitalia are thoroughly cleansed. In males, prepuce adhesions may have to be lysed to expose the meatus and prevent infection. The area of interest is draped. In females proper flexion and abduction of the hip with external rotation is required and the labia has to retracted. In males the urethra is

anesthetized and lubricated with 2 percent xylocaine jelly injected with a syringe alone into the meatus. The catheter is passed gently through the meatus. A stilette can be used with the catheter for better control but in such cases it is important that the urethra is not traumatized. The catheter may coil in the dilated posterior urethra in boys with posterior urethral valves. Gentle manipulation, using a coude tip catheter or doing a pre-rectal examination and straightening the posterior urethra can be tried in such cases. The Foley's bulb is inflated with 2-3 ml saline and drawn back till the bladder neck. In neonates a 5 feeding tube can be used for catheterization. Proper fixation of such a catheter using micropore is necessary to prevent dislodgment.

## 70.17 Suprapubic Tap

Daljit Singh, Puneet A Pooni

In the pediatric ER, suprapubic tap is generally indicated to obtain urine for analysis and culture as part of sepsis workup in a neonate, and in small children suspected to have UTI. Aspiration may be necessary for relieving urethral obstruction, particularly in boys with tight phimosis. This procedure is feasible mainly in children below 2 years of age as the distended bladder is an intra-abdominal organ.

The materials required for performing this procedure include: (i) 10-20 ml syringe; (ii) 1 percent lidocaine; (iii) sterile container for specimen; and (iv) sterile sheets and gloves.

### Technique

1. The child is restrained in a supine, frog like position. The bladder is palpated or percussed to confirm that it is full. The procedure may need to be postponed if urine has been passed in the preceding hour. To prevent urination during the procedure, gentle penile pressure may be applied in males and anterior rectal pressure in females.

2. Suprapubic area is cleaned with povidine-iodine and alcohol, and draped. The site of tap is located as 1-2 cm above the upper edge of pubic symphysis in the midline.
3. A 21 or 22 gauge needle attached to 10-20 ml syringe is inserted at 10°-20° to the perpendicular, aiming slightly caudal towards the coccyx. Gentle negative pressure is maintained as the needle is advanced till urine is obtained, taking care not to enter beyond the depth of 2.5 cm.
4. 5-10 ml of urine is aspirated for examination. In case there is occlusion of the needle tip with mucosa, it needs to be rotated gently.
5. After removal of the needle, the puncture site should be covered with sterile gauze piece or band-aid.

**Complications:** It is safe procedure in most infants. Transient hematuria may occur after the procedure and is usually microscopic. The primary complication is transient gross hematuria lasting less than 24 hours in 0.6 percent of patients. Improperly performed procedure carries a potential risk of intestinal perforation, peritonitis, hematoma, abdominal wall abscess and bacteremia.

## 70.18 Hydrostatic Reduction of Intussusception

DK Gupta

Non-operative reduction using barium or air is now the accepted modality of treatment for intussusception. However, there are a few definite contraindications for the procedure: (i) Presence of pneumoperitoneum (suggestive of perforation); (ii) Peritonitis; and (iii) Symptoms of more than 48 hours duration.

Patient preparation before attempting hydrostatic reduction is vital and includes: (i) Nasogastric decompression, (ii) Securing IV line and adequate hydration, (iii) Avoiding hypothermia, (iv) Surgical consultation and preparing operating theater, if required, and (v) Obtaining consent and explaining risks to parents. The role of sedation and glucagon (which may aid in reduction) is controversial.

### Procedure

Balloon catheters are usually not used for barium reduction. A large bore catheter is inserted per-rectally and the buttocks are taped tightly. The enema tubing is connected to a bag of thinned contrast, which is placed about 1 m (or 3 feet) above the table top. Repeated

infusions of barium for around 5 minutes are used and the reduction can be attempted for up to 45 minutes. The intussusception appears as a convex intraluminal filling defect and the contrast will be seen going around the intussusceptum. The bag of contrast can be raised safely to a height of around 150 cm if reduction is not occurring. The “rule of three” is frequently used to guide barium reduction but is not an absolute value-3 attempts of 3 minutes each with the barium column at a height of 3 feet above the table.

Successful reduction is indicated by (i) Free flow of contrast into the terminal ileum, (ii) Normal post evacuation film, and (iii) Passage of barium with loose greenish stools and relief of symptoms.

Pneumatic reduction using an insufflator has also been described and can be done under ultrasound guidance. The success rate of barium reduction is around 60-80 percent and is lower with longer duration of symptoms, presence of a lead point and evidence of complete small bowel obstruction. There is also a 5-10 percent recurrence rate, which usually occurs within 72 hours.

## 70.19 Tracheostomy

Tarun Gera, Anjali Seth

A tracheostomy involves the construction of a channel between the trachea and the skin surface of the neck in the midline. Historical accounts of this procedure are available as far back as 3500 years ago. Initially it was performed for choking caused by inhalation of foreign bodies, drowning or trauma to the upper respiratory tract. Later, common indications were laryngotracheobronchitis and diphtheria. The poliomyelitis epidemic of the 1950s stimulated the use of tracheostomy for mechanical ventilation, leading on to similar treatment in tetanus, cardiac surgery, severe burns and now in the care of the preterm infant. With improvement in antibiotics available and the surgical technique, the mortality from the procedure has also greatly improved.

### Anatomy and Physiological Aspects in Children

In children there are certain differences in both the anatomy and the physiology of the respiratory tract as

compared to an adult, making the procedure slightly more complex. These include:

1. The air passages in children are both absolutely and relatively smaller.<sup>1</sup>
2. The larynx is higher in the child. The cricoid cartilage lies at the level of the 3rd cervical vertebrae in the infant and descends to the 6th cervical vertebrae at puberty.
3. The thyroid cartilage does not assume its adult configuration until adolescence. The cricoid, then, is the easiest and the only landmark to identify in children.
4. The recurrent laryngeal nerves lie just lateral to the trachea. In addition, a pretracheal pad of fat is generally present in infants.
5. The articulation between the head and neck is more mobile in infants and the chin may easily deviate from the midline during surgery.
6. In extension, the mediastinal contents may enter the neck so that the surgeons may encounter the pleural

dome, the large vessels crossing the midline and rarely, the thymus. Hence low tracheostomy must always be avoided in smaller children.

### Indications

Because of the relative ease of endotracheal intubation, tracheostomy is now indicated only in those cases in which intubation is not feasible. Some specific indications for tracheostomy are:

1. **Congenital laryngeal abnormalities**
  - a. Bilateral vocal cord paralysis.
  - b. Congenital subglottic stenosis and cysts.
  - c. Laryngeal webs.
  - d. Subglottic hemangiomas.
  - e. Laryngomalacia (rarely).
2. **Prolonged ventilation:** Benefits of a tracheostomy in long-term mechanical ventilation include improved airway suctioning, better patient comfort, absence of laryngeal complications, easier tube changes and capabilities for oral nutrition. Also, ventilator dependent patients may tolerate weaning attempts better when spontaneously breathing through a tracheostomy that contributes less to airway resistance compared to an oral endotracheal tube. Optimal timing, however, for conversion from endotracheal intubation to tracheostomy in most patients is controversial. A decision to continue endotracheal intubation for several weeks is encouraged by the avoidance of tracheostomy complications such as tracheal stenosis. Prolonged endotracheal intubation, on the other hand is not risk free; there is potential for laryngeal stenosis which progresses in severity with duration of intubation. Therefore based on the available clinical data endotracheal tube intubation is recommended for patients requiring assisted ventilation for less than 7 days.<sup>2</sup> After 7 days of intubation the patient is re-evaluated; if extubation appears likely before the 11th day then tracheostomy is not performed but if extubation cannot be foreseen on the 7th day, conversion to tracheostomy should be strongly considered. Realizing that no general principle works for every patient, the decision to perform tracheostomy must often be individualized; the agitated difficult to sedate patient may benefit from earlier surgery, while the patient at higher risk for surgical complications may be allowed more time for possible extubation.
3. **Supralaryngeal obstruction**
  - a. Pierre Robin syndrome.
  - b. Obstructive sleep apnea.
  - c. Craniofacial injury.

#### 4. **Acquired laryngeal abnormalities**

- a. Acquired subglottic stenosis.
- b. Laryngeal papillomatosis.

#### 5. **Acute infection**

- a. Epiglottitis.
- b. Acute laryngotracheobronchitis.

#### 6. **Miscellaneous**

- a. Diphtheria.
- b. Inhaled foreign body.

### The Procedure

#### *Preoperative Preparation*

Antibiotics are not indicated routinely. A sample of sputum should be taken for culture and sensitivity in readiness for a possible postoperative infection. Blood loss during this procedure is minimal but blood should always be crossmatched for infants in whom the blood volume is very small. The infant or the child is laid supine on the operating table with the neck in hyperextended position.

#### *Operative Technique*

A vertical skin incision is preferred in infants and smaller children, since it runs in the line of the trachea and provides improved access. The midline is also less vascular and therefore preferable. The horizontal incision is preferred by some surgeons in older children as the scar formed is cosmetically better.

The cricoid cartilage is palpated and a vertical skin incision, 1.5 cm long, is made. If a horizontal incision is to be employed, it should be of similar length in a skin crease midway between the cricoid and the suprasternal notch. Blunt dissection is then carried out in the subcutaneous planes till the trachea is reached. It is important not to open up tissue planes unnecessarily as this encourages surgical emphysema later. It is sometimes a problem to identify an individual tracheal ring. This may be facilitated by either exposing the cricoid cartilage and numbering the rings from that level or by the identification of the thyroid isthmus, which consistently overlies the second, third and fourth tracheal rings, as a landmark. Some authorities feel that the isthmus should always be cut and sutured<sup>3</sup> in order to facilitate recannulation later, but it is simpler to free the isthmus from the underlying trachea and retract it superiorly or inferiorly for the exposure of relevant tracheal rings. In the older patients there has been a considerable debate on the best form of tracheal incision-vertical or trapdoor (H type) but in the infants it is generally agreed that the vertical

incision is the simplest and the best as it results in less stenosis and less airway resistance.

