INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

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- Editorial Board

FROM THE EDITOR'S DESK

The Journal Committee of IJPP wishes all our readers a very Happy New Year 2005.

I sincerely thank all the Office Bearers and members of IAP Executive Board 2004 for electing me as Editor-in-Chief of IJPP and giving me an opportunity to serve another tenure from 2005 to 2007. IJPP is entering the 13th year since its inception in 1993. It has undergone various transformations and modifications all these years. The journal has become very popular among practicing pediatricians and postgraduates. Today IJPP serves as a desktop reference and ready reckoner among practitioners. The Editorial Board is striving its best to maintain the academic standard and scientific content to suit the needs of all cadres in day to day practice.

This issue on "Management update II" will highlight the current guidelines and approaches for some important clinical conditions. Management of shock written by Dr.S.Shanthi is well written and the key message is comprehensive. She has stressed the importance of identification of shock and early intervention to avoid multisystem organ failure and death. Current guidelines in the management of septic shock is well narrated by Dr.Indumathi Santhanam and she has also mentioned the need to remember the key points in dealing with such a condition in the emergency room. In his article on acute renal failure in children, Dr.Sanjeev Gulati has given a detailed account on the diagnostic evaluation and management. The current scenario of management of drug resistant tuberculosis in children at global as well at the national level is discussed well by Dr.Soumya Swaminathan. The salient general principles on impaired consciousness and coma management is narrated in detail by Dr.Leema Pauline et al.

The diagnostic and treatment modalities on neonatal and childhood hypothyroidism written by Dr.Meena P.Desai is very descriptive. She has also mentioned the importance of early recognition of this eminently treatable condition. Dr.Ashish Bavdekar et al have dealt in detail on the current management of acute liver failure in children.

I hope the readers will find the article on probiotics in children by Dr. R. Anitha Srilakshmi et al to be informative and useful in clinical practice. We sincerely thank Dr.Vijayalakshmi et al for their continued contribution to the popular column on "Radiologist talks to you". The Journal Committee is thankful to all the other authors for their contribution to IJPP under various columns.

Dr. A. Balachandran
Editor-in-Chief

CHECK LIST

CHECKLIST FOR INDIAN JOURNAL OF PRACTICAL PEDIATRICS

The checklist must accompany the manuscript.

General

- Original articles which have not been published elsewhere are invited and should be sent to the Editor. They are considered for publication on the understanding that they are contributed to this journal solely.

- Four complete sets of the manuscript are submitted.

- Manuscript is typed double-space throughout with wide margin on one side of paper only including the list of references and tables.

- Manuscript is arranged as follows: Title page, text, acknowledgements, references, tables, figure legends, figures.

- All pages are numbered at the top of the right corner, beginning with the title page.

- The letter of submission has been signed by all authors.

Submission of "Floppy Disc"

Two copies of the articles plus a floppy disc of the wordprocessed manuscript and a list of any nonstandard characters that were used in the disc should be submitted in the usual manner. The preferred storage medium is a 3.5 inch disc in MS-Word compatible format. The publisher is under no obligation to use the submitted floppy disc, but will make every attempt to do so.

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- Only generic names should be used

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MANAGEMENT UPDATE

MANAGEMENT OF SHOCK

*** Shanthi S**

Abstract: Shock is a medical emergency. Early identification and management in the compensated stage is essential to prevent progression to Multi Organ Dysfunction Syndrome (MODS) and cardiopulmonary failure. Shock is characterised by signs of decreased organ perfusion. Hypovolemia is the commonest cause of shock in children followed by sepsis. Shock can occur in the presence of normal blood pressure. Hypotension is a late sign of shock and indicates decompensation. Aggressive fluid resuscitation in the first hour, often termed the golden hour, is life saving in septic and hypovolemic shock. Inotropes and vasodilators are needed in cardiogenic and septic shock. Blood products should be given in shock accompanying trauma.

Keywords: Hypovolemic shock, cardiogenic shock, resuscitation.

Shock is an acute, complex state of circulatory dysfunction that results in failure to deliver sufficient amounts of oxygen and other nutrients to meet tissue metabolic demands. Many common childhood illnesses such as trauma, gastroenteritis, infection and accidental drug ingestion can lead to shock. Unless shock is identified early and appropriate intervention

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instituted, the child in shock will follow a common pathway to multisystem organ failure and death.

Classification of shock

Compensated shock is defined by the presence of systolic BP within the normal range with signs and symptoms of inadequate tissue and organ perfusion. Vital organ function is maintained.

Decompensated shock is present when signs of shock are associated with systolic hypotension.

Shock can also be classified based on the etiology as given in Table 1.

a) **Hypovolemic shock** is characterized by inadequate intravascular volume relative to the vascular space. It is the most common type of shock occurring in children.

b) **Cardiogenic shock:** It is often secondary to myocardial dysfunction. It is present in all forms of prolonged shock regardless of etiology. Cardiogenic shock is identified by the presence of one or more of the following features in addition to other signs of hypoperfusion: 1) systemic edema or pulmonary edema (lung crepitations on auscultation) or both, 2) increased work of breathing, 3) grunting, 4) gallop rhythm, 5) enlarged liver and 6) heart murmur Cardiogenic shock should be suspected when there is shock with increased work of breathing.

c) **Distributive shock** is characterized by inappropriate distribution of blood flow. Septic shock is a form of distributive shock. Abnormal hemodynamic responses constitute a primary hallmark of septic shock.

Table 1.Classification of shock based on etiology[1]

Cardiogenic	: Arrhythmias, cardiomyopathy, heart failure, valvular disease, myocardial contusion, myocardial infarction
Hypovolemic	: **Gastroenteritis, hemorrhage:** volvulus, peritonitis
Distributive	: **Septicemia,** anaphylaxis, vasodilating drugs, anesthesia, spinal cord injury
Obstructive	: **Tension pneumothorax, hemopneumothorax,** cardiac tamponade, pulmonary embolism
Dissociative	: Profound anemia, carbon monoxide poisoning, methemoglobinemia

(common causes are emboldened)

Diagnosis

Early recognition and management of shock is possible by doing a rapid cardiopulmonary assessment of a critically ill child, which uses the ABCDE approach.

A-Airway: Assess airway patency. If the child can speak or cry, this indicates that the airway is patent. Decide if the airway is a) patent b) maintainable with head positioning, suctioning or adjuncts c) unmaintainable and requiring intervention such as intubation.

B-Breathing: Assess the adequacy of breathing. This focuses on

a) Respiratory rate (RR): It is often increased in shock to promote the excretion of carbon dioxide and to compensate for metabolic acidosis.

b) Work of breathing (WOB): Presence of recession, accessory muscle use, flare of the alae nasi, grunt, stridor or wheeze indicate increase in work of breathing. However the WOB is often normal in shock. This is referred to as effortless or quiet tachypnea. If tachypnea is associated with increase in WOB, suspect cardiogenic shock.

c) Breath sounds-should be equal on both sides.

d) Chest expansion: Adequate chest expansion indicates good tidal volume.

C-Circulation: Assess the adequacy of circulation by evaluating the following signs

a) Heart rate (HR): Tachycardia, though not a very sensitive sign, is the earliest sign of shock and is an attempt to maintain cardiac output (CO). Bradycardia in a child with shock is caused by hypoxia and acidosis and is a preterminal sign[1]. The normal range of heart rate is given in table 2.

Table 2. Normal HR in children[2]

Age	Awake rate	Mean	Sleeping rate
NB- 3mo	85-205	140	80-160
3mo-2yrs	100-190	130	75-160
2-10 yrs	60-140	80	60-90
>10 yrs	60-100	75	60-90

b) Pulse volume: This is assessed by simultaneously palpating the central(femoral) and distal(dorsalis pedis) pulses.Weak or absent distal pulses is caused by peripheral vasoconstriction which occurs as a compensatory measure to preserve blood flow to the vital organs(heart, brain).Absent distal pulses usually indicate decompensated shock[2]. Loss of central pulses is a premorbid sign requiring very rapid intervention. In early

septic shock there is a high output state and low systemic vascular resistance leading on to bounding distal pulses.

c) Core peripheral temperature gap: This is clinically assessed by checking skin temperature. When CO declines cooling of the skin begins peripherally in the fingers and toes and proximally extends towards the trunk. A core/toe temperature difference of more than 2°C is a sign of poor skin perfusion.

d) Capillary refill: This is assessed by lifting the extremity slightly above the level of the heart and applying enough pressure just to blanch the skin for 5 seconds[1]. Normal capillary refill time (CRT) is 2 seconds. Prolonged CRT is seen in shock, rising fever or a cold ambient temperature. Hence CRT should be evaluated in the context of other signs of shock.

e) Blood pressure (BP): Shock can occur in the presence of normal, low or high BP. Children's cardiovascular system compensates well initially in shock[1]. Hypotension is a late and often sudden sign of decompensation and if not reversed will be rapidly followed by death.

According to Emergency Cardiac Care guidelines 2000, hypotension or decompensated shock is characterized by the following limits of systolic blood pressure (SBP) as given in table 3.

Table 3 Hypotension in relation to age

Age	BP mm of Hg
Term (0-28 days)	< 60
1-12 months	< 70
1-10 yrs	< 70 + (2 x age)
> 10 yrs	< 90

f) Skin color: Mottling, pallor and peripheral cyanosis often indicate poor skin perfusion.

g) Liver span: The measurement of liver span will be useful to find out about the probable etiology of shock (increased in cardiogenic shock) and in assessing fluid overload during treatment of shock.

h) Urine output: It is decreased or absent in shock. Normal urine output is 1-2ml/kg/hour in children. Hourly measurement is useful in monitoring progress.

D-Disability: A rapid measure of the level of consciousness should be recorded using the AVPU scale.

A-Alert, **V-**Responsive to voice, **P-** Responsive to pain, **U-**Unresponsive

Early signs of brain hypoperfusion are agitation and confusion, often alternating with

Table 4. Investigations in shock

Biochemical	Hematological	Sepsis screening	Others
Electrolytes	CBC, peripheral smear	Culture of blood,	CXR (for cardiac size,
BUN	PT (prothrombin time)	urine, CSF, exudates,	pneumothorax, pneumo-
Creatinine	PTT (partial thromboplastin	abscesses, and	nia and pleural fluid.)
Glucose	time)	cutaneous lesions.	ABG (to monitor
Liver function tests	Fibrinogen		progression of acidosis,
Calcium	Fibrin degradation products		diffusion and ventilation
Phosphorus	Type and cross-match blood		problems associated with
Cardiac enzymes as			ARDS) ECG and ECHO
indicated			(for cardiac function)

drowsiness. Infants may be irritable but drowsy with a weak cry and hypotonia. Loss of eye contact (not focussing on parent's eyes) in infants more than 2 months is an early and ominous sign of cortical hypoperfusion or cortical dysfunction[2].

Pupillary size and reaction should be noted. Note the child's posture. Children in shock are usually hypotonic. The presence of convulsive movements should be noted. Intermittent flexor or extensor posturing may occur with prolonged cerebral hypoperfusion or extreme hypoxia[2].

E-Exposure: Look for a rash; if it is present ascertain if it is purpuric. Look for evidence of poisoning, trauma or acute abdomen.

Investigations

Any child presenting with shock needs to undergo the basic investigation profile as given in Table 4.

Monitoring

The following parameters should be monitored continuously: Respiratory rate and pattern, heart rate, alterations in peripheral perfusion, color, BP, mental status, temperature, O_2 saturation with pulse oximeter and ECG monitor (Lead II).

Management of shock

The initial management follows certain priorities, regardless of etiology and is directed to reverse or halt further tissue injury. Since the first hour is considered as the golden hour shock should be aggressively managed during this period. Evaluation and treatment should take place simultaneously.

General principles

1. Resuscitation: Management of airway, breathing and circulation (ABC) takes precedence followed by a systematic approach to fluid therapy, pharmacological support and diagnostic evaluation.

2. Treat the underlying cause: Surgery may be needed to control hemorrhage. Identification of sepsis and eradication of microorganisms, draining abscesses etc should be done. Arrhythmias should be managed appropriately. Do pericardiocentesis / thoracocentesis if obstructive cause is suspected.

3. Treat associated metabolic disturbances.

4. Supportive therapy to prevent/treat multiorgan dysfunction syndrome (MODS): Management of multisystem deterioration with shock states is as important as treatment of the underlying condition. Renal, gastrointestinal, central nervous system and hematological abnormalities in shock need to be diligently searched for, identified and treated.

Resuscitation

Resuscitation is the most important aspect in the management of shock. ABC takes precedence and is managed as per the PALS guidelines.

Airway: Establish an adequate airway. Children with severe shock may require immediate endotracheal intubation to reduce the work of breathing and increase O_2 delivery.

Indications for intubation in shock

a) Decreasing vital capacity, increasing RR or rapidly progressive disease.

b) Inability to protect airway, low Glasgow Coma Scale (GCS) - less than eight.

c) Severe pulmonary edema or marked respiratory distress requiring PEEP

d) Cardiogenic shock.

e) Severe metabolic acidosis

Breathing: All children in shock should receive high flow oxygen. If the child is hypoventilating respiration should be supported with O_2 via a bag valve mask device followed by intubation and ventilation.

Circulation: 1) Vascular access must be rapidly established with two large bore short length intra vascular catheters. If an intravascular access could not be achieved, an intraosseous line should be started. 2) Take blood for investigations. 3) Attach a cardiac monitor. 4) If tachyarrhythmia is identified as the cause of shock, treat the underlying arrhythmia.

Fluid therapy: Once vascular access is achieved all forms of shock should be treated with fluids, since it augments preload. Ringer lactate (RL) or Normal Saline 0.9%(NS) is appropriate for initial crystalloid infusion.