The incision is made through the second, third and fourth tracheal rings. Placement too close to the first ring risks cricoid cartilage damage with subsequent subglottic stenosis of the larynx. A low tracheostomy below the fourth ring places the tip of the tracheostomy tube against the anterior tracheal wall at the level of the innominate artery hazarding vascular erosion and subsequent hemorrhage. The incision is made in a controlled manner from below upwards to avoid damage to the mediastinal contents. The procedure may be assisted by the insertion of a silk suture to either side of the midline. However, some surgeons believe that these sutures weaken the anterior tracheal wall and the threads become sodden and somewhat of an obstacle during subsequent care of the tracheostomy.

The endotracheal tube is now withdrawn just proximal to the incision. Once the stoma is created, the lumen is evaluated and a tracheostomy tube selected that occupies two-thirds to three-quarters of tracheal diameter. The tracheostomy tube is inserted under direct vision. After being satisfied that the tube is in place and both the lungs are being ventilated, the endotracheal tube is then completely withdrawn.

No sutures are required around the skin incision as it fits comfortably around the tube. A tight fit is to be avoided since it predisposes to surgical emphysema. The tube may be held in place by suturing the flanges to the neck skin. A tape is then tied from one side of the flange to the other round the back of the neck. All manipulations are done keeping the neck in slight flexion. If they are done with the neck extended the tube will loosen on subsequent flexion and accidental decannulation will occur.

### *Postoperative Care*

#### *Immediate postoperative period*

For the first few days after the tracheostomy the child should be hospitalized, preferably in an intensive care unit.

Immediately on arrival an X-ray of the chest and neck is taken to confirm that the tip of the tracheostomy tube is not low enough to impinge on the carina or enter the right main bronchus. The X-ray would also reveal the presence of surgical emphysema, if present. Initially the child must be started on intravenous fluids. However, oral feeds can be started within a few hours of the procedure. The maintenance of adequate hydration is of utmost importance in order to prevent tracheal crusting. In cases of chronic obstruction of airways, the sudden reduction of dead space can cause apnea. In such

children the dead space can be increased with the aid of suitable attachments. It is essential that humidified air be supplied to the infant. Following the surgical insult, the trachea and bronchi produce excessive secretion. Because the cough reflex is lost suction at periodic intervals is important. The child should be carefully watched in the immediate postoperative period for any signs of emphysema or pneumothorax. One week after the procedure the track is well formed and the tube can be changed.

### *Long-term Care of the Tracheostomy*

Long-term care requires active participation of the parents. They should be explained in detail the need for the tracheostomy and should be involved in all steps of care.

1. **Stoma and skin care:** Gentle cleaning with normal saline or a mild antiseptic solutions will keep the skin dry, clean and free from irritation and infection. Creams and ointments are avoided. If the skin becomes sore it needs to be cleaned more frequently and a non-adherent dressing applied and changed when necessary. Cotton wool based dressing should not be used. Granulomata around the tube may be treated with topical application of silver nitrate.
2. **Irrigation and suction:** Regular suction is very important. Tenacious secretions may be loosened by instillation of saline into the trachea prior to suction. Suction should be performed prior to feeds or mealtimes and avoided immediately afterwards.
3. **Changing the tapes:** Tapes should be changed daily or whenever they become dirty or wet. It is important to obtain the correct tension when the tapes are being changes. With the child sitting up, with his neck flexed forwards, it should be possible to insert just one finger between the tapes and the neck.
4. **Changing the tube:** It is usually sufficient to change the tube once a week and it is advisable to do so prior to feeds or mealtimes. However, if the secretions are tenacious the tube is more likely to become crusted and needs to be changed more frequently.
5. **Chest physiotherapy:** With time the secretion tend to diminish and the need for chest physiotherapy is eliminated. However, if the child suffers from respiratory infection the secretions become more plentiful, requiring regular physiotherapy for their mobilization and removal.

### **Complications of Tracheostomy**

The complications can be divided into 'early' and 'late' with a dividing line of one week into the postoperative period.

### Early Complications

1. **Apnea:** This is more likely to occur in smaller children with chronic airway obstruction. Sedation should be avoided in such children. The dead space can be increased temporarily by a suitable attachment to the tracheostomy tube.
2. **Air leak**
  - a. **Surgical emphysema:** It is commonly seen immediately after the operation. Usually it resolves without any treatment. The position of the tube and tightness around the stoma should be checked.
  - b. **Pneumomediastinum:** This is to be managed in a similar manner as surgical emphysema.
  - c. **Pneumothorax:** A low tracheostomy predisposes to a pneumothorax and a tight stoma aggravates the situation. These should be avoided and the condition be treated on its own merits.
3. **Accidental decannulation:** This is serious complication in the first 2-3 days because the fistula track will not have formed and the slit incision given in children makes recannulation difficult. In such a situation recannulation under direct vision or endotracheal intubation should be performed.
4. **Creation of a false passage:** The changing of the tube or its reinsertion may lead to creation of false passage, leading to obstruction or pneumothorax.
5. **Obstruction:** The most common cause of obstruction is accumulation of mucus and crusts in the tube or in the lumen of the trachea. This can be prevented by adequate humidification and suction and maintenance of adequate hydration. In preterm neonates intermittent obstruction by the baby's chin is a recurrent problem and can be prevented by a suitable attachment to the tube.
6. **Hemorrhage:** Bleeding from the dissection field is usually trivial. Serious hemorrhage may occur due to erosion of a large vessel, most commonly due to secondary infection. However, this rarely occurs in the first week.
7. **Chest infections:** Pulmonary infection is a problem in infants with previous pulmonary pathology. This group of patient should, therefore, be started on prophylactic antibiotics in the preoperative period. A sample of tracheal aspirate for culture and sensitivity should be taken to guide further treatment.

### Late Complications

All the complications seen in the first postoperative week may occur in the later period as well. The most significant problems are accidental decannulation and obstruction.

1. **Accidental decannulation:** This is less dangerous in the later period because the track is well formed. However, there is a significant risk of stenosis of the track within 10 minutes of decannulation. Good securing of the tracheostomy tube is most important to avoid decannulation.
2. **Obstruction:** This may be caused by a granuloma or by a mucus plug.
3. **Hemorrhage:** Hemorrhage due to erosion of a large vessel can be prevented by proper positioning of the tube and prompt treatment of infection. Hemorrhage and mediastinitis are caused by erosion of the tracheal wall by the tip of the malpositioned tube.
4. **Chest infections:** Pulmonary infection is a problem in infants with previous pulmonary pathology. This group of patients should, therefore, be started on prophylactic antibiotics in the preoperative period. A sample of tracheal aspirate for culture and sensitivity should be taken to guide further treatment.

### Decannulation

The eventual outcome and removal of the tracheostomy depends upon the original lesion.

#### Assessment before Decannulation

Tracheostomized children should be regularly assessed and should follow the clinical criteria given below before they are considered for decannulation:

1. The child should be well with no signs of aspiration during eating or drinking.
2. The original condition for which the tracheostomy was placed should have resolved or improved.
3. The next consideration is comorbid factors such as the patient's cardiac, pulmonary or neurologic status.
4. One must consider the need for a tracheostomy if surgery that might affect the airway, (e.g. craniofacial reconstruction) is planned.
5. Temporary occlusion of the tube with the finger permits respiration to continue adequately through the glottis.
6. Radiography and xerography of the larynx and the trachea, in a temporarily extubated child, will demonstrate any narrowing of the airway and is useful.
7. Physiological assessment<sup>4</sup> can be done by comparing the peak inspiratory flow through the tracheostomy tube and the mouth.
8. One approach to decannulation includes airway endoscopy. A light inhalational anesthetic is administered through the tracheostomy tube. If the epiglottis and other parts of the larynx are not

stimulated, the child will tolerate fiberoptic nasopharyngolaryngoscopy, without coughing or breath holding. Vocal cord motility is observed. The nose and pharynx are observed for obstruction. The rigid laryngoscope may be used to confirm the findings of fiberoptic endoscopy, as well as to check sites not well assessed by fiberoptic endoscopy, (e.g. valleculae, pyriform sinuses, post-cricoid portion of the hypopharynx, laryngeal ventricles, anterior commissure, the intra-arytenoid region and the subglottis). If a doubt of adequate vocal cord motility exists, the arytenoids are palpated to check for fixation. The ventilating bronchoscope is used to assess the subglottis, trachea and bronchi. The tracheostomy entry into the trachea is assessed, both with the tracheostomy tube in place and with tracheostomy tube withdrawn. Special attention is given to whether suprastomal granulation tissue exists and whether the anterior tracheal wall is collapsed posteriorly by the tracheostomy tube; granulation tissue, if present, is removed.

The process of decannulation can be performed in two ways. Most commonly, the tube is removed and the track is allowed to close down and heal. Some practitioners prefer to excise the track and allow it to heal by first intention. However, in both the methods the safety of decannulation must be ensured by a prior decannulation trial. The basic principle of the trial is to carry out progressive blockage of the tube lumen. The child is watched carefully for any signs of respiratory distress as he carries out normal physical activities. When downsizing is poorly tolerated, some authors advocate a fenestrated tracheostomy tube to aid in decannulation.<sup>5,6</sup>

During the whole process of decannulation, the following simple precautions must be observed:

1. Essential emergency equipment, including a laryngoscope, tracheostomy tube, retractors and tracheal dilators, must be available at all times.
2. Humidification must continue as before.
3. There is no indication for routine antibiotics, mucolytics and steroids before decannulation.

The commonest problem with decannulation are those of suprastomal granulations and tracheal narrowing, both of which are well treated by surgical decannulation<sup>7</sup> where the tracheostomy track is excised and the stoma is examined under direct vision. It allows direct access to the tracheal stoma and permits removal of any possible obstruction under direct vision. The suturing of the tracheal stoma reconstitute the cylindrical wall of the trachea and thus increases the strength of the tracheal wall around this weakened point. The removal of the fibrous track hastens healing with better cosmetics results.