Hypovolemic shock : In hypovolemic shock fluid should be given rapidly. The first bolus of 20 ml /kg of NS or RL is administered as rapidly as possible. Reassess the child for signs of shock. If signs of shock persist, a second 20 ml /kg bolus should be administered. Additional boluses should be infused as indicated by repeated assessments of the patient.A child with hypovolemic shock often requires 40-60 ml/kg. (Fig 1)

The amount of fluid necessary to restore effective circulating blood volume depends upon the amount lost (deficit) and the rate of ongoing loss. Replacement of losses can be guided by body weight changes, careful monitoring of intake and output and repeated physical examination. The end point of fluid resuscitation is restoration of RR and HR to normal ranges, normalization of peripheral perfusion and establishment of adequate urine output. Increase and normalization of BP alone is not the end point for shock correction. If shock improves with fluid boluses, maintenance fluids can be administered and vital signs monitored.

A child with a non hemorrhagic hypovolemic shock should usually respond to 2-3 boluses of crystalloids. If a child is unresponsive to this amount of fluid resuscitation, the child must be evaluated for complicating factors like unrecognized pneumothorax, pericardial effusion, sepsis, surgical problems, myocardial dysfunction, and adreno cortical insufficiency.

Shock not responding to initial fluid therapy, whatever be the etiology needs continuous hemodynamic monitoring. A central venous catheter should be inserted for measurement of central venous pressure (CVP) which will guide further management. These patients may need inotropic agents. In the hypotensive patient, a CVP of less than 10mm Hg, in the absence of pulmonary edema should be carefully augmented by fluid infusion until that level of preload is reached. Shock persisting in the face of a CVP> 10 mm Hg is an indication for placement of a flow directed thermo dilution pulmonary artery catheter. Fluid administration should be discontinued when ventricular filling pressure rises without evidence of improvement in cardiovascular performance.

In hypovolemia due to blood loss, if shock persists despite two boluses of crystalloids, blood (packed RBC-10ml/kg) must be transfused The possibility of occult intra thoracic or intra abdominal bleeding must be considered and early surgical intervention may be indicated.

If hypovolemia exists concurrently with hypoproteinemia 5%albumin or FFP 5-10ml/kg over 30 minutes may have to be given with careful monitoring. This infusion may be repeated until the patient is hemodynamically stable or the CVP increases[3]. (Fig. 1)

Cardiogenic shock

In cardiogenic shock fluid therapy should be carefully instituted as these patients have normal

or increased intravascular volume. An initial bolus of NS 10 ml/kg over 20 minutes should be given monitoring the liver span, cardiopulmonary status, and signs of fluid overload. If the liver span increases or fluid overload occurs the fluid should be stopped. If severe myocardial dysfunction is present a smaller 5-10 ml/kg fluid bolus should be given. If signs of shock persist, inotropes should be started.

Pharmacological agents in shock (Table 5)

1) Inotropes: Inotropes are drugs, which improve myocardial contractility. They are very useful in cardiogenic shock and septic shock. Inotropes are rarely indicated in hypovolemic shock. They are indicated in fluid refractory shock. The catecholamines are the most potent inotropic agents

Table 5. Drugs used in shock management[4]

Drug	Effect(s)	Dose range	Comments
Dopamine	Strengthens contractions (through out dose range) Increases renal blood flow (low/intermediate doses) vasoconstriction (high doses)	2-20 μg/kg/min	Increasing risk of dysrhythmias at high dose. Should be administered in central vein.
Epinephrine	Increases heart rate and strength of contractions. Potent vasoconstrictor	0.05-3.0 μg/kg/min	May lessen renal perfusion Causes high O_2 consumption in the heart. High risk of dysrhythmias.
Dobutamine	Increases strength of heart contraction Little effect on heart rate. Peripheral vasodilator especially in vessels to viscera	1-20 μg/kg/min	Has very weak vasoconstriction (high dose). Good for cardiogenic shock, strengthens heart contraction and produces afterload reduction
Norepinephrine	Strong vasoconstrictor. Weak effect on strength of heart contraction	0.05-1.5 μg/kg/min	Produces short-run rise in blood pressure (high SVR). Causes increase in O_2 consumption, tendency for dysrhythmias
Phenylephrine	Strong vasoconstrictor. Can be used to slow tachycardia through reflex cardiac slowing	0.5-2.0 μg/kg/min	Can cause sudden hypertension. Causes increase in O_2 consumption
Amrinone	Potent inotrope. Peripheral vasodilator	Load with 1.5-5 mg/kg/ bolus over 20 min. followed by 5-10 μg/kg/min	Phosphodiesterase inhibitor- slows cyclic AMP breakdown
Nitroprusside	Vasodilator (mainly arterial)	0.5-8.0 μg/kg/min	Rapid effect. Prolonged use (>48 hr risks cyanide toxicity)
Nitroglycerine	Vasodilator (mainly venous)	1.0-20 μg/kg/min	Rapid effect. Risk of high intracranial pressure .

available. They also possess chronotropic properties and complex effects on vascular beds of the various organs of the body. There is no usual drug or dose in shock; instead therapy must be continuously tailored to the patient's hemodynamic response. The doses can be increased every 15-20 minutes if there is no response.

Dopamine is commonly used for the treatment of hypotension or poor peripheral perfusion with adequate intravascular volume

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│                          ┌─────────────────────────────────────────────┐ │
│                          │ Suggestive findings:                        │ │
│                          │ Tachycardia, tachypnea, hypotension, delayed│ │
│                          │ capillary refill, acidosis, oliguria,       │ │
│                          │ altered mental status                       │ │
│                          └─────────────────────────────────────────────┘ │
│                                            │                              │
│                                            ▼                              │
│  ┌─────────────────────────┐    ┌─────────────────────────────────────┐  │
│  │ Improved vital signs,   │    │ Oxygen, oximetry                    │  │
│  │ mental status,          │◄── │ Assess airway and ventilation/      │  │
│  │ perfusion, and urinary  │Improved│ stabilize if necessary          │  │
│  │ output (>1 ml/kg/hr)    │    │ IV: 0.9% NS or RL 20ml/kg           │  │
│  └─────────────────────────┘    │ Lab: CBC, electrolytes, glucose,    │  │
│               │                  │ ABG, group and cross match          │  │
│               │                  │ Control losses                      │  │
│               │                  │ Urinary catheter, NG tube           │  │
│               ▼                  └─────────────────────────────────────┘  │
│  ┌─────────────────────────┐         │ Not improved                      │
│  │ Replace ongoing losses  │         ▼                                   │
│  │ Oxygen                  │    ┌─────────────────────────────────────┐  │
│  │ Establish etiology      │◄── │ Repeat crystalloid infusion         │  │
│  │ Frequent reevaluation   │Improved│ (0.9% NS or RL) 20 ml/kg x 2    │  │
│  └─────────────────────────┘    │ Reevaluate                          │  │
│                                  │   Ventilation and oxygenation       │  │
│                                  │   Vital signs including temperature,│  │
│                                  │   oximetry                          │  │
│                                  └─────────────────────────────────────┘  │
│                                        │ Not improved                     │
│                                        ▼                                   │
│                                  ┌─────────────────────────────────────┐  │
│                                  │ Search for alternative etiologies.  │  │
│                                  │ Consider central venous pressure    │  │
│                                  │ (CVP) and other monitoring          │  │
│                                  │ Careful fluid administration based  │  │
│                                  │ on CVP and other parameters         │  │
│                                  │ Consider need for pharmacologic     │  │
│                                  │ therapy                             │  │
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Fig 1. Algorithm for management of hypovolemic shock[3]

and a stable rhythm. It is usually started at 10 µg/kg/min and then titrated to effect till 20 µg/kg/min is reached.If there is no response adrenaline is started.

Dobutamine is preferred in cardiogenic shock because it is a very selective stimulant of beta1 receptors. It is used in normotensive or hypertensive shock. Often started at 10 µ g/kg/min, it is titrated to response.

Adrenaline is preferred in post arrest shock states, cardiogenic shock not responding to dobutamine and septic shock. It is started at a dose of 0.1µ g/kg/min and titrated to effect.

Noradrenaline is useful in warm septic shock because of its alpha-adrenergic effect. It is also useful in spinal shock and anaphylaxis.

The drugs mentioned above are preferably administered in central vein and should not be mixed with bicarbonate containing solution.

2) **Vasopressors:** increase systemic and pulmonary vascular resistance and are most commonly employed in shock associated with low systemic vascular resistance. Eg:Norepinephrine, isoproterenol and phenylephrine.

3) **Vasodilators:** reduce systemic and pulmonary vascular resistance. These are the only class of agents that can increase cardiac output and simultaneously reduce myocardial oxygen demand. They reduce ventricular after load, which improves stroke volume and cardiac output.

4) **Inodilators** combine inotropic stimulation of the heart with the vasodilatation of the systemic and pulmonary vascular beds. They act via a potent and selective inhibition of phosphodiesterase type 3. These drugs increase cardiac output with little effect on myocardial oxygen demand and produce little change in heart rate[5]. They are particularly useful in the treatment of cardiogenic shock and selected children with septic shock. Amrinone and milrinone come under this group. The bolus dose should be given carefully, as rapid infusion may cause hypotension. They have long half-lives; milrinone is preferred over amrinone as the latter causes thrombocytopenia. The dose of milrinone: loading dose 50-75 µg/kg followed by a continuous infusion rate of 0.5-0.75 µg/kg/min.

Digitalis glycosides should be avoided in cardiogenic shock because of narrow therapeutic to toxic ratio, long half-life, clearance which depends on normal renal or hepatic function.

Preparation of vasoactive drug infusions in infants and children is shown in Table 6.

Correction of metabolic abnormalities:

a) **Acidosis:** must at least be partially corrected if base deficit is >6mEq/L[6].

Table 6. Preparation of vasoactive drug infusions in infants and children[2]

Medication	Dilution	Delivery Rate
Epinephrine Norepinephrine	0.6 x body weight (kg) equals milligrams to add to sufficient diluent to create a total volume of 100 mL	1 mL/h delivers 0.1 µg/kg per minute
Dopamine Dobutamine Sodium nitroprusside	6 x body weight (kg) equals milligrams to add to sufficient diluent to create a total volume of 100 mL	1 mL/h delivers 1.0 µg/kg per minute

Calculation: deficit in mEq HCO_3 = weight in kg X base deficit X O.3

Complete correction of the calculated base deficit is not indicated, so generally 1/2 of the calculated dose is administered which is approximately equal to a HCO_3 dose of 1mEq/kg. So, 1-2mEq/kg of $NaHCO_3$ is given as a slow infusion over 20 minutes.

b) **Hypocalcemia:** can impair myocardial function. Administer calcium, as 10% calcium gluconate 100 mg/kg if ionized calcium is less than 0.9 mmol.

c) **Hypoglycemia** is very common in shock states. It should be closely monitored and if present should be managed with 2ml/kg of 25%dextrose IV stat.

d) **Electrolyte abnormalities:** Hyponatremia, hypernatremia, hyperkalemia, and hypokalemia should be corrected.

Other considerations in the management of shock

Nutrition: Early initiation of enteral feeding as soon as cardiovascular stability is reached is vital especially in septic shock as septic patients develop protein energy malnutrition very soon. Early enteral feeding prevents gut mucosal atrophy and bacterial translocation.

General Principles in the Management of cardiogenic Shock[7]

Minimize myocardial oxygen demands: Intubation, mechanical ventilation, maintain normal core temperature, provide sedation, correct anemia

Maximize myocardial performance: Correct dysrhythmias, optimize preload, salt and water restriction, augment preload by fluid challenges, diuretics, venodilators for congestion

Improve contractility: Provide oxygen, guarantee ventilation, correct acidosis and other metabolic abnormalities, inotropic drugs

Reduce afterload: Provide sedation and pain relief, correct hypothermia, appropriate vasodilator use.

Exclude congenital or traumatic heart lesions

Explore surgical options.

Prognosis in shock

Most patients do not die in the acute hypotensive /hypoxemic phase of shock but as a result of one of the complications associated with shock state. Multi organ system failure increases the probability of death

One organ system involved - 25% mortality; Two organ systems involved - 60% mortality; Three or more organs involved - > 85% mortality

However early recognition, intervention and rapid transfer of critically ill children to a pediatric intensive care unit may improve survival.

Key points to remember

- *Shock can occur in the presence of normal BP.*
- *Hypovolemia is the commonest type of shock seen in children.*
- *Fluid replacement is essential in the initial management of all types of shock.*
- *Inotropes are very rarely needed in hypovolemic shock.*
- *Frequent reassessment and close monitoring are vital for optimum management of shock.*
- *Early identification of shock and intervention prevent progression to irreversible shock*
- *Cardiogenic shock should be suspected when there is shock with increased work of breathing.*

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CD REVIEW

Articulations in Pediatric Rheumatology

Presented by : IAP Rheumatology Chapter

Number : 4 VCD's

Review : The IAP Rheumatology Chapter has done a wonderful and commendable job of compiling the important aspects in pediatric rheumatology in the form of set of 4 VCD's. The articulations in pediatric rheumatology starts with the basic VCD wherein the staff/physiotherapist gives a good insight as to how to go about examining the movements in each joint, range of movement, limitations if any in the joint etc., It is indeed a very nice move by the chapter to start with this as we pediatricians need to recall / recollect / brush up the basics of joint mobility while dealing with children with rheumatological problems. The second CD gives an overview of symptomatology in pediatric rheumatology. The message that rheumatological complaint is not equal to rheumatological disorder is presented in a very clear and simplified way. The approach to acute arthritis gives a clear-cut view of conditions presenting as acute arthritis as well as a brief review about dermatomyositis and rheumatic fever. The sections on how reactive arthritis following infections can mimic rheumatological disorders should be an eye opener for pediatricians. Also the need to curb the practice of ordering investigations for even minor joint problems is clearly brought out. Overall it is a very neat compilation, which should find a place in every pediatrician's clinic for perusal.