With advances in neonatal medicine, mechanical ventilation, cranial and thoracic surgery the number of surgeries is bound to increase. As we step into the new millennium we anticipate further improvements in the surgical techniques and in the types of tubes available, with reduction in the morbidity and mortality associated with this procedure.

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# Annexures

## **Annexure I: Dosages of Some Common Drugs**

*Ashok K Deorari, Rakesh Lodha*

## **Annexure II: Reference Laboratory Values**

*Tarun Gera*



**Annexure I : Dosages of Some Common Drugs**

Ashok K Deorari, Rakesh Lodha

S. No.	Name of the Drug (Dosage modification necessary in R = Renal Failure H = Hepatic Failure)	Age Group	Route (Duration of IV dose infusion in parenthesis)	Total Dose (mg/kg/24 hr unless otherwise stated)	Dosage interval (Hours)	Preparation	Strength (Syr/Susp./Liq. mg/per 5 mL) Drops Amps mg/ml Tabs/ Cap in mg Total Vials- content in mg	Remarks (C/I-Contraindications)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
1.	Acetaminophen (R,H) (Paracetamol)	NB IN, CH	PO PO IM	5 mg/kg/dose 60 5 mg/kg/dose	4 4-6 PRN.	Drops Syr/Susp Tab Amp	100, 150 120 500, 650 150	Analgesic, antipyretic but not anti-inflammatory. Moderate overdose-hypoglycemia, dizziness, disorientation, reversible jaundice. Massive overdose-Hepatic necrosis. Antidote-N-acetylcysteine.
2.	Acetazolamide (R) Hydrocephalus As adjunct to antiepileptic drugs	IN, CH IN, CH	PO	30-50 8-30	6-8 6-12	Tab	250	
3.	Acetylcysteine (H) Antidote for acetaminophen toxicity	IN, CH	IV	140 mg/ kg loading dose, followed by 70 mg/kg/dose every 4 hours for a total of 17 doses	4 hrly	Amp	200	
4.	ACTH	IN, CH	IM, SC	5-8 U/kg/day	12-24	Repository gel	20 U 40 U 80 U	C/I CHF. Ocular herpes. Gel stored refrigerated. Warm to room temp. before use.
5.	Acyclovir (R) Herpes encephalitis Varicella-zoster	NB, IN, CH CH	IV (60 min) PO	30-45 500 mg/m <sup>2</sup> /dose 20 mg/kg/dose	8 8 6	Tab Vial	200, 400, 800 250	
6.	Adenine arabinoside (Vidarabine)	NB IN, CH	IV IV	15-30 15	Constant infusion For 12 hr per day x 10 days	Amp	200	For Herpes simplex infections resistant to acyclovir.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
7.	Adenosine PSVT	NB IN CH	IV	0.05 mg/kg IV push, increase bolus dose by 0.05 mg/kg every 2 min till clinical response (max dose 12 mg)	-	Amp	3 mg	May cause bronchoconstriction in asthmatics. Continuous ECG, BP, RR monitoring required.
8.	Adrenaline Bronchodilator Resuscitation	IN, CH NB, IN, CH	SC IV, Intratracheal Nebulization	0.01 ml/kg/dose 0.1 ml/kg of 1:10,000		Amp of 1:1000 Soln	1 mL = 1 mg	May be repeated after 15-20 minutes for 1-2 doses. 1:10000 preparation needed for IV and endotracheal use; prepare by diluting with normal saline. Unstable in alkaline solutions.
9.	Albumin	NB, IN, CH	IV	0.5-1 g/kg/dose		Soln	5% 10% 25%	
10.	Amikacin (R)	NB, IN CH	IM, IV IM, IV	See newborn Table 15-25	8	Vial	100, 250, 500	Auditory and nephrotoxic. Toxicity is potentiated by concomitant use of other nephrotoxic drugs, and furosemide.
11.	Amiodarone (H)	IN, CH	IV	5 mg/kg over 30 min followed by continuous infusion at the rate of 5 µg/kg/ min (max dose of 15 µg/kg/min or 20 mg/kg/ 24 hr)		Amp	150 mg/ 3 mL	
12.	Aminophylline Loading Maintenance Apnea of prematurity	IN, CH IN, CH Preterm	IV (5-15 mins) IV IV followed by IV/PO	5 mg/kg/dose 15-20 (continuous infusion) 5 mg/kg/ loading 2 mg/kg/dose	6 6-8 8	Amp	100	No loading dose for patients already on oral theophylline.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
13.	Amlodipin (H)	CH	PO	0.1- 0.6 mg/kg	12- 24	Tab	2.5, 5, 10	
14.	Amoxycillin (R)	IN, CH	PO IV (15-30 min)	20-40 40-80	8 8	Drops Susp Cap Distab Vial	100 125, 250 250, 500 125, 250 100, 250, 500	Oral absorption better than ampicillin
15.	Amoxycillin + clavulanic acid (R)	NB, IN, CH	PO IV	Amox 30- 50 Amox 50-100	8 8	Tab/Susp.  Vial	Amox 250 + clav 125; 200 + 28.8 Amox 1000 + clav 200	GI disturbances more frequent than with amoxycillin alone
16.	Amphotericin B (R, H)	NB, IN, CH	IV Over 4-6 hr	Test dose: 0.1 mg/kg followed by 0.25 mg/kg/day. Increase gradually to 1 mg/kg/day.	OD	Vial	50 mg	Diluent 5% dextrose, strength of diluted solution = 0.1mg/mL. Not to be mixed with other solutions or drugs.
17.	Ampicillin (R) Septicemia Meningitis Other infections	NB, IN, CH NB, IN, CH NB, IN,CH	IV IV PO	100-200 200-400 50-100	4 4-6 4-6	Syr/Susp Vial Drop	125, 250 100, 250, 500, 1000 100	Food interferes with absorption. 1 gm Amp = 3 mEqNa
18.	Aminocaproic acid (H, R) (hemostatic agent)	CH	IV	100-200 mg/kg loading Maintenance 100 mg/kg/dose	6	Vial	250 mg/mL	
19.	Amrinone	NB  CH	IV  IV	0.75 mg/kg IV over 2-3 min, then 3-5 µg/kg/min continuous IV infusion 0.75 mg/kg bolus, infusion 5-10 µg/kg/min		Amp	5	
20.	Allopurinol (H, R)	IN, CH	PO	10	8-24	Tab	100	Establish high urine output. Interacts with azathioprine and mercaptopurines.
21.	Amantadine (H, R)	CH	PO	4-8	8	Cap	100	C/I Epilepsy.

Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
22.	Ampicillin + Sulbactam (H, R)	IN, CH	IV, IM	Ampi 100	6	Vials	Ampicillin 1 g Sulbactam 0.5 g	Effective against $\beta$ Lactamase producing organisms too.
23.	Antihemophilic factor, human		IV	Dose (U) Wt (kg) x 0.5 x desired increase in factor VIII (% of normal)		Inj	200 U, 250 U, 500 U, 750 U, 1000 U, 1500 U	
24.	Anti-Rh immunoglobulin	Rh-ve mother with Rh+ve babies	IM	250-300 $\mu$ g single dose within 72 hours of delivery or abortion		Vial	100, 250, 350 $\mu$ g	Mother should have negative indirect Coombs test during pregnancy.
25.	Anti-snake venom antisera (polyvalent)	IN, CH	IV (Infusion)	Initial 50 mL (dose up to 150-200 mL may be required)		Vial	10 mL	To be diluted with 250 mL of IV fluids and given slowly 20 mL/kg/hr. In severe cases doses of 100-200 mL may be required. Sensitivity test to equine serum is must. Desensitization has to be done in sensitive individuals.
26.	Artemether	IN, CH	IM	3.2 mg/kg D <sub>1</sub> followed by 1.6 mg/kg	24 (for total 5 days)	Amp	40, 80	
27.	Atenolol (R)	IN, CH	PO	1-2	12-24	Tab	50,100	C/I-Bradycardia, heart block, CCF, Asthma.
28.	Atropine Usual dose Organophosphorus poisoning	IN, CH	SC IV	0.01 mg/kg/dose Repeat PRN. 0.05 mg/kg/dose every 10-20 min until atropine effect, then every 1-4 hr for 24 hr		Amp	0.6	C/I-Tachyarrhythmias
29.	Atracurium besylate	IN CH	IV IV	0.3-0.4 mg/kg/dose 0.4-0.5 mg/kg/dose Continuous infusion: 0.4-0.8 mg/kg/hr	PRN	Amp	10	

Contd...

Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
30.	Azithromycin (H, R)	IN, CH	PO	10 mg/ kg day 1, followed by 5 mg/kg day 2- day 5	24	Susp Tab	100/ 5 mL 200/ 5 mL 250, 500	
31.	Aztreonam (R)	IN, CH	IV, IM	90-120	6- 8	Vial	500, 1000	
32.	Baclofen (R)	CH	PO	10-15 mg/ day (max dose: < 8 yr- 40 mg/d; ≥8 yr- 60 mg/ d)	8	Tab	10, 20	
33.	Beclomethasone	CH	Inhalation  Nasal spray	400-800 µg/day  50-100 µg/d	8-12  12-24	Metered dose inhaler  Rotacaps  Nasal spray	50,100 200 µg per actuation  100, 200 µg  50 µg per actuation	Can cause hoarseness, oral candidiasis or aspergillosis Rinse mouth and gargle with water after inhalation.
34.	Betamethasone	IN, CH	PO IV	0.06-0.25 1-4 mg total	6-12	Tab Inj.	0.5 4	Dose varies with the disease
35.	Benzathine Penicillin (R); Primary Prevention	< 27 kg > 27 kg	Deep IM	0.6 megaunits (total) 1.2 megaunits (total)	3-4 wk	Vial	0.6, 1.2, 2.4 megaunits	Sensitivity test is needed before each dose.
36.	Budesonide	IN, CH	Inhalation (MDI, nebulization)	100-800 µg/d	12	Metered dose inhaler Amp	100 µg/200 µg per actuation 250 µg/mL 500 µg/mL	
37.	Calcium gluconate (elemental calcium 9%)	NB, IN, CH	IV	1-2 mL/kg of 10% soln. Per dose 25-50 elemental calcium	6-8	Amp	10% Soln.	IV infusion is given under cardiac monitoring; do not mix with alkali solution.
38.	Captopril (R)	NB IN CH	PO PO PO	0.1-0.4 mg/kg/dose  0.5-0.6 0.5-1 (max 6 mg/ kg/ day)	6-24  6-12 4-8	Tab	25, 50	May cause renal impairment. C/I-Aortic stenosis, renal artery stenosis. Dose may be increased gradually to get desired effect.

Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
39.	Carbamazepine (H, R)	IN, CH	PO Initial Maintenance	10 30-40	8-12 8-12	Tab Syr	100, 200, 400 100	Stimulates hepatic microsomal enzymes. Dosage of other drugs such as phenobarbitone, valproic acid, phenytoin should be adjusted, if given simultaneously. INH inhibits metabolism. Discontinue if evidence of bone marrow depression.
40.	Caspofungin (H)	CH	IV	50 mg/ m <sup>2</sup> /dose; max 50 mg/ day	24	Vial	50	
41.	Cefazolin (H, R)	NB, IN, CH	IV (15-30 min) IM	40 50-100	12 6	Vial	125, 250 500, 1000	Can cause pseudomembranous enterocolitis. Refrigerate reconstituted solution.
42.	Cefaclor (R)	IN, CH	PO	20-40	8-12	Syr Cap	125, 187 250	Absorption unaffected by food intake
43.	Cefepime (R)	NB, IN, CH	IV	< 14 days age: 60 ≥14 days age: 100	12	Vial	500, 1000, 2000	In serious infections, meningitis and neutropenia, dose of 150 mg/ kg/day can be given in 3 divided doses
44.	Cefixime (R)	IN, CH	PO	8	12	Susp Tab	50, 100 100, 200	In enteric fever, dose of 20 mg/kg/day is used
45.	Cefoxitin (R)	NB IN, CH	IV, IM IV, IM	100 80-160	12 4-6	Vial	1, 2g	
46.	Cefoperazone (H)	NB, IN, CH	IV	100-150	8-12	Vial	250, 500, 1000	Not recommended in meningitis
47.	Cefoperazone + sulbactam (1: 1)	IN, CH	IV	100-150 mg/kg/d of cefoperazone	8-12	Vial	1 g = 500 mg each of cefoperazone and sulbactam	
48.	Cefpodoxime (R)	IN, CH	PO	10	12	Susp Tab	50, 100 100, 200	
49.	Cefuroxime (R) UTI Meningitis Other infections	IN, CH NB IN, CH NB IN, CH	PO IV IV IV, IM IV, IM	250 total dose 100 200-240 30-100 50-100	12 12 6-8 8-12 6-8	Vial Tab	250, 750 125, 250	

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
50.	Cefotaxime (R) Other infections	NB < 7 days > 7 days IN, CH IN, CH	IV, IM IV, IM IV, IM IV	100 150 100-200 200	12 8 6-8 6	Vial	250, 1000	Excellent CSF penetration; ineffective against enterococci and listeria. Contains 2.2mEq Na/g of salt.
51.	Bacterial Meningitis	IN, CH	IV	200	6	IV		
51.	Ceftazidime (R)	NB	IV	See newborn table		Vial	250, 500, 1000	Possesses anti-pseudomonal activity Excellent CSF Penetration.
	Meningitis	IN, CH		150	8			
	Other infections	IN, CH		100-150	8			
52.	Ceftizoxime (R)	IN (> 3 mo)	IV	30-60	8-12	Vial	500, 1000	Refrigerate reconstituted soln. More effective against gram positive organisms.
	Severe infections	IN, CH		100-150	8-12			
53.	Ceftriaxone (H)	NB, IN, CH	IM, IV	50-100	12	Vial	250, 500, 1000	May cause Pseudomembranous colitis. Amp, containing 1% lignocaine is provided with IM preparations. Displaces bilirubin from albumin binding sites.
	Meningitis			80-100	12			
	Typhoid			75	12			
54.	Chloramphenicol (R, H)	NB	See newborn chart			Syr/Susp	125	Newborns may develop gray baby syndrome
		IN, CH	PO, IV (15-30 mins)	50-100	6	Cap Vial	250, 500 500, 1000	
55.	Chloroquine (R) Therapeutic	CH	PO(PC)	10 mg/kg (base) stat followed by 5 mg/kg after 6 hours, then 5 mg/kg OD x 2 days 5mg/kg(base) per dose 12 hrly 5 mg base/kg/weekly		Tab Syr Amp.	150 mg base 50 mg base 40 mg base for parenteral therapy. IV preparation can be dilute with 10 mL/kg of isotonic saline and infused over 3-4 hrs.	Repeat treatment if vomiting occurs within 30 mins of giving drugs persistent vomiting, severe illness calls for parenteral therapy. IV
	Prophylaxis		IM, IV PO					
56.	Chlorpromazine (H)	IN, CH	PO	2	4-6 PRN	Tab	10, 25, 50 100	Overdose may produce Parkinsonian syndrome.
			IM Slow IV	2 1-2 mg/kg/dose	24 2-4 hrly	Syr Amp.	5, 25 25	

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
57.	Chlorthalidone	CH	PO	1-2	24	Tab	100	
58.	Ciprofloxacin	NB, IN, CH	PO IV	10-15 5-10	12 12	Tab IV infusion	250, 500 750 200 mg/100 mL 100 mg/50 mL	Inhibits metabolism of theophylline. Arthropathy in juvenile animals. Food, antacids interfere with absorption.
59.	Cisapride	IN, CH	PO	0.5-1	6-8	Susp	5	C/I-GI hemorrhage, intestinal perforation. < 34 wks GA
60.	Clarithromycin (R)	CH	PO	15	12	Susp Tab	125, 250 250, 500	
61.	Clindamycin (R)	NB<7 days > 7 days IN, CH	PO PO	10-15 15-20 20-40	12 6-8 6-8	Cap Amp	75, 100, 150 150	Pseudomembranous enterocolitis.
62.	Clofazimine (H,R) Leprosy Lepra reaction	CH	PO PO	1-2 100 mg/dose	OD Twice or thrice daily for 21 days	Cap	50 100	Turns body secretions and excreta red, brownish black
63.	Clonazepam (R)	CH	PO	Start 0.01-0.05 Increase to >0.3 mg/kg/d	12	Tab	0.5- 2	Concomitant use of valproic acid may produce petittimal status
64.	Clonidine	CH	PO	5-10 µg/ kg/day; can be increased gradually to 25 µg/ kg/day in 4 divided doses	8-12	Tab	100, 200 µg	
65.	Cloxacillin (R)	IN, CH	PO IV	50- 100 100- 200	6 6	Syr Cap Vial	125 250, 500 250, 500 1000	Inj stable at room temperature for 3 days.
66.	Codeine phosphate (H, R) Antitussive Analgesic	IN, CH IN, CH	PO PO	1-1.5 4	4 PRN 4-6 PRN	Syr Tab	10 15, 30, 60	Avoid use in neonates

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
67.	Cyclosporin (R, H)	IN, CH IV (2-6 hrs)	PO	14-18 initial 1-2 wks there after 5-10 2-6	OD 12-24 12-24	Solin Amp	100 50	Monitor levels of cyclosporin
68.	Deferoxamine (R) Acute iron intoxication	CH CH	SC IV	50 mg/kg/total over 6-8 hrs 15 mg/kg/hr (max 6 g/day)		Vial	500 mg	C/I: ARF unless hemodialysis is done simultaneously
69.	Deoxycorticosterone acetate (DOCA)	IN, CH	IM	1-5 mg/dose	OD	Inj	5	
70.	Desmopressin (DDAVP)	IN (> 3 mo) CH	Intranasal	10-20 µg total	12-24	Solin Inj	10 µg/ metered spray 4 µg /ml	Avoid in renal impairment, hypertension
71.	Dexamethasone Airway edema/extubation (start 12-24 hr before extubation) Bacterial meningitis Cerebral edema	NB CH IN, CH IN, CH	IV IV IV IV	0.25 mg/kg/dose 0.5-2 mg/kg/day 0.6 mg/kg/d 1-2 mg/kg loading; 1-1.5 mg/kg/d	12 hr (3-4 dose) 6 hr (4-6 dose after extubation) 6 hr (4 days) 4-6 hr	Tab Vial	0.5 mg 8 mg, 100 mg	
72.	Dextran	CH	IV	20 mL/kg infusion over 1-2 hrs		Dextran 40 Dextran 70		Plasma volume expander
73.	Diazepam (H, R)	NB IN, CH	IV, PO IV, PO PR	0.1-0.3 mg/kg/dose 0.1-0.5 mg/kg/dose 0.3-0.5 mg/kg/dose		Tab Syr Amp	2.5 2 5	IV given slowly (< 1 mg/min) undiluted; higher doses for tetanus neonatorum.
74.	Diazoxide (R) Hypertension Hyperinsulinemic hypoglycemia	CH	IV PO	2-5 mg/kg/dose 8-15	Bolus 8-12	Amp Syr	15 50	Repeat after ½ hour if necessary. Switch to oral medication as early as possible