MANAGEMENT UPDATE

CURRENT GUIDELINES IN THE MANAGEMENT OF SEPTIC SHOCK

*** Indumathi Santhanam***

Abstract: Septic shock is a common problem in children. Early recognition and appropriate management can prevent the very high mortality associated with septic shock. A high index of suspicion is needed to identify the warm septic shock. Altered mental status and decreased peripheral perfusion in any ill looking child with fever should alert the physician to the possibility of septic shock. Aggressive fluid resuscitation in the first hour has improved survival in septic shock.

Keywords: Septic shock, goal directed

Mortality in severe sepsis and septic shock is unacceptably high. Hence the Pediatric Advanced Life Support Course Book-2000 published a new algorithm for the management of pediatric and neonatal septic shock[1]. In 2003, the American College of Critical Care Medicine developed a document to provide pediatric practitioners with an expert opinion and evidence based, age specific, stepwise approach to hemodynamic support of septic shock in neonates and children[2]. More recently critical care experts representing 11 international organizations, under the auspices of the surviving sepsis campaign developed management guidelines for severe sepsis and septic shock[3].

At the 2001 International Sepsis Definitions Conference the following were defined

Definitions

Sepsis as hyperthermia or hypothermia, tachycardia (may be absent in the hypothermic patient), evidence of infection, and at least one of the following signs of organ dysfunction; altered mental status, hypoxemia, bounding pulses or increased lactate.

Warm shock: Decreased perfusion including flash capillary refill, bounding peripheral pulses, flushed peripheries or decreased urine output <1ml/kg/hr.

Cold shock: Decreased perfusion including decreased mental status, capillary refill >2 seconds, diminished peripheral pulses, mottled cool extremities or decreased urine output <1ml/kg/hr.

Fluid refractory dopamine resistant shock: Shock persists despite >60 ml/kg fluid resuscitation and dopamine infusion to 10 microgram /kg/min in first hour

Catecholamine resistant shock: Shock persists despite use of catecholamines such as epinephrine or nor-epinephrine

Refractory shock: Shock persists despite goal directed use of inotropic agents, vasopressors, vasodilators and maintenance of metabolic (glucose and calcium) and hormonal (thyroid and hydrocortisone) homeostasis.

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Immediate resuscitation in the emergency room (The first hour)

Goals: are to (a) maintain airway, oxygenation and ventilation. (b) maintain circulation (defined as normal perfusion and blood pressure). (c) maintain threshold heart rates.

Therapeutic end points include CRT < 2 seconds, normal pulses with no differential between central and peripheral pulses, warm extremities, and urine output >l ml/kg/hr, normal mental status and normal blood pressure for age.

Monitoring should include SaO_2 by pulse oximeter, continuous ECG, blood pressure, temperature, urine output, glucose and ionized calcium.

Airway and breathing: Children with septic shock usually have an adequate airway and are provided with supplemental oxygen (10 L/min) through a non- rebreathing mask. The work of breathing should be monitored vigorously since lung compliance and work of breathing can change very rapidly during fluid administration. Rapid sequence intubation is performed when the work of breathing increases, hypoventilation occurs, GCS becomes less than 8 or the patient is moribund. The decision to intubate in the emergency room is based on the clinical features mentioned above and not on blood gas analysis. Pulmonary edema is anticipated and ventilatory support is required in up to 80% children[4]. Volume resuscitation and the use of ketamine as an induction agent are recommended to prevent worsening of positive pressure ventilation associated hypotension.

Circulation: Profound venodilation and capillary leaks require that virtually all patients with septic shock require aggressive volume resuscitation. Two large intra-venous cannulae (or intra-osseous) are inserted. Isotonic fluid boluses of 20ml/kg are pushed to a total of 60ml/kg in the first 15 minutes. Fluid is rapidly administered with the goal of attaining normal perfusion, blood pressure and an urine output >1ml/kg/hr. Though most children will require only 40 to 60 ml/kg some children might require as high as 200 ml/kg in the first hour. There is no data, which indicate better clinical outcomes with use of either crystalloid or colloid as initial fluids for resuscitation. In fluid responsive shock, continued monitoring of RR, HR, peripheral perfusion, BP, GCS and urine output is essential. If the liver span increases, work of breathing increases, fresh rales appear or gallop rhythm occurs more fluid is not advised even if shock persists. At this point, the airway must be rapidly secured using rapid sequence intubation technique and early ventilation is initiated. Dopamine infusion is started through a peripheral line.

Blood glucose should be checked and hypoglycemia corrected. Ionized calcium is measured and documented hypocalcemia is corrected within the first 15 minutes after arrival.

Cardiovascular therapy: Children who have fluid refractory shock require vasoactive support in addition to further fluid resuscitation. Dopamine is the first line drug and is started at 10 micrograms/ kg /min at 15 minutes. If fluid refractory shock persists with high blood pressure dobutamine may be started. However, dopamine or dobutamine resistant shock must be recognized quickly and at 45 minutes epinephrine started for cold shock or nor- epinephrine for warm shock with the aim of restoring normal perfusion and blood pressure. Where shock exists with normal or high blood pressure after load reducing drugs such as nitroglycerin, nitroprusside or inodilators such as amrinone and milrinone are used.

Hydrocortisone therapy: Lack of response to epinephrine (hypotensive cold shock) or nor-epinephrine (warm shock) could result from adrenal insufficiency. Though the proper dosage

has been poorly investigated the PALS guidelines suggests a dose of 2mg/kg as a bolus followed by a 2mg/kg infusion over 24 hours. In children at risk for adrenal insufficiency eg. Waterhouse Friderichsen/ purpura fulminans, prior steroid exposure and CNS disease, hydrocortisone is given in shock doses of 50mg/kg followed by an infusion of 50mg/ kg over 24 hours.

Antibiotics: Although survival from sepsis and septic shock can only occur if the infection is eradicated, administration of antibiotics should never supersede or postpone volume and cardiovascular resuscitation. Antibiotics and anti-fungal agents should be administered according to age, setting and resistance patterns in the first hour of recognition of severe sepsis after appropriate cultures are obtained.

Source control: Patients presenting with severe sepsis should be evaluated for focus of sepsis in order to eliminate the source. Wound debridement, abscess drainage, removal of infected catheter, pericardiocentesis or empyema drainage should be performed at the earliest.

Stabilization beyond the first hour

Hemodynamic support can be required for days in fluid-refractory shock. Ceneviva et al[5] found, that unlike adults who predominantly have high cardiac output/low vascular resistance shock, children with fluid refractory- dopamine resistant shock have varied hemodynamic states. These include low cardiac output/ high systemic vascular resistance (60%), low cardiac output / low systemic vascular resistance (20%) and high cardiac output / low vascular resistance. During the course of management the hemodynamic status of the child could change from one state to another.

Role of invasive monitoring

Virtually no invasive monitoring is necessary in children with fluid responsive shock. Refractory

shock, however, requires more specific delineation of hemodynamics. Due to fluctuations in the hemodynamic status of the child in shock, the guidelines suggest that invasive monitoring is needed when poor perfusion, reduced urine output, acidosis or hypotension persist despite goal directed therapy.

Normal perfusion pressure is considered necessary for organ perfusion. Central venous access and intra-arterial lines help to monitor perfusion pressure i.e. (Mean arterial pressure – Central venous pressure). Therapy is aimed at maintaining perfusion pressure at normal levels for age.
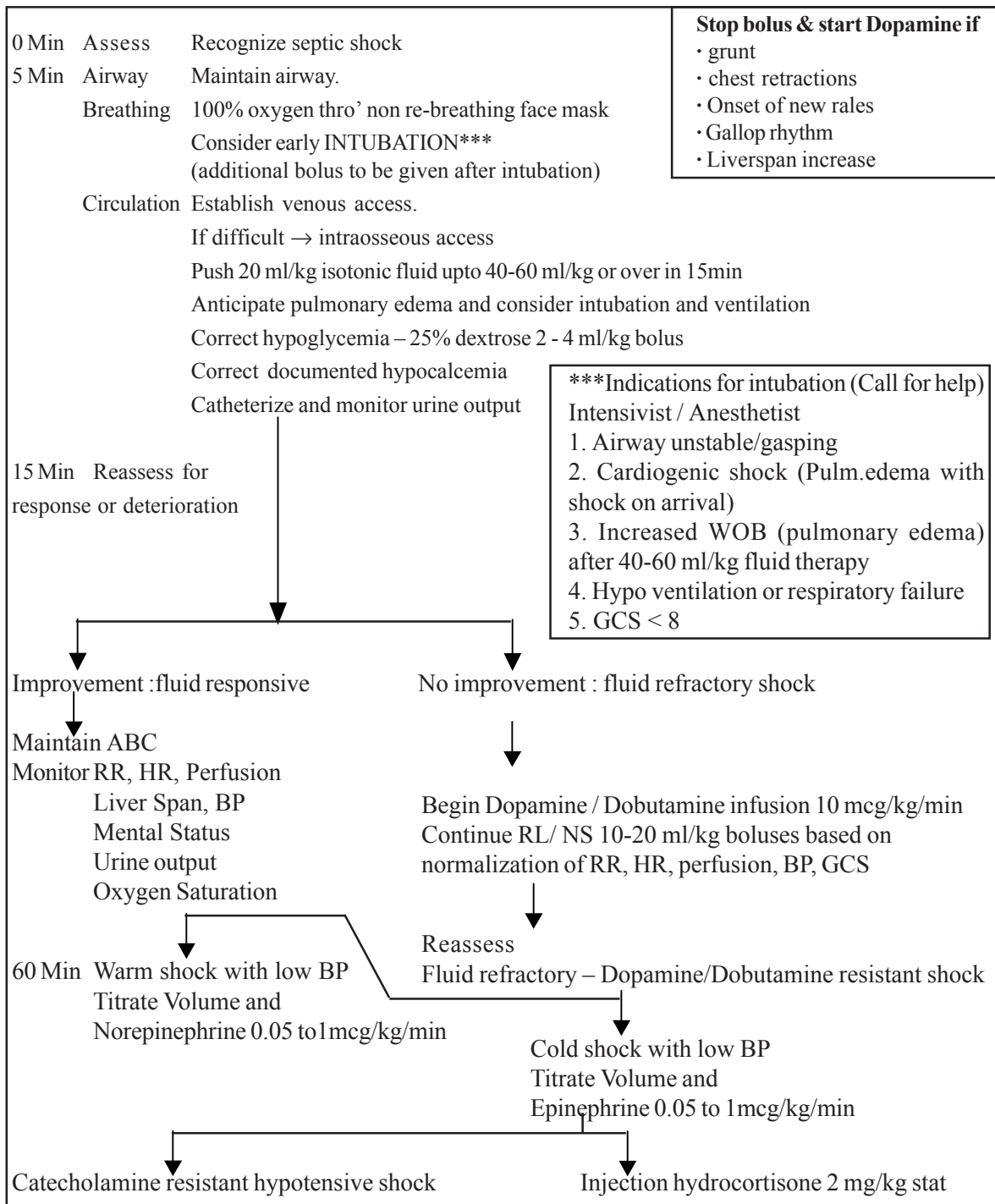
The central venous access also helps to obtain blood for assessment of superior vena cava oxygen saturation. A value > 70% is associated with improved mortality in septic shock. Further, the guidelines suggest that for those patients who remain in shock despite therapy directed towards normalization of clinical signs of perfusion, perfusion pressures and superior vena cava oxygen saturation >70%, pulmonary artery catheterization is performed for monitoring cardiac index.

Refractory shock: Children with catecholamine resistant shock may have other unrecognized morbidities such as pneumothorax, pericardial effusion, blood loss, necrotic tissue, hypoadrenalism or hypothyroidism etc.

General considerations in the intensive care unit

In children with hemoglobin < 10 gm/dl packed red blood cell transfusion is given.

Mechanical ventilation: The principles of lung protective strategies are applied for children as they are for adults. Current recommendation suggests setting a tidal volume at 6ml/kg with a goal of maintaining end inspiratory plateau pressures at < 30 cm H_2O. Permissive

Stop bolus & start Dopamine if
· grunt
· chest retractions
· Onset of new rales
· Gallop rhythm
· Liverspan increase

0 Min   Assess   Recognize septic shock

5 Min   Airway   Maintain airway.

        Breathing   100% oxygen thro' non re-breathing face mask

                      Consider early INTUBATION***
                      (additional bolus to be given after intubation)

        Circulation   Establish venous access.

                      If difficult → intraosseous access

                      Push 20 ml/kg isotonic fluid upto 40-60 ml/kg or over in 15min

                      Anticipate pulmonary edema and consider intubation and ventilation

                      Correct hypoglycemia – 25% dextrose 2 - 4 ml/kg bolus

                      Correct documented hypocalcemia

                      Catheterize and monitor urine output

***Indications for intubation (Call for help)
Intensivist / Anesthetist
1. Airway unstable/gasping
2. Cardiogenic shock (Pulm.edema with shock on arrival)
3. Increased WOB (pulmonary edema) after 40-60 ml/kg fluid therapy
4. Hypo ventilation or respiratory failure
5. GCS < 8

15 Min   Reassess for
response or deterioration

Improvement :fluid responsive

No improvement : fluid refractory shock

Maintain ABC
Monitor RR, HR, Perfusion
        Liver Span, BP
        Mental Status
        Urine output
        Oxygen Saturation

Begin Dopamine / Dobutamine infusion 10 mcg/kg/min
Continue RL/ NS 10-20 ml/kg boluses based on
normalization of RR, HR, perfusion, BP, GCS

Reassess
Fluid refractory – Dopamine/Dobutamine resistant shock

60 Min   Warm shock with low BP
         Titrate Volume and
         Norepinephrine 0.05 to1mcg/kg/min

Cold shock with low BP
Titrate Volume and
Epinephrine 0.05 to 1mcg/kg/min

Catecholamine resistant hypotensive shock

Injection hydrocortisone 2 mg/kg stat

Fig. 1 Management of Pediatric Septic shock in the Emergency Room

hypercapnia may develop with such settings but can be tolerated with patients with acute lung injury/ ARDS. Permissive hypercapnia is not useful in patients with metabolic acidosis and contraindicated in patients with raised intra-cranial pressures. Minimal positive end expiratory pressures should be set to prevent lung collapse at end expiration.