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
75.	Dicyclomine (R,H)	NB IN, CH	PO PO	2.5-5 mg/dose total 5-10 mg/dose	6-8 6-8	Drops Susp Tab Inj	10 10 20 10	
76.	Digoxin (R) Digitalizing dose (mg/kg)  Maintenance	Premature NB, CH IN  NB IN, CH	IV IM, IV PO IM, IV PO  PO PO	0.015-0.025 0.01-0.03 0.04 0.03-0.04 0.05  0.05-0.01 0.015	   12-24	Elixir Tab Amp	0.25 0.25 0.25	Half of digitalizing dose is given as loading followed by ¼ after 8 hours and rest ¼ after another 8 hours. Maintenance begins 24 hr after the digitalizing dose Toxicity increases by calcium channel blockers. IV calcium should be given to digitalized patients. C/I: ventricular tachycardia and ventricular premature beats.
77.	Dimercaprol (BAL) (H) (R)	IN, CH	IM	12-24	4	Amp	50	Antidote for As, Au, Hg and Pb poisoning
78.	Diphtheria antitoxin (ADS-equine)  Pharyngeal and laryngeal Nasopharyngeal  Extensive disease or with > 3 days duration	IN, CH	IV	20,000-40,000 U total dose 40,000-60,000 U total dose 80,000-1,00,000 U total dose		Amp	10,000 u 20,000 u	Test sensitivity to horse serum. Sensitive patients must be desensitized.  IV given diluted 10-20 in isotonic saline, rate 1 ml/min.
79.	Dobutamine	NB IN, CH	IV (Constant infusion)	2-20 µg/kg/min 5-20 µg/kg/min		Vial	250 mg	Not to be mixed with NaHCO <sub>3</sub>
80.	Domperidone	IN, CH	PO	0.6-1.2	8	Tab Drops Susp	10 1 5	Extrapyramidal reactions less than metoclopramide
81.	Dopamine	NB IN, CH	IV Constant infusion	2.5-20 µg/kg/min 2.5-40 mg/kg/min		Amp 5 mL	40 mg/mL	C/I obstructive cardiomyopathy. Not to be mixed with sodium bicarbonate.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
82.	Doxapram HCl	NB	IV	Start with 0.5 mg/kg/hr and increase by 0.5 mg/kg/hr to a maximum of 2.5 mg/kg/hr		Amp	20 mg/mL	Constant infusion for apnea of prematurity failing the ophylline therapy. Not to be mixed with sodium bicarbonate.
83.	Enalapril (R)	IN, CH	PO	0.1- 1.0	12- 24	Tab	2.5, 5	
84.	Enoxaparin (R)	IN, CH	SC	< 2 mon- 1.5 mg/kg/ dose ≥ 2 mon- 1 mg/kg/dose	12 12	Inj	100 mg/ mL	
85.	Erythromycin (R)	IN, CH	PO	30-50	6	Tab	100,125,250, 500	C/I, Hepatic dysfunction and gastritis.
			IV	15-20	6	Susp Drops Inj.	125 100 1 g	
86.	Ethosuximide (H, R)	IN, CH	PO	20-40	12	Tab Syr	250 250	
87.	Fentanyl (R)	NB, IN, CH	IV	1-5 µg/kg/dose Continuous infusion: 1-5 µg/kg/hr	1-4 hr	Amp	50 µg	Rapid infusion may lead to chest wall tightness
88.	Fluconazole (R)	CH	PO,IV	3-6	12-24	Inj Cap, Tab	2 mg/mL 50, 100, 150, 200	
89.	Flucytosine (R)	NB,IN,CH	PO,IV	50-150	6-8	Tab Inj.	500 10 mg/mL	For cryptococcal meningitis along with Amphotericin B.
90.	Fludrocortisone acetate (R)	Any age	PO	5 µg/kg	OD	Tab	100 µg	
91.	Fosphenytoin (R)	CH	IV	Loading dose in status epilepticus: 15-20 mg Phenytoin equivalent (PE)/kg. Maintenance 4- 6 mg PE/ kg/ d	24	Inj	50 mg PE per mL	

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
92.	Fluticasone (H)	IN, CH	Inhalation	100-500 µg/d	12	MDI	50, 125 µg actuation	
93.	Formoterol	IN, CH	Inhalation	24-48 µg/d	12-24	MDI	12 µg per actuation	
94.	Ganciclovir (R)	IV	NB IN, CH	12 Induction: 10 Maintenance: 5	12 12 24	Vial	500	
95.	Gentamicin (R)	NB IN, CH	IV, IM IV, IM (30-60 min)	See Newborn table 5-7.5	6-8	Amp Ped Amp	40 10	
96.	Glycerol	IN, CH	PO	0.5-1g/kg/ dose	6	Bottles of 300 mL	1 g/mL	
97.	Heparin	NB, IN, CH	SC, IV	100 U/kg/dose 15-35 U/kg/hr	6 Continuous infusion	Vial	1000 U/5mL 5000 U/5mL	Adjust dose to maintain PT between 2-3 times normal.
98.	Hepatitis B specific Globulin	NB, IN, CH	IM (Deep)	0.5 mL within 12 hr of birth 0.06-0.1 mL/kg single dose		Amp	0.5, 1, 5 mL	Advised at the time of exposure to infected blood and infants of HBsAg+ve mothers.
99.	Human normal immunoglobulin Primary Immunodeficiency Attenuation of measles Hepatitis A	NB, IN, CH	IV  IM (Deep)	0.2-0.6 mL/kg once every 3-4 wks. 0.3 mL/kg stat within 6 days of exposure 0.02-0.04 mL/kg stat		Vial	10% and 16.5%	Administration of live vaccines should be delayed for 6 weeks following immunoglobulin administration
100.	Human rabies specific immunoglobulin	IN, CH	IM, Local	20 U/kg		Vial	150 U/mL	Post-exposure; As much as possible is infiltrated locally and the rest is given IM, if patient presents within 24 hours of bite. Total dose given IM if case presents within 1-7 days. Rabies vaccination administered simultaneously at different sites.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
101.	Hydralazine (R)	CH	PO IV, IM	1-3, 5 0.15 mg/kg/dose	6	Tab Amp	25, 50 20	C/I-Porphyrria Repeat IM/IV dose every 30-90 mins till desired is obtained.
102.	Hyoscine butylbromide	CH (6-12 years)	PO IM, IV	10 mg total dose 10-20 mg bolus	8	Tab Amp	10 20	Intestinal and biliary colic
103.	Ibuprofen (R) JRA	CH	PO PO	20-40 30-70	4-6 4-6	Tab Susp	200, 400 100	Avoid aspirin simultaneously; give with food or milk. C/I- Hypersensitivity to NSAIDs.
104.	Imipenem/cilastatin	IN, CH	IV IM	60-100	6	Vial	500, 1000 mg of imipenem	
105.	Indomethacin Anti-inflammatory Nephrogenic diabetes Insipidus Closure of ductus	CH CH NB	PO PO IV	1-3 3-5 0.2 mg/kg start irrespective of age allowed by 0.1-0.2	6-8 8 8	Cap Vial	25, 50 1 mg	C/I-Peptic ulcer, GI hemorrhage Doses of IV preparation not to be diluted.
106.	Insulin (Plain) DKA		IV	0.1 U/kg 0.1 U/kg/hr in half normal saline continuous infusion till blood sugar comes down to 300 mg/dL		Vial	40, 80 U	Low dose regimen for diabetic ketoacidosis
107.	Ipratropium	IN, CH	Inhalation MDI Nebulization	50-100 µg/d 250 µg – 500 µg per dose	6-12 4-6	MDI Nebulization solution	20 µg per actuation 250 µg/mL	
108.	Kanamycin (R)	NB IN, CH	IM, IV IM, IV (30 min)	See newborn table 6-15	12-24	Vial	500, 1000	Avoid using with other nephrotoxic drugs.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
109.	Ketamine	IN, CH	IV	0.5 mg-2 mg/kg stat 3-7 mg/kg stat Supplemental doses 1/3rd of initial dose	-	Vial	10 mg/mL 50 mg/mL	Increases respiratory secretions; Administer atropine 0.01 mg/kg
110.	Labetalol Hypertensive crisis		IV PO	0.2-2 mg/kg/hr 5-10	Continuous infusion 12	Tab Amp	50, 100 5	C/I-Asthma, CHF, Heart block
111.	Lactulose	< 2 years > 2 years	PO	2.5-10 mL/day 40-90 mL/day	6-8 6-8	Syr	10 g/15 mL	For hepatic encephalopathy, titrate dose to produce 2-3 loose stools per day.
112.	Lignocaine hydrochloride (H) Loading Maintenance	NB, IN, CH	IV (2-4 mins) IV	1-2 mg/kg 20-50 µg/kg/min		Vial  Continuous infusion	2% soln 1 mL = 21 mg	Dose may be repeated every 5-10 min. ECG monitoring necessary. Most useful in controlling life threatening arrhythmias esp. those associated with digitalis.
113.	Linezolid	NB, IN, CH	IV	< 7 days age: 20 ≥ 7 days age: 30	12 8	IV infusion	600 mg 300 mL	Protect infusion from light
114.	Lorazepam (R)	NB, IN, CH	IV PO	0.05 mg/kg dose stat 0.05-0.1	6	Tab Amp	1,2 2	May be repeated after 15-20 mins. for 2 doses.
115.	Lytic cocktail Pethidine Promethazine Chlorpromazine		IM (deep)	2, <50 mg 1, ≤ 25 mg 1, ≤ 25 mg	Single dose			May cause sudden hypotension.
116.	Magnesium sulfate (R) Cathartic Hypomagnesemia Asthma	CH IN, CH CH	PO IM IV IV	250 mg/kg/dose 100 mg/kg/dose 100 mg/kg slowly/dose 50-100 mg/kg/dose	4-6	Amp	1%, 10% 20%, 50%	50% solution preferable for IM and 1% solution for IV use. 1% solution contains 10 mg magnesium /mL (0.08 mEq magnesium/ml)

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
117.	Mannitol Cerebral edema	IN, CH	IV (30-60 mins.)	(1-2.5 g/kg/dose)	6-8	Bottles (20%)	250 mL and 500 mL	C/I-active intracranial bleeding, pulmonary edema. 20% Solution
118.	Mephentermine		IV (slow)	0.4 mg/kg/dose bolus		Vial	15, 30 mg base	Indications-hypotension following surgery or anesthesia. C/I-Hypovolemic shock
119.	6-Mercaptopurine (R)	IN,CH	PO	2.5	OD	Tab Vials	50 1,2,4,6	Reduce dose to 1/3-1/4 allopurinol is given concurrently.
120.	Meropenem (R)	NB, IN, CH	IV	60- 120	8	Vial	1 g	
121.	Methylene blue (R)		IV (5 min)	1-2 mg/kg/dose		Amp	1%	Treatment of symptomatic methemoglobinemia.
122.	Methyldopa (R)	CH	PO	10-40	8-12	Tab	250	C/I-Hepatic dysfunction, pheochromocytoma, depression
123.	Methylprednisolone		PO IV (30 min)	1-2 20-30 mg/kg	6-8	Tab Inj	2, 4, 16 500,1000	Frequency of bolus dose depends on clinical condition.
124.	Metoclopramide (R) Chemotherapy-induced emesis	NB IN, CH	PO PO,IM IV (5 min)	0.1-0.3 0.4-0.5 2-3 mg/kg/dose	8 6	Tab Syr Amp	10 5 5	Dystonic reactions may occur. Antidote-diphenhydramine
125.	Metolazone (H, R)	CH	PO	0.2-0.4	12-24	Tab	0.5, 5	
126.	Metoprolol (H) Hypercyanotic spell	CH	PO IV	1-5 0.1 mg/kg/dose	12	Tab Inj	50, 100 1	Selective beta-blocker. C/I CHF, heart block.
127.	Metronidazole (H, R) Amebiasis Trichomoniasis Giardiasis Anaerobic infection	CH CH NB, IN, CH NB, IN, CH	PO PO IV IV	30-50 15 15 mg/kg stat 15 mg/kg/stat then 20-40	8 8 8 8	Susp Tab Inj. (100 mL)	100,200 200,400 5 mg/mL	Therapy for 5-7 days in giardiasis and trichomoniasis and 10 days in amebiasis.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
128.	Midazolam (H, R)	NB	IV	0.2-0.5 µg/kg/min continuous infusion or 0.05-0.15 µg/kg 0.05-0.2 µg/kg/od 1-2 µg/kg/min or 0.5-0.2 µg/kg 0.15 µg/kg iv loading; continuous infusion 1-8 µg/kg/min	2-4 hr 2-4 hr	Vial	5 mg, 10 mg	
129.	Milrinone (R)	IN, CH	IV	50 µg/kg loading dose; continuous infusion: 0.25-1 µg/kg/min maintenance	Continuous infusion	Inj	1 mg/ mL	In children with low/ borderline BP, loading dose may be avoided
130.	Morphine (R)	NB IN, CH	SC, IM, IV SC, IM, IV (5 min)	0.05-0.1 mg/kg/dose 0.1-0.2 mg/kg/dose	4-6 PRN	Amp	10, 15, 25	Overdose may cause respiratory depression; antidote-nalorphine/naloxone.
131.	Naloxone HCl	NB, IN, CH	SC, IV, IM	0.1 mg/kg/dose		Amp	400 µg/mL	To be repeated after 2-3 mins PRN up to 3 times, and thereafter 1-2 hr till opioid depression persists. Not to be given to infants to addictive mothers.
132.	Naproxen (H, R)	(CH > 2 yr)	PO	10-20	12	Tab	250	C/I-Peptic ulcer syndrome.
133.	Neostigmine (R)	NB IN, CH	PO IM, SC PO IM, SC	1 mg/dose 50-250 µg/dose 1.3 mg/dose 250-500 µg/dose	4 4-6 4	Tab Amp	15 0.5, 2.5	Dose to be administered 30 min prior to feeds C/I: intestinal and urinary obstruction.
134.	Netilmicin (R)	NB < 7 days > 7 days, IN, CH	IM, IV (30-60)	5 7.5 5-7.5	12 8 8	Amp	10, 25, 50 100, 200, 300	Less nephrotoxic compared to other aminoglycosides.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
135.	Nifedipine	IN, CH	SL, PO	0.25-0.5 mg/kg/dose	6-8	Cap Tab (Retard preparation)	5, 10 20	Concurrent administration with $\beta$ blockers may lead to hypotension, angina and cardiac failure.
136.	Nitrazepam	IN, CH	PO	0.5-1	12-24	Tab	5, 10	Used in myoclonus, psychomotor epilepsy, absence seizures and infantile spasms.
137.	Nitroglycerine (H, R)	IN, CH	IV	0.5-10 $\mu$ g/kg/min	Continuous infusion	Amp	50 mg	Venodilator
138.	Nitroprusside (H, R)	IN, CH	IV	Start at 0.3-0.5 $\mu$ g/kg/min; Usual dose 3-4 $\mu$ g/kg/min; max-10 $\mu$ g/kg/min	Continuous infusion	Vial	50 mg	Protect from light
139.	Norepinephrine	IN, CH	IV	0.1-2 $\mu$ g/kg/min	Continuous infusion	Amp	1 mg	Increase systemic vascular resistance; moderately inotropic
140.	Ondansetron (H)	IN, CH	IV PO	0.15-0.45 kg/dose <4 years 2 mg 4-11 years 4 mg $\geq$ 12 years 8 mg	8 4 4 4	Tab Amp	4 mg, 8 mg 2 mg/mL	
141.	Oseltamivir (R)	IN, CH	PO	< 15 kg – 60 mg 15-23 kg – 90 mg 24-40 kg – 120 mg >40 kg – 150 mg	12	Cap Syrup	75 mg 12 mg/ mL	
142.	Pancuronium (H, R)	IN, CH	IV	0.04-0.1 mg/kg/dose	Repeat q 20-30 min	Amp	1 mg 2 mg	
143.	Pantoprazole	CH	IV	1- 2	12- 24	Inj	40 mg	
144.	Paraldehyde	NB IN, CH	IV, PR IV, IM PR	0.2 mL/kg/dose 0.15 mL/kg/dose 0.3 mL/kg/dose equally diluted with liquid paraffin		Amps		Use glass (not plastic) syringes. PR preferred route as IM is painful and can cause pulmonary edema and hemorrhage. Dilute 1:10-1:25 for IV use.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
145.	Penicillin, benzyl (R) Infections other than meningitis  Meningitis	NB < 2000 g NB > 2000 g IN, CH  NB < 2000 g > 2000 g IN, CH	IM, IV IM, IV IM, IV  IM, IV IM, IV	50,000 U 75,000 U 25,000 -50,000 U 1,00,000 U 1,50,000 -2,00,000 U 2,00,000 - 4,00,000 U	12 12 4-6  12 8 4-6	Vial	5,00,000 10,00,000 20,00,000	Sodium potassium content 1.68 mEq/1 million units.
146.	Penicillin Procaine (R)	NB IN, CH	IM IM	50,000 U 25000- 50,000 U	OD OD	Vial	4,00,000 U	
147.	Pentazocine	CH	PO,IM,IV	0.5-1	4	Tab, Inj	30	
148.	Pethidine (H, R)	NB IN, CH	IM, SC SC, IM	0.5 mg/kg/dose 1-1.5 mg/kg/dose	6 PRN 4-6 PRN	Amp	50	Antidote naloxone, nalorphine. May produce seizures, coma in sensitive patients.
149.	Phenobarbitone (H, R)  Anticonvulsant Status epilepticus		PO IV	4-6 10-20 mg/kg loading followed by 5-10 mg/kg/dose/PRN; maximum 40 mg/kg/total	12-24	Susp Amp	20 200	Porphyria Unsuitable for long term use if produces hyperactivity, irritability
150.	Phenoxybenzamine Initial Maintenance		PO	0.2 1-2	6-12 6-12	Cap	10	Control of hypertension in pheochromocytoma
151.	Phenytoin (H, R) Status epilepticus  Long-term  Ventricular tachyarrhythmia	NB, IN, CH  NB, IN, CH  NB, IN, CH	IV  PO  IV Over 5 mins(>0.5 mg/kg/min)	15-20 mg/kg/ loading dose (<1 mg/kg/min) 3-8  2-4 mg/kg/dose	8-12 12-24	Tab Susp Amp	100 125/5 mL 30/5 mL 50	Monitor heart rate can be diluted with saline but not with dextrose. C/I-Porphyria Blood levels increased by dexamethasone. Very effective for digoxin induced arrhythmias and late ventricular arrhythmias following repair of congenital cardiac defects.

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(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
152.	Physostigmine	CH	IM, IV SC	0.001-0.03 mg/kg/dose	Repeat q 15-20 min to desired effect or a maximum dose of 20 mg	Amp		
153.	Piperacillin (R)	NB IN, CH	IM, IV (15-30 min)	100 200-300	12 4-6	Vial	1 g	Effective against <i>Klebsiella</i> and <i>Pseudomonas</i> ; contains 1.85 mEq Na/g salt.
154.	Pralidoxime (PAM) (R)		IV, IM (5-10 min)	25-50 mg/kg/stat.	Rpt.8-12 hr PRN	Vial	1 g	Antidote for organophosphate poisoning.
155.	Prazosin (R) Initial Maintenance	CH	PO	0.1 0.1- 0.4 (Max daily dose = 20 mg)	6 6	Tab	0.5, 1, 2	Dose may be increased up to 15 mg; orthostatic hypotension common
156.	Prednisolone	IN, CH	PO (PC)	1-2	6-8	Tab	5, 10, 20	Activity of steroid is reduced by rifampicin and hydantoin. May flare up TB, other infections.
157.	Primaquine	IN, CH	PO	0.55 (= 0.3 mg base)	OD	Tab	26.5 mg = 15 mg base	C/I-G6PD deficiency
158.	Procainamide (R)	IN, CH	PO IV	20-30 3-6 mg/kg/dose followed by continuous infusion of 20- 80 µg/kg/min	4-6	Tab Inj.	250 100	Too rapid or overdose produces hypotension; Monitor blood pressure and QT interval during therapy C/I-2nd, 3rd degree heart block

Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
159.	Propofol Continuous sedation	CH	IV	1.5-3 mg/kg/dose over 1-2 min 5 mg/kg/hr for 30 min gradually increase to 12 mg/kg/hr	-	Vial	100, 200, 500	Hypoperfusion may occur; in critically ill children, propofol infusion syndrome (acute bradycardia progressing to asystole combined with lipemic plasma, fatty liver enlargement, metabolic acidosis with negative base excess > 10 mmol (-1), rhabdomyolysis or myoglobinuria) has been reported.
160.	Propranolol (R, H) Supraventricular and ventricular tachycardia  Prevention of cyanotic spell Antihypertensive Migraine prophylaxis	NB  IN, CH  IN, CH  IN, CH	IV (10 min)  PO IV (10 mins)  PO PO PO	0.05-0.15 mg/kg/dose Rpt. after 10 mins then 8 hr. 0.5-1 0.01-0.1 mg/kg/dose 4 0.5-2 1-2	6-8 6-8 PRN 6-8 6 6-8 6-8	Tab Inj.	10, 40 1	C/I-Asthma, CCF.
161.	Prostaglandin E <sub>1</sub>	NB	IV	0.05-0.4 µg/kg/min; After opening of the ductus, dose reduced to 0.01 µg/min	Continuous infusion	Amp	500 µg	Platelet aggregation defect
162.	Protamine sulfate	IN, CH	IV	1 mg protamine for 100 U of heparin		Amp	10 mg	Calculate dose carefully based on duration of time since last heparin dose using heparin elimination half life (n/hr) to estimate heparin stores.