Mechanically ventilated patients should be maintained semi-recumbent with head of the bed elevated 45 degrees to prevent ventilator-associated pneumonia.

Ventilated patients should undergo trials of spontaneous breathing when they are arousable, hemodynamically stable (weaned off inotropic agents), low ventilatory and end-expiratory pressure requirements, low FiO_2 requirements which can be delivered by low flow devices and potentially no serious conditions. Successful trials of spontaneous breathing hasten weaning.

Sedation, analgesia and neuromuscular blockade: Appropriate sedation and analgesia for mechanically ventilated patients are the standard of care in children with septic shock. However, neuromuscular blockade should be avoided if at all possible in septic shock patients due to the risk of prolonged neuromuscular blockade following discontinuation.

Glycemic control: Infants are at great risk of developing hypoglycemia and an infusion of maintenance fluid (10% glucose with 0.45% NS) is recommended. Frequent glucose monitoring is needed to maintain a tight control of blood sugar.

Stress ulcer prophylaxis: Coagulopathy and mechanical ventilation are risk factors for gastrointestinal bleeds. Stress ulcer prophylaxis is usually provided using H_2 receptor blockers, though its effect is not known.

DVT prophylaxis: 25% of deep vein thrombosis is associated with the placement of femoral central venous catheters. However there is no evidence to support the use of DVT prophylaxis with heparin in children.

Protein C and Activated Protein C: Not routinely indicated though it is known that Protein C reaches adult values in children greater than 3 years suggesting a need for supplementation. One study using protein C concentrate showed an improvement in sepsis related coagulation disturbances. However there was no improvement in mortality.

Granulocyte macrophage colony stimulating factor: Not useful in children with septic shock with normal immune competence. White cell transfusions and colony stimulating factors have improved outcomes in neutropenic sepsis secondary to chemotherapy or primary white cell immune deficiencies.

Renal replacement therapy : Peritoneal dialysis is useful in anuric or severe oliguric children with fluid overload.

Intravenous immnoglobulin: There is no evidence to support the use of polyclonal intravenous immunoglobulin in the management of septic shock.

Key points to remember

- *Recognize septic shock by looking for evidence of decreased mental status and peripheral perfusion in any ill looking child with fever*

- *Early goal directed therapy in the first hour of identification of septic shock offers the best chance of survival.*

- *Avoid mistaking the flushed warm peripheries in the presence of abnormal mental status, tachypnea and tachycardia in a febrile child as normal. Recognize warm septic shock.*

· *If shock is unresponsive to 40 ml/kg fluids call for help (anaesthetist or intensivist) in order to electively intubate prior to shifting to an ICU.*

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NEWS AND NOTES

NNF MANUAL OF NEONATAL CARE.

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MANAGEMENT UPDATE

ACUTE RENAL FAILURE IN CHILDREN

* *Sanjeev Gulati*

Abstract: *Acute renal failure (ARF) is often transient and usually reversible. The cause of ARF is classified as pre renal, intrinsic (renal) and post renal. Clinical examination, investigations should be planned to arrive at early and accurate diagnosis. Diet, fluid, electrolyte and acid base management, dialysis when indicated, care to prevent ATN are important aspects of medical treatment of ARF. Surgical intervention is needed when there is obstruction. In those with renal damage, long term follow up is required.*

Keywords: *Acute renal failure, diagnosis, treatment*

Acute renal failure (ARF) is defined as an abrupt or rapid decline in renal function. A rise in serum blood urea nitrogen (BUN) or serum creatinine concentrations, with or without a decrement in urine output, usually is evidence of ARF[1]. The condition often is transient and usually completely reversible.

Frequency

This varies greatly depending on the clinical setting. Acute tubular necrosis (ATN) is the most frequent cause of hospital acquired ARF. In adults, incidence of ATN is approximately 1% at admission, 2-5% during hospitalization, and 4-15% after cardio-pulmonary bypass[2]. ATN occurs in approximately 5-10% of newborn ICU patients and 2-3% of pediatric ICU patients. The incidence is particularly high in children undergoing cardiac surgery and is about 5-8%[3,4].

Pathophysiology

ARF may occur in 3 clinical settings, (1) as an adaptive response to severe volume depletion and hypotension, with structurally and functionally intact nephrons (2) in response to cytotoxic insults to the kidney, with structural and functional damage; and (3) with obstruction to the passage of urine. Therefore, ARF may be classified as prerenal, intrinsic and postrenal[1]. While these classifications are useful in establishing a differential diagnosis, many pathophysiologic features are shared among the different categories.

ATN usually occurs after an acute ischemic or toxic event and it has a well-defined sequence of events. The initiation phase is characterized by an acute decrease in GFR to very low levels, with a sudden increase in serum creatinine and blood urea nitrogen (BUN) concentrations. The maintenance phase is characterized by a sustained severe reduction in GFR, and this phase continues for a variable length of time, most commonly 1-2 weeks. Because the filtration rate is so low during the maintenance phase, the creatinine and BUN continue to rise. The recovery phase, in which tubular function is restored, is characterized by an increase in urine volume (if oliguria was present during the maintenance phase) and by a gradual decrease

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in BUN and serum creatinine to their preinjury levels. This sequence of events is not always apparent and oliguria may not be present. The reason for this lack of a uniform clinical presentation is a reflection of the variable nature of the injury[1,5].

Classifying ARF as oliguric or nonoliguric based on daily urine excretion is useful from the management and prognostic point of view[6,7]. Oliguria is defined as a daily urine volume of less than 400 ml/m²/d or 1 ml/kg/hr. Anuria is defined as a urine output of less than 50 ml/d or <0.5 ml/kg/hr and if abrupt in onset, is suggestive of obstruction[2,5]. Stratification of renal failure along these lines helps in decision-making (eg, timing of dialysis) and seems to be an important criterion for patient response to therapy.

Etiology

The causes of acute renal failure (ARF) are conventionally and conveniently divided into 3 categories: prerenal, renal, and postrenal.

1. Prerenal ARF involves an essentially normal kidney that is responding to hypoperfusion by decreasing the glomerular filtration rate (GFR).

2. Renal or intrinsic ARF refers to a condition in which the pathology lies within the kidney itself.

3. Postrenal failure is caused by an obstruction of the urinary tract.

ATN is the most common cause of ARF in the renal category. ATN is the second most common cause of all categories of ARF in hospitalized patients, with only prerenal azotemia occurring more frequently. The history, physical examination and laboratory findings, especially the renal ultrasound and the urinalysis are particularly helpful in identifying the cause of ARF. Obstruction and hemolytic uremic syndrome are other important causes of ARF in outpatients. Glomerulonephritis and interstitial nephritis can also present as ARF[4,8,9].

The common causes of ATN in neonates are as follows:

- Ischemia - Perinatal asphyxia, respiratory distress syndrome, hemorrhage (eg. maternal, twin-twin transfusion, intraventricular), congenital cyanotic heart disease, shock/sepsis

- Exogenous toxins - Aminoglycosides, amphotericin B, maternal ingestion of ACE inhibitors or NSAIDs

- Endogenous toxins - Hemoglobin following hemolysis, myoglobin following seizures

- Kidney disease - Renal vein thrombosis, renal artery thrombosis, renal hypoplasia and dysplasia, autosomal recessive polycystic kidney disease, bladder outlet obstruction

In older children the distribution is slightly different and the causes are as follows:

- Ischemia - Severe dehydration, hemorrhage, shock/sepsis, burns, third space losses in major surgery, trauma, nephrotic syndrome, cold ischemia in cadaveric kidney transplant, near drowning, severe cardiac or pulmonary disease

- Exogenous toxins - Drugs that impair autoregulation (eg. cyclosporine, tacrolimus, ACE inhibitors, NSAIDs), direct nephrotoxins (eg. aminoglycosides, amphotericin B, cisplatin, contrast agents, cyclosporine, tacrolimus)

- Endogenous toxins - Hemoglobin release (eg. transfusion reactions, malaria, snake and insect bites, glucose 6-phosphate dehydrogenase deficiency, extracorporeal circulation, cardiac valvular prostheses),

myoglobin release (crush injuries, prolonged seizures, malignant hyperthermia, snake and insect bites, myositis, hypokalemia, hypophosphatemia, influenza)

History

Children with hospital-acquired ATN frequently have no specific symptoms. However, the signs may include a pericardial friction rub, asterixis, hypertension or edema. The diagnosis is at times suspected when urine output diminishes and usually is made by the documentation of successive elevations in BUN and serum creatinine. Careful evaluation of the hospital course usually reveals the cause of ARF. In patients with community-acquired ARF, a thorough history and physical examination are invaluable in pinpointing the etiology. In children, HUS followed by ischemic ATN (caused by severe hypovolemia, shock, trauma, sepsis, burns and major surgery) are the most common forms[8,9]. Also common is nephrotoxic ATN, caused by a variety of drugs. Their deleterious effect is markedly enhanced by hypovolemia, renal ischemia or other renal insults.

Diagnostic evaluation of ARF

One important question is how to assure that an early diagnosis of acute renal vasoconstriction can be made prior to the occurrence of tubular dysfunction, thus providing the potential to prevent progression to established ARF. In this regard, past diagnostics relied on observation of the patient response to a fluid challenge: decreasing levels of blood urea nitrogen (BUN) indicated the presence of reversible vasoconstriction, while uncontrolled accumulation of nitrogenous waste products, i.e., BUN and serum creatinine, indicated established ARF. This approach, however, frequently led to massive fluid overload in the ARF patient with resultant pulmonary congestion, hypoxia and premature need for mechanical ventilatory support and/or

hemodialysis. On this background the focus turned to an evaluation of urine sediment and urine chemistry to differentiate between renal vasoconstriction with intact tubular function and established ARF. It was well established that if tubular function was intact, renal vasoconstriction was associated with enhanced tubular sodium reabsorption. Specifically, the fraction of filtered sodium that is rapidly reabsorbed by normal tubules of the vasoconstricted kidney is greater than 99%. Thus, when nitrogenous wastes, such as creatinine accumulate in the blood due to a fall in glomerular filtration rate (GFR) secondary to renal vasoconstriction with intact tubular function, the fractional excretion of filtered sodium (FE_{Na} = [(urine sodium x plasma creatinine) / (plasma sodium x urine creatinine)]) is less than 1%[2,8]. An exception to this physiological response of the normal kidney to vasoconstriction is when the patient is receiving a diuretic, including mannitol or has glucosuria, which decreases tubular sodium reabsorption and increases FE_{Na}. It has recently been shown in the presence of diuretics that a rate of fractional excretion of urea (FE urea) of less than 35 indicates intact tubular function, thus favoring renal vasoconstriction rather than established ARF as a cause of the azotemia. Also, renal vasoconstriction in a patient with advanced chronic renal failure may not be expected to be associated with an FE_{Na} of less than 1 because of chronic adaptation to an increased single-nephron GFR. Specifically, the adaptive decrease in tubular reabsorption to maintain sodium balance in chronic renal disease may make the interpretation of FE_{Na} difficult in this setting[1].

The approximately 80% diagnostic specificity of FE_{Na} in distinguishing azotemia associated with renal vasoconstriction and intact tubular function from established ARF with tubular dysfunction may result from limited sensitivity of this parameter or perhaps more likely, the patient may actually be progressing from a prerenal

azotemic state to established ARF. With established ARF the urine-concentrating capacity is abolished; thus measurement of urinary osmolality may complement the use of FE_{Na} in the diagnostic separation of renal vasoconstriction from established ARF in the patient with a rising BUN measurement and serum creatinine level. Since advanced age and low protein intake may diminish maximal urinary osmolality, this diagnostic parameter may be less sensitive than FE_{Na} in the azotemic patient. Increased excretion of tubular epithelial cells, indicated by examination of the urinary sediment, is characteristic of established ARF but also has limitations in diagnostic value particularly in nonoliguric ARF. It also should be pointed out that some causes of ARF, including radiocontrast media and myoglobinuria, may be associated with an FE_{Na} of less than 1. This may be related to the early presence of severe renal vasoconstriction and intact distal tubule function, which can occur in the presence of proximal tubule injury.

Investigations

Urinalysis: The urinalysis is normal or near normal in prerenal disease; hyaline casts may be seen but this is not an abnormal finding. The centrifuged sediment of urine is particularly helpful because it may reveal pigmented, muddy brown, granular casts, suggesting that established ATN

is present. However, it is important to remember that these casts may be absent in 20-30% of patients with ATN. In addition to the routine urinalysis, urine electrolytes may also help to differentiate ATN from prerenal azotemia[2,8]. The urinary sediment, electrolyte, and osmolality findings that can help to differentiate ATN from prerenal azotemia are illustrated in Table 1

Fractional excretion of a substance is calculated by the formula (U/P)z/(U/P)Cr X 100, where z is the substance, U and P represent urine and plasma concentrations, and Cr stands for creatinine.

Serum chemistry: By definition, BUN and serum creatinine concentrations are increased in ARF. In addition, hyponatremia, hyperkalemia, hypermagnesemia, hypocalcemia, and hyperphosphatemia may be present. A metabolic acidosis is also found.

CBC : May reveal anemia. Not only is erythropoietin production decreased in ARF, but dysfunctional platelets (from uremia) also make bleeding more likely.