Contd...

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Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
163.	Quinidine (H, R)	IN, CH IN, CH	PO IM, IV	30 mg/kg/day 2-10 mg/kg/dose	4-6 3-6 PRN	Tab Inj	200 (sulfate) 80 (gluconate)	Quinidine sulfate is given orally and gluconate given IM, IV. Test dose of 2 mg/kg given PO to exclude idiosyncrasy. Not to be given in neonates; Erratic absorption with IM use. Preferred for oral use on long term.
164.	Quinine sulphate Quinine dihydrochloride	IN, CH IN, CH	PO IV	25-30 20 mg/kg salt diluted (conc 1 mg/mL of saline) over 4 hr as loading then 10 mg base/kg 8 hourly as 4 hr infusion	8	Tab Amp	150, 300 300	Quinine dihydrochloride 12 mg = 10 mg base Arrhythmias and hypotension may occur, monitor blood sugar for hypoglycemia.
165.	Ranitidine (H, R)	NB, IN, CH	IV PO	1-3 2-6	6-12 8-12	Tab Amp	150, 300 25	
166.	Ribavirin (H, R)	IN, CH	PO	10	6-8	Cap Syr Powder	100, 200 50 6 g	6 g powder is dissolved in 300 ml water. Nebulised for 12-18 hr/24 hr for 3-7 days. For RSV bronchiolitis.
167.	Salmeterol	IN, CH	Inhalation	50-100 µg/d	12	MDI	25 µg per actuation	
168.	Spironolactone (R)	CH	PO	1.5- 3	6- 12	Tab	25, 100	C/I-Hyperkalemia, renal failure.
169.	Succinyl choline (H)	In, CH	IV	1- 2 mg/ kg/ dose; maintenance: 0.3-0.6 mg/ kg/ dose every 5-10 min	PRN	Inj	20 mg/ mL; 50 mg/ mL	
170.	Sulfadoxine + Pyrimethamine (R)	IN, CH	PO	1.25 mg/kg of pyrimethamine	OD	Tab Syr	25 of pyr 25 of pyr/ 10 mL	For chloroquine resistant malaria

Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
171.	Sulfamethoxazole-Trimethoprim (H, R) Severe UTI and Shigellosis <i>P. jiroveci</i> infection	IN (> 2 mo) CH	PO  IV (60-90 min)	6-12 TMP 30-60 SMX 8-10 TMP 40-50 SMX 15-20 TMP 75-100 SMX	12  6-8  6-8	Syr  Ped Tab Tab Inj	40 TMP  20, 40 TMP 80, 160 TMP 16 mg/mL (IV)	IV preparation to be diluted 20-25 times and administered as infusion.
172.	Terbutaline (R)	CH	PO SC	0.1-0.15 0.01-0.02 mg/kg/ dose Nebulization 5-8 µg/kg inhalation at a time		Tab Syr Amp Nebulizer soln	2.5, 5 1.5 0.5 10 mg/mL	Being selective β blocker, is more potent than adrenaline in equivalent dose. Subsequent SC doses may be repeated at 15-20 minutes interval.
173.	Tetanus immunoglobulin Prophylaxis	NB, IN, CH	IM	500-3000 U 4 U/kg	Stat	Vial	250 U	Not to be given IV; refrigerate
174.	Theophylline (H) Asthmatic Maintenance Neonatal apnea	< 36 wk > 36 wk	PO PO	20 10 1-2 mg 2-4 mg	6 6 8-12 8-12	Tab, Syr	Of variable Strengths	Theophylline concentration of aminophylline is 85%, monoethanolamine salt 75% and choline salt 64%. Switch to oral as early as possible. C/I-cardiac arrhythmias. Erythromycin, ciprofloxacin cause increased serum concentrations.
175.	Thiopentone (H, R) Refractory status epilepticus	CH	IV	5 mg/ kg loading dose followed by 0.5-4 mg/kg/hr		Vial	500, 1000	
176.	Thyroxine	NB > 1-2 yrs	PO PO	10-15 µg 5 µg	OD	Tab	25, 50, 100, 200 µg	
177.	Tobramycin (R)	NB  IN, CH	See newborn table IM, IV (30-60 min)	5-7.5	8-12	Amp	10, 20, 40	

Contd...

Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
178.	Triamterene (H, R) CH	CH	PO	2-4 (max. 6)	12-24	Tab	50	Combined with Benzthiazide. C/I-Renal failure, hyperkalemia.
179.	Triclofos Sleep Sedation	IN, CH	PO	20-40 mg/kg/dose 10-20 mg/kg/dose		Syr	500	C/I-severe hepatic or renal impairment.
180.	Valproic acid (H)	CH	PO	15 10 Increase weekly by 5-10 mg/kg up to 30-60	8-12 12	Tab Syr	200 200	May retard hepatic drug metabolizing enzymes. Increases level of phenobarbitone. May precipitate absence status if used with clonazepam. Children <2 yr may have fatal hepatic dysfunction. C/I-Hepatic dysfunction.
181.	Vancomycin (R) Pseudomembranous colitis	NB < 1 wk > 1 wk IN, CH	IV PO, IV 10	20-30 20-30 40-60 40-50	12 8 6 6-8	Vial Cap	500 125, 250	Useful for pseudomembranous enterocolitis; drug of choice for methicillin resistant <i>Staphylococcus aureus</i> .
182.	Vasopressin (H) Diabetes insipidus Bleeding esophageal varices		SC, IM IV	5-10 U/dose 0.33 U/kg is loading followed by 0.002-0.01 U/kg/min	4	Amp	(20 units/mL)	Aqueous vasopressin 5-10 units may be tried to differentiate central form nephrogenic diabetes insipidus.
183.	Vecuronium (H, R)	NB, IN, CH	IV	0.1 mg/kg/dose followed by 0.05- 0.1 mg/ kg/ dose ever 1- 2 hr. Infusion: 1- 1.5 µg/kg/min	PRN			

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Contd...

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
184.	Verapamil (H, R)	IN CH Maintenance	IV IV PO	0.1-0.2 mg/kg over 2 mins 0.1-0.3 mg/kg over 2 mins 1-2	8	Tab Amp	40, 80 120 2.5	C/I-cardiogenic shock, AV block, sick sinus syndrome. Avoid use in neonate and infants, hypotension or bradycardia; antidote-calcium gluconate.
185.	Vit K Prophylaxis Therapeutic	NB IN, CH NB, IN, CH		0.5-1 mg stat 1-2 mg stat 2-10 mg/dose OD for 3 days		Amp	10 mg/mL	
186.	Voriconazole (H, R)	IN, CH	IV	Loading dose: 6 mg/kg/dose – 2 doses. Maintenance: 8	12 12	Vial	200	
187.	Warfarin (H, R)	CH	PO	0.05- 0.3	24	Tab	5	Prothrombin time to be maintained at 1.5- 2 times normal.

# Annexure



# Reference Laboratory Values

Tarun Gera

## A. Coagulation Profile and Hematology

Analyte or Procedure	Specimen	Reference Values
Activated partial thromboplastin time (APTT)	Plasma (citrate)	25-35 s Infants <90 s
Clotting time Lee-White, 37°C	Whole blood	Glass tubes 5-8 min (5-15 min at RT) Silicone tubes about 30 min prolonged
Factor I, see <i>Fibrinogen</i>		
Factor II	Plasma (citrate)	0.5-1.5 U/mL or 60-150% of normal
Factor IV, see <i>Calcium</i>		
Factor V		0.5-2.0 U/mL or 60-150% of normal
Factor VII		65-135% of normal
Factor VIII		60-145% of normal
Factor VIII antigen		50-200% of normal
Factor IX		60-140% of normal
Factor X		60-130% of normal
Factor XI		65-135% of normal
Factor XII		65-150% of normal
Factor XII (fibrin stabilizing factor, FSF)	Whole blood (citrate, oxalate)	Minimal hemostatic level 0.02-0.05 U/mL 1-2% of normal
Fibrin degradation products (D-dimer)	Plasma (citrate)	Adults 68-494 µg/L Mean 207
Fibrinogen	Whole blood (sodium citrate)	Newborn: 125-300 mg/dL Adult: 200-400
Prothrombin time (PT) One-stage (Quick)	Whole blood (sodium citrate)	In general, 11-15 s (varies with type of thromboplastin) Newborn prolonged by 2-3 s
Thrombin time	Whole blood (sodium citrate)	Control time ± 2 s when control is 9-13 s
Bleeding Time (Ivy)		Normal 2-7 min