Other tests : A suspicion of rhabdomyolysis may be confirmed by direct determination of urinary myoglobin and elevation of serum creatine kinase (specifically the CK3 isoenzyme). Children with

Table 1. Laboratory findings used to differentiate prerenal azotemia from ATN

Parameters	Prerenal Azotemia	ATN / Intrinsic Renal Disease
Urine osmolarity (mOsm/kg)	>500	<350
Urine sodium(mmol/L)	<20	>40
Fractional excretion of sodium (%)	<1	>2
Fractional excretion of urea (%)	<35	>50
Urine sediment	Bland and/or nonspecific	May show muddy brown granular casts

rhabdomyolysis usually also display marked increase in serum potassium and phosphate. In the tumor lysis syndrome following cancer chemotherapy a marked elevation in serum uric acid occurs along with hyperkalemia and hyperphosphatemia.

Hypomagnesemia is a prominent finding in nephrotoxic ATN, particularly associated with gentamicin, amphotericin B, cisplatin or pentamidine administration. Serum levels of nephrotoxins should be determined and serially followed, particularly when using gentamicin, vancomycin, cyclosporine, or tacrolimus.

Although ARF is usually secondary to ischemic or nephrotoxic injury, other causes of intrinsic ARF should be kept in mind and excluded by history, physical examination, and laboratory evaluation. Laboratory evaluation should include urine cultures and serologic tests (including C3 and C4 in all patients), and lupus serology and hepatitis profile when appropriate.

Imaging studies : Renal ultrasound is a simple procedure that should be undertaken in all patients who present with ARF. Exceptions to this rule may include children with unmistakable prerenal failure from well-documented dehydration who respond promptly to fluid therapy or children with renal insufficiency secondary to obvious glomerular disease, hypoxia-ischemia, or exposure to nephrotoxins. Ultrasound provides important information regarding kidney size, contour, echogenicity, corticomedullary differentiation and blood flow.In ischemic or nephrotoxic ATN, the kidneys are of normal size or slightly enlarged, with increased echogenicity. With prolonged ATN, renal cortical necrosis may result in decreased kidney size. Bilateral small scarred kidneys are indicative of chronic renal disease. Congenital disorders, such as polycystic kidney disease and multicystic dysplasia are detected easily. Calculi and tumors also are evident. Hydronephrosis is suggestive of urinary tract obstruction and accompanying hydroureter and thickened bladder wall are consistent with bladder outlet obstruction. A Doppler study is important in the evaluation of vascular obstruction. CT scan or MRI are extremely useful, both to exclude obstructive uropathy and to measure renal size and cortical thickness[8] .

Treatment

As with most disease conditions, the earlier an intervention can be instituted in acute renal ischemia, the more favorable the outcome[2,8,10].

Prevention of ATN: Vigorous prophylactic fluid administration is perhaps the only successful measure to prevent ATN in situations where renal hypoperfusion or toxic injury is anticipated as those following cardiac surgery, cadaveric kidney transplantation, major trauma, burns, hemoglobinuria, myoglobinuria, tumor lysis syndrome, radiocontrast administration, amphotericin B therapy and cisplatin infusion. The prophylactic use of diuretics or dopamine prior to the above procedures is not recommended at this time. Several studies, albeit uncontrolled, suggest that diuretics may be beneficial when administered during the early phase of ATN. Although they do not appear to alter the course of the ARF, they may convert an oliguric to a nonoliguric ARF, which is more easily managed because it obviates the need for fluid restriction and allows for maximal nutritional support. The current recommendation is that a trial of intravenous furosemide infusion should be attempted in children with oliguria of less than 48 hours duration who have not responded to adequate hydration. The dose of furosemide should be in the high range (2-5 mg/kg). Some evidence suggests that in the prevention of crush syndrome, early administration of mannitol, before muscle toxins and breakdown products are released into the circulation, may protect from the development of ATN.

Fluid management: The major goal of fluid management is to restore and maintain intravascular volume. ATN may present with hypovolemia, euvolemia or volume overload and an estimation of fluid status is a prerequisite for initial and ongoing therapy. This is accomplished by measuring input and output, serial body weights, vital signs, skin turgor, capillary refill, serum sodium, and FE_{Na}.

Children with intravascular volume depletion require prompt and vigorous fluid resuscitation. Initial therapy includes isotonic sodium chloride solution or lactated Ringer solution at 20 mL/kg over 30 minutes. It can be repeated twice if necessary, after careful monitoring to avoid possible fluid overload. Potassium administration is contraindicated until urine output is established. If anuria persists after three fluid boluses (confirmed by bladder catheterization), central venous monitoring may be required to guide further management.

Oliguria in the presence of volume overload requires fluid restriction and possibly intravenous administration of furosemide. Children with established ATN may not respond to furosemide, in which case consider fluid removal by dialysis or hemofiltration, especially if signs of pulmonary edema are evident.

Input and output records, daily weights, physical examination, and serum sodium concentration guide ongoing therapy. A bedside indicator of appropriate fluid therapy is a body weight decrease of approximately 0.5% per day as a result of caloric deprivation; serum sodium concentration should remain stable. A more rapid weight loss and increasing serum sodium indicate inadequate fluid replacement. An absence of weight loss with decreasing serum sodium suggests excess free water.

During the recovery phase, children develop significant polyuria and natriuresis and may become dehydrated if appropriate adjustments in fluid requirements are not made.

Electrolytes and acid-base balance: If serum potassium levels exceed 5.5-6.5 mEq/L, eliminate all sources of potassium from the diet or intravenous fluids and administer a cation exchange resin such as sodium polystyrene sulfonate (Kayexalate). Kayexalate requires several hours of contact with the colonic mucosa to be effective; the rectal route of administration is preferred. Complications of this therapy include hypernatremia and constipation. An attempt can be made to lower serum potassium concentration by increasing the dose of diuretics in those patients responding to them.

Emergency treatment of hyperkalemia is indicated when serum potassium exceeds 6.5 mEq/L or tall peaked T waves are evident on the ECG. Presence of ECG changes requires the immediate administration of calcium gluconate (with continuous ECG monitoring) to counteract the effects of hyperkalemia on the myocardium. Nebulized albuterol/salbutamol and/or intravenous insulin, dextrose remain the most efficacious first line agents. In addition to Kayexalate, administer intravenous sodium bicarbonate, which causes a rapid shift of potassium into cells. Such therapy should be used with caution because it can precipitate hypocalcemia and sodium overload. The definitive therapy for significant hyperkalemia in oliguric ATN frequently includes dialysis. The forms of therapy outlined above serve to tide over the crisis, while arrangements are being made for dialysis.

The primary treatment of hyponatremia is free water restriction. Serum sodium of less than 120 mEq/L may require hypertonic (3%) sodium chloride infusion, especially if CNS dysfunction is present. Administration of hypertonic sodium chloride could precipitate CNS dysfunction and may be used only with extreme caution in critical care settings.

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Management of hyperphosphatemia includes dietary restriction and oral phosphate binders (calcium carbonate or calcium acetate). Hypocalcemia usually responds to oral calcium salts used for control of hyperphosphatemia but may require 10% calcium gluconate infusion or intravenous Calcitriol, if severe.

Metabolic acidosis of ATN is usually mild and does not require treatment. Moderate acidosis (pH <7.3) should be treated with oral sodium bicarbonate or sodium citrate. Severe acidosis (pH <7.2), especially in the presence of hyperkalemia, requires intravenous bicarbonate therapy. Adequate ventilation is necessary in order to exhale the carbon dioxide produced. Bicarbonate administration may precipitate hypernatremia or hypocalcemia. Children who cannot tolerate a large sodium load (ie, those with CHF) may be treated in an intensive care unit (ICU) setting with intravenous tromethamine (THAM), pending institution of dialysis.

Medications: Avoid nephrotoxic agents as they may worsen the renal injury and delay recovery of function. Such agents include contrast media, aminoglycosides and NSAIDs.

Prescribing medication in ATN requires knowledge of the route of elimination and modifications in dose or frequency should be made based on residual renal function. When making these adjustments, patients in the early phase of ATN with a rising serum creatinine should be assumed to have a GFR of less than 10 mL/min, irrespective of the serum creatinine value.

Dialysis: The goal of dialysis is to remove endogenous and exogenous toxins and to maintain fluid, electrolyte and acid-base balance until renal function returns. Indications for acute dialysis are not absolute and the decision to use this therapy depends on the rapidity of onset, duration, and severity of the abnormality to be corrected.

The choice between hemodialysis and peritoneal dialysis depends on the overall clinical condition, availability of technique, etiology of the ATN, institutional preferences and specific indications or contraindications[10,11].

In general, peritoneal dialysis is a gentler and preferred method in infants and younger children. Specific contraindications include abdominal wall defects, bowel distention, perforation or adhesions, and communications between the abdominal and chest cavities.

Hemodialysis has the distinct advantage of rapid correction of fluid, electrolyte, and acid-base imbalances and may be the treatment of choice in hemodynamically stable patients especially older children. Disadvantages include the requirement for vascular access, large extracorporeal blood volume, heparinization and skilled personnel. An important advance has been the use of biocompatible synthetic dialysis membranes such as polysulfone. These membranes should minimize complement activation and neutrophil infiltration into the kidney. Their use generally is recommended in children with ARF, although not all studies have documented beneficial effects.

Over the past decade, continuous veno-venous hemofiltration (CVVH) has emerged as an alternative therapy primarily for children with ATN who require fluid removal who are unstable or critically ill. The major advantage of this technique lies in the ability to remove fluid in a hypotensive child in whom hemodialysis may be relatively contraindicated and peritoneal dialysis inefficient[12].

Common indications for dialysis in ATN

1. Fluid overload that is unresponsive to diuretics

2. Fluid overload that hinders adequate nutritional support

3. Hyperkalemia with oliguria

4. Symptomatic acid-base imbalances

5. Refractory hypertension

6. Symptomatic uremia (pleuritis, pericarditis, CNS symptoms)

Surgical care : Patients with ARF secondary to obstruction frequently require urologic care. The site of obstruction determines the therapy.

Obstruction of the bladder neck in neonates caused by posterior urethral valves must be immediately relieved by gentle insertion of a fine urethral catheter. The subsequent management of choice is endoscopic ablation of the valves. A temporary cutaneous vesicostomy may be required in a small infant.

Diet and activity: Children with ARF are frequently in a highly catabolic state. Aggressive nutritional support is important. Adequate calories to account for maintenance requirements and supplements to combat excessive catabolism must be provided. Oral feeding is the preferred route of administration. Infants should receive a low-phosphorus diet (Similac PM 60/40), and older children should be placed on a low-potassium, low-phosphorus diet. Additional calories may be supplied by fortifying foods with polycose and medium-chain triglyceride (MCT) oils. Children who have nausea or anorexia may benefit from parenteral feedings or intravenous hyperalimentation. If adequate nutrition cannot be achieved because of fluid restriction, consider early institution of ultrafiltration or dialysis. Children with ARF usually are hospitalized, and activity is restricted; however, strict bed rest does not accelerate recovery.

Kidney biopsy: Biopsy is rarely necessary. It should be performed only when the exact renal cause of ARF is unclear and the course is protracted. Prerenal and postrenal causes must be ruled out first. The diagnosis of ATN is made on a clinical basis, ie, with the help of detailed and accurate history, thorough physical examination and pertinent laboratory examinations and imaging studies. A more urgent indication for renal biopsy is in the setting of clinical and urinary findings that suggest renal vasculitis rather than ATN; the diagnosis needs to be established quickly so that appropriate immunomodulatory therapy can be initiated. The biopsy is performed under ultrasound or CT scan guidance after ascertaining the safety of the procedure. A biopsy may also be more critically important in the setting of a renal transplant patient to rule out rejection.

Mortality / Morbidity

For ARF the mortality rate is 20-50% in patients with underlying medical illnesses, but the mortality rate is as high as 60-70% for patients in a surgical setting. If multiorgan failure is present, especially severe hypotension or acute respiratory distress syndrome, the mortality rate ranges from 50-80%[4,8,13].

With dialysis intervention, the frequency of uremia, hyperkalemia, and volume overload as causes of death have decreased. The most common causes of death now are sepsis, cardiovascular and pulmonary dysfunction, and withdrawal of life support.

Factors that are associated with an increased mortality rate include poor nutritional status, male sex, the presence of oliguria and multi-organ failure.

Complications

1. Infections develop in 30-70% of patients with ARF. These include infections of the respiratory system, urinary tract and indwelling catheters. Impaired defenses due to uremia and excessive use of antibiotics and invasive maneuvers may contribute to the high rate of infectious complications.

2. Cardiovascular complications are primarily a result of fluid and sodium retention. They include hypertension, CHF and pulmonary edema.

3. Hyperkalemia results in ECG abnormalities and cardiac arrhythmias.

4. Other complications

    Gastrointestinal (eg, anorexia, nausea, vomiting, ileus, bleeding)

    Hematologic (eg, anemia, platelet dysfunction)

    Neurologic (eg, confusion, asterixis, somnolence, seizures)

    Electrolyte disturbances (eg, hyponatremia, hyperkalemia, hypocalcemia, hyperphosphatemia)

    Metabolic acidosis

Prognosis

Prolonged duration of the ARF, clinical course and the need for dialysis are major factors projecting a poor prognosis. Patients with ARF who require dialysis have a 50–70% mortality rate. Infection and cardiopulmonary complications are the major causes of death in patients with ARF[4,8,13].

Despite significant advances in supportive care and renal replacement therapy, the high mortality rates in the setting of multiorgan failure have not improved in the past few decades. Patients die, not because of renal failure but rather because of serious involvement of other systems during the period of ARF[14].

On the other hand, prognosis for children with ARF from prerenal causes or in the absence of significant comorbid conditions is usually quite good if appropriate therapy is instituted in a timely fashion. Most patients recover adequate renal function to lead normal lives. Some are left with permanent renal damage. In those left with mild-to-moderate renal damage further deterioration in kidney function may occur later in childhood; therefore, long-term follow-up is required in these patients.

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NEWS AND NOTES

REFRESHER TRAINING PROGRAMME IN PEDIATRIC DERMATOLOGY

Organised by IAP Dermatology Group – Chennai

Venue	:	Kanchi Kamakoti CHILDS Trust Hospital., Chennai
Date	:	23rd and 24th April 2005 (9.00am to 5.00pm)
Registration fees	:	Rs 3000/- (Three Thousand only)
Eligibility for registration	:	Ordinary/Life members of IAP only.
Course capacity	:	30 (thirty) only on first come first serve basis

COURSE HIGHLIGHTS

♦ Discussion of common pediatric dermatological problems seen in day to day practice with special emphasis on diagnosis and treatment

♦ Clinical case demonstration and case discussion

♦ Live demonstration of minor procedures

♦ Lectures by experienced teachers

Registration fees of Rs.3000 will include a course module, working lunch, tea and snacks for both days. Kindly note this will not include breakfast, dinner, accommodation and transport/travel to and from venue.

Those interested to enroll in the course are requested to send their willingness to the under mentioned address on or before 15th March 2005. *Please send the registration fee only after you get the application form and confirmation of enrollment from the Course Director.*

Address for communication:
Dr.Jayakar Thomas. M.D., D.D., M.N.A.M.S., Ph.D.
Course Director, # 2 West Mada Church Road, Royapuram, Chennai – 600 013

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MANAGEMENT UPDATE

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DRUG RESISTANT TUBERCULOSIS IN CHILDREN

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Abstract : Drug resistant tuberculosis is rare in children but the prevalence is likely to increase with rising rates of drug-resistant tuberculosis in adults. Primary drug resistance where the child acquires infection with a resistant organism is more common than secondary/acquired resistance. When resistance occurs to isoniazid alone, treatment with rifampicin, ethambutol and pyrazinamide with or without an aminoglycoside, is usually successful. However, when Multi Drug Resistant Tuberculosis (MDRTB) occurs (resistance to isoniazid and rifampicin with or without resistance to other drugs), treatment is more complicated, toxic and less likely to be successful. Outcome of MDRTB is poor. Surgery may occasionally be required. Prevention of drug resistant TB in children by proper identification and treatment of disease in adult is better.

Key words : Drug resistant turberculosis, MDRTB, Children

Drug resistant tuberculosis (TB) has become more common in many parts of the world, due to medical as well as social and economic factors. Adult patients develop both new or previously treated MDRTB. In children, tuberculosis is usually paucibacillary, which makes the development of drug resistance through treatment less likely. Most cases are due to recent transmission of infection from adult contacts. Management of drug resistant TB requires an understanding of mycobacterial function and properties.

Microbiologic basis for treatment of tuberculosis

Types of bacterial population

M.tuberculosis exists as distinct bacterial populations in the host, each with different rates of metabolic activity and replication. The tubercle bacillus can be killed only during replication and being an obligate aerobe, its activity varies with oxygen supply. Bacilli are present in extra cellular locations within cavity walls (rapidly multiplying) and also within the caseous material. In addition, they are present within macrophages as they are able to resist lysosomal killing. Cavitary lesions with high oxygen tension lead to a very large bacterial population (10^7-10^9), closed caseous lesions with neutral pH have moderate numbers of bacilli (10^5-10^7) replicating intermittently while the bacterial population in macrophages with acidic pH (10^4-10^6) is small and multiplies very slowly[1,2].

Presence of natural drug resistant mutants

Another important consideration is the occurrence of natural drug – resistant mutants in bacterial population of *M.tuberculosis*[3]. The mean frequency of these mutants is 1 in 10^5 bacilli for streptomycin, 1 in 10^6 for isoniazid and 1 in 10^7 for rifampicin. The chance that a mutant is

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Table 1: Bacillary population and drug actions

Bacillary population	Drug
Group – A Metabolically active, continuously growing bacilli in neutral pH	Streptomycin Isoniazid Rifampicin
Group – B Dormant most of the time, occasionally growing for short periods	Rifampicin Isoniazid
Group C Intracellular bacilli in acidic pH	Pyrazinamide
Group D Dormant bacilli	No drug

naturally resistant to two drugs is very small (10^{-11} to 10^{-13}). If patients are treated with a single drug, the drug resistant mutants will selectively multiply. A cavity with 10^9 bacilli would therefore have several hundred drug-resistant mutants whereas lesions of primary tuberculosis or extra pulmonary TB have few , if any, mutants.

Actions of anti-tuberculosis drugs

Anti tuberculosis drugs work in 3 ways: bactericidal, sterilizing and prevention of resistance. Each drug acts in a slightly different manner (Table 1). The large population of actively replicating extracellular tubercle bacilli (Group A) are rapidly killed by isoniazid, rifampicin and streptomycin. Rifampicin and isoniazid kill organisms in closed caseous lesions (Group B) while intracellular organisms (Group C) are affected mainly by pyrazinamide. Thus a combination of isoniazid, rifampicin and pyrazinamide would take care of bacilli in different stages of metabolic activity, producing sterilization of the lesion.

Lag phase

M.tuberculosis exhibits a lag period in growth in response to anti-TB drugs. After exposure to the drug, the growth of the bacillus is inhibited for a variable period of time ranging from 2 to 40 days. This property enables intermittent administration of drugs with good therapeutic effect. However, it is important that the peak drug concentration achieved should be above the MIC. A controlled clinical trial undertaken at the Tuberculosis Research Centre (TRC) Chennai, had shown that a 6-month intermittent regimen of pyrazinamide, rifampicin and isoniazid in the intensive phase followed by isoniazid and rifampicin was as effective as a daily oral regimen of rifampicin and isoniazid, for the treatment of pulmonary TB in children[4]. Various attempts to reduce the frequency to once a week have not been successful; hence intermittent chemotherapy should be given at least twice preferably three times a week.

Types of drug resistance

Drug resistance in TB may be broadly classified as primary and acquired. Drug resistance in a patient who has never received anti-TB treatment previously is termed as **primary resistance**. **Acquired resistance** is that which occurs as a result of previous anti-tuberculosis treatment. The term **initial resistance** is used to indicate primary resistance and resistance among patients whose history of

previous chemotherapy is not known. The WHO and the International Union against Tuberculosis and Lung Diseases (IUATLD) have now replaced the term primary resistance by the term "drug resistance among new cases" and acquired resistance by the term "drug resistance among previously treated cases" [5]

Epidemiology of drug resistance

Although drug resistance was observed in *M.tuberculosis* isolates even in the early days of chemotherapy, the current threat is due to the emergence of strains resistant to the most potent anti-TB drugs viz., isoniazid (H) and rifampicin (R) i.e. multi-drug resistant (MDR TB). The level of initial drug resistance is considered to be an epidemiological indicator to assess the success of the National TB Programme (NTP). Since current drug resistance data has a bearing on the design of the treatment regimens and policies, reliable information of the same at the national level is both urgently and regularly needed.

Causes of drug resistance

Factors related to the development of drug resistance include: inadequate or inefficient administration of effective treatment; use of sub-standard drugs; inadequate or irregular drug supply; interruption of chemotherapy due to side effects; non-adherence of patients to the prescribed regimens; availability of anti-TB drugs over the counter without prescription; illiteracy; low socio-economic status and ignorance of the patients; massive bacillary load; and laboratory delays in identification and susceptibility testing of *M.tuberculosis* isolates leading to continued infection by drug resistant patients in the community.

The only definitive way of diagnosing *M.tuberculosis* drug resistance is by isolating the strain and assessing its susceptibility pattern which takes months. New rapid culture and susceptibility tests namely BACTEC, mycobacterial growth indicator tube (MGIT) and luciferase reporter assay have been developed which offer the possibility of early sensitivity results. In addition, advanced molecular biologic techniques like polymerase chain reaction, DNA fingerprinting and SSCP (single strand conformation polymorphism) are rapid and help by identifying the mutations that cause drug resistance. However, these are not available for routine use.

Molecular mechanisms of resistance

Drug resistance appears to be chromosomal in origin, caused by specific mutations that occur in independent genes. This type of drug resistance is not transferable from one organism to another and is not linked between antimicrobial drugs; however, the bacilli can show cross-resistance to drugs with similar structure. The molecular mechanism of rifampicin resistance in most *M.tuberculosis* is a missense mutation in the gene (*rpoB*) encoding the *beta* unit of the RNA polymerase. Several workers have studied resistance to INH, the most important anti-tubercular drug. Some strains of *M.tuberculosis* that are resistant to INH have reduced catalase-peroxidase activity. A specific gene (*kat* G) controls this activity. A complete absence of k*at G* from the chromosome has been detected in some strains of INH resistant *M.tuberculosis.* Another gene (*inh A)* is also thought to be involved in INH resistance. Mutations in the 16 s ribosomal RNA gene are associated with resistance to streptomycin. With the emergence of MDR strains of *M.tuberculosis*, resistance has also been observed to quinolones with a missense mutation at the area *gyrA*.

The global drug resistance scenario

Based on the WHO/IUATLD Guidelines, a total of 72 surveillance projects on anti-TB drug resistance were completed in 65 countries during the period 1994-99. The median value for

resistance to any drug among new cases was found to be 11% (range 1.7% - 41%). The highest median value for any single drug was 7% for isoniazid (range 0.0% - 31.7%). The median prevalence of MDR-TB in new cases of tuberculosis was 1% (range 0.0% - 14.1%). The highest prevalence was reported from Estonia (14.1%). Among previously treated cases, median prevalence of resistance to any drug was 33.4%. The median prevalence of MDR-TB among treated cases was 9.3%, ranging from 0% in four geographical settings to 48.2% in Iran[6].

TRC studies on prevalence of primary drug resistance in adults

Studies undertaken by the Tuberculosis Research Centre (TRC), Chennai in the late 80's in North Arcot district, Tamil Nadu state and in Pondicherry, 1999-2000[7,8,9], revealed initial resistance to rifampicin to range from 1.0% - 4.4% while the prevalence of MDR TB was around 1% - 3%. Results of a recently completed study in the Wardha district revealed resistance to isoniazid, rifampicin and to both drugs to be 15.2%, 0.5% and 0.5% respectively. Another study carried out in Jabalpur district revealed resistance to isoniazid, rifampicin and to both drugs to be 17%, 2% and 1% respectively (TRC 2002, unpublished)

Data on drug resistance from adult patients admitted to controlled clinical trials on short course chemotherapy with rifampicin-containing regimens conducted at the TRC, Chennai involving almost 3500 patients over the last 3 decades, showed that for isoniazid, the resistance rates ranged from 10-16% and for streptomycin from 8-13%. Resistance to rifampicin started appearing in the 1990s and still remains at around 1%. Resistance to both isoniazid and rifampicin (MDR) is 1% or less.

Since 1999, studies carried out in the model DOTS area in Thiruvellore district of Tamil Nadu, on drug resistance among patients with no history of previous treatment revealed resistance to isoniazid and MDR to be 11.8% and 1.6% respectively (TRC 2004, unpublished). Likewise, a study on drug resistance carried out on HIV/ TB patients (2000-02) revealed resistance to isoniazid and MDR to be 13% and 4.3 % respectively (TRC 2003, unpublished)

Drug-Resistant Tuberculosis in Children

Patterns of drug resistance in children tend to mirror those found in adult patients in the population. As it is difficult to culture *M.tuberculosis* from children with TB the clue to drug resistance usually comes from the adult contact. Drug resistant tuberculosis should be suspected in the following circumstances:

1. The child is in contact with a known case of drug – resistant tuberculosis

2. Child's adult contact has been on chronic irregular treatment and continues to be sputum positive

3. Adult contact died after taking irregular treatment

4. Child showed some initial improvement to anti-tuberculosis treatment but then deteriorated (clinically and radiologically)

5. Child with pulmonary TB relapses after incomplete or incorrect TB treatment.

All attempts to isolate the organism must be made by examining sputum or gastric lavage. In some cases, the culture and sensitivity results of the source (contact) case may be available. In one study, the correlation between the drug susceptibility results of the child's and adult source cases isolates was 68%. If there is no known source case, there can be a significant delay in starting treatment for MDRTB.[10]

Table 2: Pharmacology of some commonly used second line antituberculous drugs

Drug	Daily dose (mg/kg) and route	CSF penetrability, anti mycobacterial activity	Adverse effects
Thioamides: Ethionamide Prothionamide	10-20 , oral	Good, bactericidal	Gastric intolerance, hepatitis
Aminoglycoside: Kanamycin Streptomycin Capreomycin	15, im	Poor, bactericidal	Auditory ,renal and vestibular toxicity
Ciprofloxacin	15,oral	Poor, bactericidal	Not recommended for pediatric use due to risk of athropathy
Ofloxacin	7.5 – 15, oral	Poor, weakly bactericidal	Can be given to children if necessary
Cycloserine	10 – 20, oral	Poor, bacteriostatic	Gastrointestinal disturbances
PAS	150-200, oral	Poor, bacteriostatic	GI disturbance
Pyrazinamide	20-30, oral	Poor, bactericidal at acid pH	Arthralgia, hepatitis
Ethambutol	15-20 oral	Poor, bacteriostatic	Visual toxicity

Prevalence of drug resistance in children

There is a paucity of reports of drug resistant TB in children due to comparatively few centers where facilities for culture and drug sensitivity exist in India. Therefore, much of the drug resistance has been presumed clinically when patients do not improve or the symptoms return after initial relief. There are no published series of multidrug resistant tuberculosis in Indian children. This may be due to the problem of isolation of *M.tuberculosis* in children due to their inability to produce sputum and non-availability of specialized investigations like gastric lavage, broncho-alveolar lavage and more sensitive culture techniques. In 1998-99 at PGI, Chandigarh four children were treated for drug resistant tuberculosis out of a total of 64 cases started on anti-tuberculosis treatment giving an incidence of 6.3% in hospitalized patients[11]. A multicentric study conducted by TRC, Chennai in children with pulmonary tuberculosis from 1995-1999 in Chennai showed a resistance pattern to isoniazid of 13% and MDRTB of 4%. [12]

Basic principles for management of drug resistant tuberculosis

Therapy for drug-resistant tuberculosis is successful when at least two bactericidal drugs to which the infecting strain of *M.tuberculosis* is susceptible are given. Exact treatment regimens

can be tailored to the specific pattern of drug resistance, if known. If not, at least 3 drugs to which the patient has not been exposed earlier should be given[12,13]. Resistance to isoniazid or streptomycin alone can usually be managed with any of the standard 4-drug regimens with good results. However, when resistance to both isoniazid and rifampicin is present (MDRTB), management is more complicated and requires the use of second line drugs. Duration of therapy is usually extended to 9-12 months if either isoniazid or rifampicin can be used and to at least 18-24 months if resistance to both drugs is present. Occasionally, surgical resection of a diseased lung or lobe is required[14].