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Analyte or Procedure	Specimen	Reference Values	
Erythrocyte count (RBC count) (millions of cells/mm <sup>3</sup> )	Whole blood (ethylenediaminetetracetic acid)	Cord blood	3.9-5.5
		1-3 d (cap)	4.0-6.6
		1 wk	3.9-6.3
		2 wk	3.6-6.2
		1 mo	3.0-5.4
		2 mo	2.7-4.9
		3-6 mo	3.1-4.5
		0.5-2 yr	3.7-5.3
		2-6 yr	3.9-5.3
		6-12 yr	4.0-5.2
12-18 yr, M	4.5-5.3		
Hematocrit (HCT, Hct) % of packed red cells	Whole blood (ethylenediaminetetracetic acid)	1 d (cap)	48-69%
		2 d	48-75%
		3 d	44-72%
		2 mo	28-42%
		6-12 yr	35-45%
		12-18 yr, M F	37-49% 36-46%
Hemoglobin (Hb) (g/dL)	Whole blood (ethylenediaminetetracetic acid)	1-3 d (cap)	14.5-22.5
		2 mo	9.0-14.0
		6-12 yr	11.5-15.5
		12-18 yr, M F	13.0-16.0 12.0-16.0
Hemoglobin A	Whole blood (ethylenediaminetetracetic acid, citrate, heparin)	> 95%	
Hemoglobin A <sub>2</sub> (HbA <sub>2</sub> )	Whole blood (ethylenediaminetetracetic acid)	Adult: 1.5-3.5% (2 SD) Lower in infants < 1 yr	
Hemoglobin (Hb) electrophoresis	Whole blood (heparin, ethylenediaminetetracetic acid, citrate)	HbA > 95% HbA <sub>2</sub> 1.5-3.5% HbF < 2%	
Hemoglobin F (%)	Whole blood (ethylenediaminetetracetic acid)	1 day	63-92
		5 day	65-88
		3 wk	55-85
		6-9 wk	31-75
		3-4 mo	<2-59
		6 mo	<2-9
		Adult	<2
Erythrocyte sedimentation rate (ESR) Westergren, modified (mm/hr)	Whole blood (ethylenediaminetetracetic acid)	Child	0-13
		Adult M, F,	0-9 0-20
Leukocyte count (WBC) ×1,000 cells/mm <sup>3</sup>	Whole blood (ethylenediaminetetracetic acid)	Birth	9.0-30.0
		24 hr	9.4-34.0
		1 mo	5.0-19.5
		1-3 yr	6.0-17.5
		4-7 yr	5.5-15.5
		8-13 yr	4.5-13.5
		Adult	4.5-11.0
Platelet count (Thrombocyte count) ×10 <sup>3</sup> /mm <sup>3</sup>	Whole blood (ethylenediaminetetracetic acid)	Newborn 84-478 (after 1 wk, same as adult) Adult 150-400	

## B. Biochemical values

Analyte or Procedure	Specimen	Reference Values	
Acetone (mg/dL)		0.3-2.0	
Alanine aminotransferase (ALT, SGPT) (U/L)	Serum	0-5 day 1-19 yr	6-50 5-45
Albumin (g/dL)	Plasma	Premature 1 day Full term <6 day <5 yr 5-19 yr	1.8-3.0 2.5-3.4 3.9-5.0 4.0-5.3
Aldolase (U/L)	Serum	10-24 mo 25 mo-16 yr	3.4-11.8 1.2-8.8
Ammonia (μmol/L)	Whole blood	<30 day 1-12 mo 1-14 yr >14 yr	21-95 18-74 17-68 19-71
Amylase (U/L)	Serum, Plasma	30-100	
Anti-streptolysin-O titer (ASO titer)	Serum	Age 2-5 yr 6-9 yr 10-12 yr	Upper limit of normal 120-160 Todd units 240 Todd units 320 Todd units
Alpha-1-Antitrypsin (mg/dL)	Serum	0-5 day 1-9 yr 9-19 yr	143-440 147-245 152-317
Aspartate aminotransferase (AST, SGOT) (U/L)	Serum	0-5 day 1-9 yr 10-19 yr	35-140 15-55 5-45
Bilirubin total (mg/dL)	Serum, Plasma	Cord blood 0-1 day 1-2 day 2-5 day >5 day	Premature Full-term <2.0 <2.0 <8.0 <6.0 <12.0 <8.0 <16.0 <12.0 <20.0 <10
Bilirubin conjugated	Serum	0-0.2 mg/dL	
C-reactive protein (ng/mL)	Serum	Cord blood 2-12 yr	52-1,330 67-1,800
Calcium, ionized (Ca) (mg/dL)	Serum, Plasma (heparin) Whole blood (heparin)	Cord blood Newborn, 3-24 hr 24-48 hr Thereafter or 2.24-2.46 mEq/L	5.0-6.0 4.3-5.1 4.0-4.7 4.8-4.92 2.24-2.46 mEq/L
Calcium, total (mg/dL)	Serum	Cord blood Newborn, 3-24 hr 24-48 4-7 d Child Thereafter	9.0-11.5 9.0-10.6 7.0-12.0 9.0-10.9 8.8-10.8 8.4-10.2

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Analyte or Procedure	Specimen	Reference Values		
Chloride (mmol/L)	Serum, Plasma (heparin)	Cord blood	96-104	
		Newborn	97-110	
		Thereafter	98-106	
Creatine kinase (U/L)	Serum	Cord blood	70-380	
		5-8 hr	214-1,175	
		24-33 hr	130-1,200	
		72-100 hr	87-725	
		Adult	5-130	
Creatine kinase isoenzymes	Serum		% MB    %BB	
		Cord blood	0.3-3.1    0.3-10.5	
		5-8 hr	1.7-7.9    3.6-13.4	
		24-33 hr	1.8-5.0    2.3-8.6	
		72-100 hr	1.4-5.4    5.1-13.3	
Adult	0-2%    0			
Creatinine (Jaffe, kinetic, or enzymatic) (mg/dL)	Serum, Plasma	Cord blood	0.6-1.2	
		Newborn	0.3-1.0	
		Infant	0.2-0.4	
		Child	0.3-0.7	
		Adolescent	0.5-1.0	
Creatinine clearance (endogenous) (mL/min/1.73 m <sup>2</sup> )	Serum, Plasma and U	Newborn	40-65	
		<40 yr, M	97-137	
		F	88-128	
Ferritin (ng/mL)	Serum	Newborn	25-200	
		1 mo	200-600	
		2-5 mo	50-200	
		6 mo-15 yr	7-140	
Glucose (mg/dL)	Serum	Cord blood	45-96	
		Premature	20-60	
		Neonate	30-60	
		Newborn		
		1 day	40-60	
		>1 day	50-90	
Child	60-100			
Glucose, 2 hr post prandial	Serum		<120 mg/dL	
Glucose tolerance test (GTT) (mg/dL) Child: 1.75 g/kg of ideal weight up to maximum of 75 g	Serum		Normal	Diabetic
		Fasting	70-105	126
		60 min	120-170	200
		90 min	100-140	200
		120 min	70-120	200
Glycohemoglobin hemoglobin A <sub>1c</sub> (% of total Hb)	Whole blood (heparin)	1-5 yr	2.1-7.7	
		5-16 yr	3.0-6.2	
Iron (µg/dL)	Serum	22-184		

Contd...

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Analyte or Procedure	Specimen	Reference Values	
Iron-binding capacity, total (TIBC) ( $\mu\text{g/dL}$ )	Serum	Infant	100-400
		Thereafter	250-400
Ketone bodies, qualitative	Serum	Negative	
Ketone bodies, quantitative (mmol/L)	Whole blood	1-12 mo	0.1-1.5
		1-7 yr	0.15-2.0
		7-15 yr	<0.1-0.5
L-Lactate (mmol/L)	Whole blood	1-12 mo	1.1-2.3
		1-7 yr	0.8-1.5
		7-15 yr	0.6-0.9
D-Lactate (mmol/L)	Plasma (heparin)	0.0-0.3	
Lead ( $\mu\text{g/dL}$ )	Whole blood (heparin)	Child	<10
		Adult	<40
		Toxic	100
Magnesium (mg/dL)	Plasma (heparin)	0-6 day	1.2-2.6
		7 d-2 yr	1.6-2.6
		2-14 yr	1.5-2.3
Methemoglobin (MetHb)	Whole blood (E,H,C)	0.06-0.24 g/dL or $0.78 \pm 0.37\%$ of total Hb	
Myoglobin	Serum	6-85 ng/mL	
Methylmalonic acid	Serum	0.03-0.26 $\mu\text{mol/L}$	
Phenylalanine (mg/dL)	Serum	Premature	2.0-7.5
		Newborn	1.2-3.4
		Thereafter	0.8-1.8
Phosphatase, acid prostatic (RIA)	Serum	<3.0 ng/mL	
Phosphatase, alkaline (U/L)	Serum	1-9 yr	145-420
		10-11 yr	130-560
		12-13 y	Male 200-495 Female 105-420
		14-15 y	130-525 70-230
		16-19 y	65-260 50-130
Potassium (mmol/L)	Serum	<2 mo	3.0-7.0
		2-12 mo	3.5-6.0
		>12 mo	3.5-5.0
Protein, total (g/dL)	Serum	Premature	4.3-7.6
		Newborn	4.6-7.4
		1-7 yr	6.1-7.9
		8-12 yr	6.4-8.1
		13-19 yr	6.6-8.2
Pyruvate	Whole blood	$0.076 \pm 0.026$ mmol/l	
Sodium (mmol/L)	Serum, Plasma (LiH, $\text{NH}_4$ H)	Newborn	134-146
		Infant	139-146
		Child	138-145
		Thereafter	136-146

Contd...

Contd...

Analyte or Procedure	Specimen	Reference Values	
Thyroid stimulating hormone (mIU/L)	Serum	Birth-4 d	1.0-38.9
		2-20 wk	1.7-9.1
		5 mo-20 yr	0.7-6.4
Thyrotropin releasing hormone (hTRH)	Plasma	5-60 pg/mL	
Thyroxine, total (µg/dL)	Serum	1-3 d	8.2-19.9
		1 wk	6.0-15.9
		1-12 mo	6.1-14.9
		1-3 yr	6.8-13.5
		3-10 yr	5.5-12.8
		Pubertal Children and Adults	4.2-13.0
Transferrin (siderophilin)	Serum	95-385 mg/dL	
Triiodothyronine, total (ng/dL)	Serum	Cord blood	30-70
		Newborn	75-260
		1-5 yr	100-260
		5-10 yr	90-240
		10-15 yr	80-210
		Thereafter	115-190
Urea nitrogen (mg/dL)	Serum, Plasma	Cord blood	21-40
		Premature (1 wk)	3-25
		Newborn	3-12
		Infant/child	5-18
		Thereafter	7-18
Uric acid (mg/dL)	Serum	1-5 yr	1.7-5.8
		6-11 yr	2.2-6.6
		12-19 yr	M: 3.0-7.7
			F: 2.7-5.7

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