Important points

1. Never add a single new drug. Add two or more drugs to which the organism is sensitive.

2. Use bactericidal drugs as far as possible.

3. If most drugs have been used by the patient add those drugs which have not been used in recent past.

4. The treatment should be directly observed. The only way to prevent the major factor of non-adherence is the introduction of DOTS whereby a health care worker/ other second party is directly involved in administration of drugs to the patient. This strategy has been shown to be successful in several developing countries in Asia and Africa. Recently, a consensus statement has been published by the IAP for the treatment of tuberculosis in children in India.[15]

INH resistant tuberculosis, usually can be treated with 9 to 12 months course of RZE. When ethambutol is used in drug resistant tuberculosis the dose should be 25mg/kg per day. Isolated rifampicin resistance is rare. When treating MDRTB, i.e. resistance to both isoniazid and rifampicin, four or more drugs should be used

and should include pyrazinamide and ethambutol. Aminoglycoside should also be used but resistance to streptomycin is common. But, cross resistance with kanamycin, capreomycin, and amikacin is uncommon. Ethionamide and Cycloserine can be used effectively in children, and they are especially helpful in cases of tuberculous meningitis as they have good CSF penetration.[10] Fluroquinolones are well tolerated and effective.

A standard regimen for treatment of suspected / proved MDR TB would be injection kanamycin given thrice weekly with ethionamide, ofloxacin / ciprofloxacin, pyrazinamide and ethambutol given daily (K_3 Emb Eth Oflo Z_7). Kanamycin is given for 3-6 months and the other drugs are continued for a total of 18-24 months (12-18 months after culture negativity) .

Indications for surgery

Surgery should be considered in a patient with bacilli resistant to all except two or three relatively weak drugs [14]. Unfortunately, many such patients have too extensive a disease and poor lung function for surgery to be possible. To avoid serious and potentially fatal complication in a patient with drug resistant tuberculosis, surgery must be done when the bacillary population is the lowest. If only a weak regimen is available, experience has shown that the most favourable time is after two months of treatment. After surgery the regimen should be continued for atleast 18 months.

Outcome of treatment

The outcome of MDRTB in adults has been notoriously poor. Earlier studies reported favourable treatment outcomes in 30-50% of adults treated for MDRTB. However, the long-term success has improved to 75% and death rate been lowered to 12%, in a recent report. This has been mainly due to surgical resection and fluroquinolone therapy[16]. Schaaf et al treated

39 children with MDRTB – 54% completed treatment and were cured, 15% defaulted, 10% died while the rest were still on treatment[10]. MDRTB is difficult to treat because of the cost and toxicity of second-line drugs and prevention is therefore better than cure.

Points to Remember

• *Drug resistant tuberculosis is being encountered more frequently in children, especially in tertiary care settings and is usually acquired from adult contacts.*

• *Resisitance to isoniazid / streptomycin can be treated with standard 4-drug regimens*

• *Treatment of MDRTB is more expensive, toxic and outcome is worse.*

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MANAGEMENT UPDATE

APPROACH TO AN UNCONSCIOUS CHILD

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Abstract: Altered states of consciousness in pediatric patients are urgent situations and coma is a medical emergency requiring rapid and organized intervention. Basic life support needs, good history and physical examination, specific laboratory and neurodiagnostic tests are of paramount importance and should proceed simultaneously in the emergency department. There are key general principles in the management of impaired consciousness or coma but specific diagnoses must be treated appropriately.

Keywords: Coma, seizure, altered sensorium, management

Coma is defined as a state of decreased consciousness from which the child cannot be aroused by ordinary verbal, physical or sensory stimuli. Consciousness refers to the state of awareness of self and environment and it consists of two components - awareness and arousal (wakefulness).

Consciousness is the result of complex interplay between the cerebral cortex and the Ascending Reticular Activating System (ARAS).

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The cerebral cortex is stimulated by the ARAS and the cerebral cortex reciprocally modulates the activity of the ARAS. Coma results from dysfunction of (i) the cerebral hemispheres, (ii) ARAS in the brainstem and (iii) both.

To be labelled as coma, unconsciousness should persist for at least one hour to distinguish it from syncope, concussion or other states of transient unconsciousness.

Etiology

A clinically relevant and practical classification of the etiology of coma includes:

(i)   Structural causes : Trauma, neoplasm, vascular disease, focal infection and hydrocephalus. An important mechanism by which structural disease causes impairment of consciousness is due to the herniation of cerebral and brainstem structures.

(ii) Metabolic / toxic causes: Hypoxic – ischemic injury, acid base or electrolyte disturbances, exogenous toxins or poisons, endogenous toxins, infection, seizures and postictal states. Metabolic, toxic or infectious encephalopathies usually have diffuse involvement of cerebral hemispheres, ARAS or both.

(iii) Psychogenic: Children with psychiatric disorders such as conversion, panic or anxiety disorders may present with neurologic symptoms including genuine or apparent impairment of consciousness. Symptoms may include dizziness, hyperventilation, paresthesias, agitation, or restlessness. The paroxysmal nature of these episodes and the

complete recovery between the episodes should suggest the diagnosis.

The causes of coma are given in Table 1. There may be considerable overlap between these categories, and it is always necessary to consider combined causes of impaired consciousness and coma.

Diagnosis

Accurate and rapid identification of the cause of coma is important to direct specific treatment. The history and physical examination are the basis for identification of the cause of coma.

History:

An accurate history of the events and circumstances before the onset of symptoms, information regarding past medical history and medication may be invaluable in determining the cause of coma. If the child requires immediate resuscitation, accompanying parents or other eyewitnesses in the emergency department are best interviewed in a quiet area to allow the most accurate elucidation of events. If the eyewitness is not with the child in the emergency department, a member of the emergency response team is assigned to interview the eyewitness by telephone.

Table 1. Causes of impaired consciousness and coma

1. **Structural intracranial disorders**
   a. Trauma
      · Concussion
      · Contusion
      · Extradural, subdural, intracerebral, subarachnoid hemorrhage / hematoma
      · Diffuse axonal injury
   b. Neoplasm
   c. Vascular disease
      · Cerebral infarction
      · Cerebral haemorrhage
      · Dural sinus thrombosis
      · Hypertensive encephalopathy
   d. Focal infection
      · Cerebritis
      · Empyema (subdural or epidural)
      · Abscess
   e. Hydrocephalus
2. **Metabolic - Toxic disorders**
   a. Global hypoxia - ischemia
      · Shock
      · Cardiac / pulmonary failure
      · Near drowning
      · Strangulation
      · Carbon monoxide poisoning

   b. Metabolic disorders
      · Hyper or hyponatremia
      · Hyper or hypoglycemia
      · Hyper or hypocalcemia
      · Acidosis
         Diabetic Ketoacidosis
         Organic acidurias
         Amino acidemias
      Hyperammonemia
         Reyes syndrome
         Urea cycle disorders
         Disorders of fatty acid metabolism
      · Mitochondrial disorders
      · Organ system dysfunction
         Hepatic encephalopathy
         Uremic encephalopathy
         Thyroid disorders
         Adrenal insufficiency
   c. Exogenous toxins and poisons
   d. Infections
      · Meningitis
      · Encephalitis
      · Acute disseminated encephalomyelitis (ADEM) cerebral malaria
   e. Seizure and postictal states

Onset: An apoplectic onset suggests a vascular catastrophy or a convulsion. Acute onset of coma following a period of normalcy suggests ingestion of a drug, toxin or poison. A gradual onset is usually the result of intracranial mass lesion, metabolic derangement or infectious process.

Fever: Fever is typical when coma is due to infectious process – meningitis, encephalitis, cerebral abscess.

Recent infectious illness: History of recent infection should lead to consideration of acute disseminated encephalomyelitis, Reye's syndrome or mitochondrial disorders.

Trauma: Coma may occur concurrent with head injury or may be preceded by a lucid interval as in epidural hematoma. The battered child syndrome should be considered whenever a vague history is elicited from caretakers.

Headache: A history of headache may suggest elevated intracranial pressure resulting from hydrocephalus or neoplasm.

Past illness: Children with diabetes mellitus are prone to hypoglycemic or hyperglycemic coma. Uremia and dialysis encephalopathy are potential causes of coma in a child with renal failure. The child with congenital heart disease may suffer from cerebral infarction or abscess. Hyperammonemic coma may develop in children with intrinsic liver disease or hereditary disorders of urea cycle metabolism.

Abnormal dietary history: History of pica suggests lead poisoning.

Episodic coma: Suggests drug ingestion, inborn errors of metabolism, epilepsy, porphyria.

General physical examination

Once the vital functions have been stabilized, a physical examination is conducted in a fashion that provides the greatest information in the shortest possible time.

Skin and mucous membranes are inspected for signs of traumatic injury, bleeding diathesis, exanthem, neurocutaneous markers and chronic systemic disturbance.

Scalp is palpated to rule out underlying skull fracture or hematoma. Anterior fontanelle is palpated to ascertain fullness. Ears, nose are examined for blood or a clear discharge that might represent CSF. Odour of exhaled breath may be useful in DKA (fruity), uremia (urine like) and hepatic coma (musty). Nuchal rigidity suggests underlying meningeal irritation. Fundoscopic examination must be conducted, as papilloedema is the hallmark of increased ICP.

Neurologic examination

The goals of the neurologic examination are: i)To determine the depth of coma, ii) To localize the process leading to coma

Level of consciousness: Many inexact terms are used to describe depressed level of consciousness (eg. drowsy, obtunded, clouded). Because of the lack of precision associated with these terms, it is much more useful to use coma scales. The most widely used is the Glasgow Coma Scale - modified for children (Table 2).

Respiration: Abnormal respiratory pattern occurs frequently with coma and can aid in localization as given in Table 3.

Pupils: Symmetry and normal reactivity to light implies structural integrity of the midbrain. Preservation of pupillary light reflex with absent corneal and oculocephalic reflexes is the hallmark of metabolic encephalopathy (Table 4).

Ocular movements: The position of the eyes at rest should be noticed.

Table 2. Modified Glasgow Coma Scale

> 5 years	< 5 years

Eye opening
  4 Spontaneous
  3 To voice
  2 To pain
  1 None	

Verbal
  5 Oriented
  4 Confused
  3 Inappropriate words
  2 Incomprehensible sounds
  1 No response to pain
	Alert, babbles, coos, words or sentences-normal
	Less than usual ability, irritable cry
	Cries to pain
	Moans to pain
	No response to pain

Motor
  6 Obeys commands
  5 Localises to supraocular pain (>9 months)
  4 Withdraws from nailbed pressure
  3 Flexion to supraocular pain
  2 Extension to supraocular pain
  1 No response to supraocular pain
	Normal spontaneous movements

Table 3. Patterns of respiration in Coma

Patterns of respiration	Site of lesion

Without localizing value
  1. Depressed respiration
  2. Cheyne Stokes respiration
  3. Neurogenic hyperventilation
	Severe coma of any cause
	Bilateral hemispherical lesions, metabolic encephalopathy
	Most often due to systemic diseases with metabolic
	acidosis or respiratory alkalosis

With localizing value
  1. Apneustic breathing
  2. Cluster breathing
  3. Ataxic breathing
	Pons
	Lower pons, cerebellum
	Medulla oblongata

Table 4. Size and reactivity of pupils in coma

Pupils	Lesion / Dysfunction
1. Pinpoint, reactive (<2mm) 2. Mid position - fixed or irregular 3. Unilateral, dilated and fixed 4. Bilateral, fixed and dilated	Pons, Opiates, cholinergic intoxication Midbrain lesion Uncal herniation Diffuse damage, central herniation, global hypoxia – ischemia, barbiturates, atropine

Conjugate deviation of the eyes to one side indicate an ipsilateral cerebral hemispherical lesion or a contralateral pontine lesion. Dysconjugate deviation either at rest or evoked by head turning indicates a brainstem lesion.

Oculocephalic (Dolls' eye) reflex: This is elicited by briskly turning the head to side to side, and vertically up and downwards. An intact response consists of full conjugate deviation of eyes opposite to the direction of head movement which implies that the brainstem is intact.

Oculovestibular reflex: The head is tilted to 30^0 above horizontal, and the ear is lavaged with 30-60 ml of ice water. A normal response consists of fast nystagmus away from the cold ear (COWS : Cold – Opposite side, Warm-Same side). Absent caloric responses are seen with deep coma of any cause. Asymmetrical response implies a brainstem lesion. Conjugate gaze paresis can result from unilateral hemispherical or pontine lesion.

Motor responses: They are the single best indicators of the depth and severity of coma.

(i) Spontaneous movements should be observed for symmetry and purpose. Preferential movement on one side indicates weakness of the unused limbs. (ii) Limb tone should be tested for symmetry. Bilaterally increased lower extremity tone is an important sign of herniation. (iii) Induced movements to painful stimuli or pressure at supra orbital space : Decorticate posturing results from damage to corticospinal tracts at the level of the deep hemispheres or upper midbrain. Extensor (decerebrate) posturing results from damage to corticospinal tracts at the level of pons or upper medulla.

Herniation syndromes: In transtentorial or central herniation, the diencephalon is displaced through the notch of the tentorium cerebelli into the posterior fossa, with progressive rostral - caudal compression and ischemia of the brainstem (Table 5).

In **Uncal herniation**, medial displacement of the uncus compresses upon the oculomotor nerve leading to unilateral dilated fixed pupil with ptosis.

Differences between metabolic and structural coma

Once the history and neurologic examination are completed, it is essential to distinguish between "metabolic" from "structural" coma. Distinguishing "metabolic" from "structural" coma provides the framework upon which rational laboratory analysis and therapeutic management is accomplished.

Toxic, metabolic, or infectious causes:

Confusion or stupor precede motor signs
Pupillary reactions preserved
Symmetrical motor responses
Asterixis, myoclonus
Hyper or hypoventilation.

Table 5. Transtentorial Brain Herniation

	Diencephalic stage	Midbrain - Pontine stage	Medullary stage
Respiration	Cheyne-Stokes	Increased respiration	Slow, irregular, gasping
Pupils	Small, reactive	Midposition, fixed	Midposition, dilated, fixed
Ocular movements	Present	Absent	Absent
Motor response	Decorticate	Decerebrate	Flaccidity

Supratentorial destructive or mass lesions:

Initial focal signs

Rostral to caudal progression

Infratentorial destructive or mass lesions:

Preceding brainstem dysfunction

Sudden onset of coma

Cranial nerve palsies

Early respiratory disturbances

Investigations

The previously well child presenting in a state of unconsciousness is the most difficult diagnostic dilemma. It is important to quickly rule out life threatening conditions in these patients.

1. Neuroimaging: Any comatose child or infant in whom the neurological findings suggest a structural lesion or in whom the clinical diagnosis is evasive, should undergo Computed Tomography of the brain. The routine study is best combined with contrast agent, if tumour or abscess is suspected. CT scan reveals the location and extent of the structural lesion. It may show signs of cerebral oedema in diffuse lesions with increased intracranial pressure. However a normal CT does not rule out underlying increased intracranial pressure.

Magnetic Resonance Imaging (MRI) of brain is also invaluable in identifying evidence of herpes simplex encephalitis or an acute demyelinating process, such as acute disseminated encephalomyelitis.

2. Biochemical investigations: Few investigations are done in all pateints but others are ordered depending upon the casuse for coma as given in Table 6.

3. Electroencephalography (EEG): The EEG is often capable of differentiating structural causes from metabolic coma, but is far from 100% accurate. Its greatest usefulness is in the diagnosis of clinically inapparent status epilepticus (nonconvulsive status epilepticus). Certain EEG patterns, such as periodic lateralised epileptiform discharges, may suggest herpes simplex encephalitis, especially in the setting of a febrile illness. Lastly, the EEG, especially when performed sequentially, provides information regarding depth of coma, the presence of brain death, or long-term outcome (Table 7).

Management

Coma is a medical and neurological emergency requiring prompt diagnosis and treatment. This consists of immediate life support and institution of specific therapy (Fig 1).

Table 6. Biochemical investigations

Indicated in all patients	Suspected Metabolic derangement	Suspected Toxin ingestion	Suspected infection
Blood sugar BUN Serum electrolytes	Urine screening Urine and plasma aminoacids Liver function tests	Toxic screening Blood lead level Urine heavy metal	CSF analysis Blood and other cultures Viral, fungal, parasites isolation
CBC Calcium Serum ammonia Arterial blood gas analysis Urine analysis	Carnitine levels Thyroid function studies Plasma cortisol Urine porphyrins		Smear for malarial parasite

Table 7. EEG findings in coma

EEG findings	Interpretation
High voltage slow waves	Underlying supratentorial lesion
Slowing of background activity	Metabolic coma
Triphasic waves	Hepatic coma
PLEDS Periodic Lateralised Epileptiform Discharges	Herpes encephalitis

Emergency measures (immediate life support): The ABCs of basic life support (Airway, Breathing and Circulation) must be evaluated and managed emergently. This should precede history taking and clinical examination.

(i)   Check airway patency

Intubate if GCS < 8 or pooling of secretions

(ii) Check breathing

Give 100% oxygen

Use bag and mask ventilation / tracheal intubation if there is respiratory depression.

(iii) Check circulation

Give intravenous normal saline or Ringer lactate 20ml / kg to maintain blood pressure and peripheral perfusion. Inotropic support if needed.

(iv) Metabolic support

Give 2ml / kg of 25% dextrose IV

(v)   If there are seizures

Give IV lorazepam 0.1-0.2 mg/kg or IV diazepam 0.3mg/kg

(vi) If increased ICP

Head end elevation to15-30 degrees

Mannitol 20% IV 0.25-0.5g/kg body weight

Hyperventilation.

(vii) Manage hypo / hyperthermia accordingly.

(viii)Immobilization of cervical spine in suspected cases of traumatic coma.

(ix) In cases of known poisoning consider specific antidotes

Specific therapy

It is dictated by the etiology of coma.

1. Space occupying lesions require prompt neuro- surgical management.

2. Antibiotics for meningitis.

3. If Herpes encephalitis is suspected - Acyclovir 10 mg/kg IV every 8th hourly for 10-14 days.

4. Antimalarials for proven or strongly suspected cerebral malaria.

5. Antihypertensives for hypertensive encephalopathy.

Prognosis

The prognosis for recovery from coma depends primarily on the cause, rather than on the depth of coma. Coma from drug intoxication and metabolic causes carry the best prognosis. Prolonged coma after a global hypoxic ischemic insult carries a poor prognosis, but most children surviving infectious encephalopathies have a good outcome with mild or moderate difficulties only. A child with either a hemiparesis or a mild extrapyramidal disorder such as chorea in the first few weeks after coma, may improve considerably, although those left with a dystonic or spastic quadriparesis are less likely to do well. Cognitive functions may recover sufficiently for children to return to their former schools, but concentration may be poor, processing speed is often reduced and there may be subtle disorders of executive function, all of which may make

Emergency   Management

Obtain history   Assess vital signs   Institute therapy

Neurological examination

Nonfocal examination   Focal hemispheric signs   Focal brainstem signs
Brainstem intact

Toxic   CNS   Structural lesion   Herniation syndromes
Metabolic   infection   (SOL, hemorrhge, infarct)

Toxic/metabolic Lumbar   CT / MRI   CT / MRI
screening   puncture

Medical treatment   Surgical treatment

Fig 1. Suggested algorithm for the diagnosis and management of coma in children

learning new material difficult. Behavioural difficulties are very common.

Early rehabilitation, by a team comprising doctors, teachers, physiotherapist, occupational and speech therapist and a psychologist is often very much rewarding. It is essential to test hearing early, particularly after meningitis. Many children, who had seizures acutely, do not develop epilepsy at follow up and may be weaned off from their anticonvulsants after three to six months.

Even if to the physician, the child has a relatively good outcome, for the family subtle changes in the personality has changed their much loved " normal " child into someone with long standing problems. There is a need for more research so that   outcome rather than survival can be improved for these less fortunate children.

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MANAGEMENT UPDATE

MANAGEMENT OF NEONATAL AND CHILDHOOD HYPOTHYROIDISM

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Abstract : *Amongst the endocrine disorders encountered in pediatric age group Primary Hypothyroidism is more common. The congenital form of this disorder (CH) has a world wide incidence of 1 in 3800 with thyroid dysgenesis as the underlying cause in majority. As routine neonatal screening for CH is not available in our country, a high index of clinical suspicion, early confirmation of diagnosis and prompt treatment with levothyroxine sodium (10 to 15 mcg/kg) initiated in very early infancy is essential in preventing future mental consequences. Appropriate counselling with emphasise on life long treatment and periodic therapeutic monitoring in children with CH is imperative. Hypothyrodism in the older age group is usually due to autoimmune thyroiditis and majority of cases require long term or life long treatment based on the initial severity of hypothyroid state.*

Key words : *Primary Hypothyroidism, Levothyroxine*

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Primary hypothyroidism is one of the most common endocrine disorders encountered in pediatric and adolescent age group. In clinical practice nearly 80% of all children referred for thyroid disorders have hypothyroidism[1]. Thyroid hormones through their actions on the metabolism of energy substrates, nutrients and inorganic ions influence almost all organ systems and biological processes in the body. During the first two decades of life, thyroid gland has immense influence on physical growth, development and maturation and during fetal and early postnatal life thyroid hormones are very crucial for brain development. These adverse effects of thyroid deprivation on the growing brain during early infancy have led to the implementation of neonatal screening for Congenital Hypothyroidism (CH) since early 1970s and early therapeutic intervention in affected newborns.

With a worldwide incidence of 1 in 3800 to 4000 births, CH constitutes one of the most important preventable causes of mental retardation[2,3]. Our experience of neonatal screening for CH in 40,000 newborns in mid 80s suggests a high incidence of CH averaging nearly 1:2640 in our country[4,5]. Socioeconomic constraints and lack of adequate infrastructure do not permit the inclusion of neonatal screening for CH in primary health care delivery system for infants in India. Hence high index of clinical suspicion with confirmation of diagnosis during early infancy and initiation of optimal therapy within first 8 to 10 weeks of life can be expected to salvage many children from incurring irreversible brain damage. Awareness about the health consequences of delayed diagnosis and

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importance of early recognition of this eminently treatable disease is essential.

Thyroid physiology as relevant to management

Basic knowledge of thyroid physiology helps in understanding some of the diagnostic and therapeutic aspects of this disorder. The key element for synthesis of thyroid hormones is iodine obtained from food sources. A daily intake of at least 150µg usually suffices. The thyroid gland is the sole source of thyroxine (T4) - about 100µg/day. Of the triiodothyronine (T3) in circulation, nearly 75% is derived from monodeiodination of T4 in peripheral tissues[6,7]. Very small amount of T3 is secreted directly by the thyroid gland except under specific circumstances. The circulating T3 and T4 are associated with carrier plasma proteins with free T4 (FT4) and free T3 (FT3) concentrations approximating about 0.03% and 0.3% respectively of the total hormone concentrations. T3 is almost four times more potent than T4 and nearly 85% of the bioactivity of T4 is attributed to T3. The body homeostatic mechanism regulates the formation of required amounts of T3 from circulating as well as intracellular T4. There is certain amount of tissue autonomy in the production of T3 from T4 and tissues differ in their capacity to produce T3[6,7]. As most of the brain cell thyroid hormone is derived from local T4 to T3 conversion. The preferred thyroid hormone preparation for treatment of CH is thyroxine. The use of T4 (levothyroxine sodium) which is preferred over other combinations of T3 and T4 (e.g. thyroid extract) or T3 alone is more logical and rational for the treatment of hypothyroidism.

The physiological variations which occur in the levels of circulating thyroid hormones have important diagnostic and therapeutic implications. The interpretation of these values should be in accordance with the age dependent variations in the pediatric age group, otherwise a normal infant can be misdiagnosed as having a disordered thyroid function. Therapeutic monitoring of children undergoing treatment should also take note of age related values of circulating thyroid hormones. At birth in most term infants the cord blood TSH is high upto 12µU/ml, T4 is above 6.5 µg/dl and T3 is low almost in the hypothyroid range. Within 30 to 60 minutes after birth there is a surge in the level of TSH almost upto 90µU/ml or more, followed by a rise in the serum T4 and T3 levels within 24 to 48 hours of birth[6,7]. If a newborn has to be assessed for thyroid function, cord blood should be drawn at the time of birth or alternatively after 72 hours so that the physiological changes in the blood levels of TSH and/or thyroid hormones do not cause problems in interpretation. The TSH surge is less marked and thyroid hormone levels are lower in preterm babies. Nearly 50% of premature infants delivered before 30 weeks of gestation may have values of serum T4 below 6.5 µg/dl as opposed to only 2 to 3% of term infants[8]. The free T4 and TSH levels however are in the normal range and also the TSH response to TRH indicating tertiary or hypothalamic hypothyroidism due to immaturity in preterm babies[8,9]. This hypothyroxinemia in preterm infants is transient and gets[8,9] corrected with progressive maturation over the next 6 to 10 weeks. Majority do not require any treatment as post natal growth and development is normal[8]. Thus interpretation of thyroid profile in preterm infants needs careful evaluation.

Subsequent to the initial TSH surge the values decline and TSH values remain constant between 1 month to adult life, below 6µU/ml, but levels of TSH upto 15µU/ml can be considered normal during infancy provided serum T4 and free T4 levels are in the upper normal range. The levels of T4 and T3 decline by three weeks but as stated earlier, remain higher during infancy and

childhood, approaching the adult normal range towards late teens. Higher weight based doses of levothyroxine are thus required during infancy and early childhood to sustain age related higher serum T4 values with adequate suppression of TSH levels.

Etiology and clinical profile

It is important to define the cause of hypothyroidism in children as there are known differences in inheritance and prognosis[6,10]. These etiological factors influence the dosage and duration of thyroid therapy and hence are important. The etiologic factors of primary hypothyroidism vary from maldevelopment (thyroid agenesis or hypoplasia) and maldescent (ectopia) known collectively as thyroid dysgenesis, dyshormonogenesis, endemic iodine deficiency, or the effect of goitrogens as well as autoimmune thyroiditis (AITD). Secondary (pituitary) and tertiary (hypothalamic) forms of hypothyroidism which are less common may be encountered at birth in early infancy or at a later age. Familial and genetically determined thyroid hormone resistance leading to autosomal dominant form of hypothyroidism is uncommon and usually manifests at a later age. The commonest cause of CH is thyroid dysgenesis which involves nearly 75% of all infants detected on screening[2]. Implementation of neonatal screening has led to the identification of transient forms of CH in 10% of babies with CH approximately 1 in 40,000 newborns[3,10], which is more often observed in prematurity usually in babies < 27 weeks and the prevalence varies geographically relative to iodine intake[3]. Maternal antithyroid medication or transplacental transfer of TSH receptor blocking antibodies can also cause transient form of CH.

The clinical profile depends on the underlying etiology, the age of onset and the duration of thyroid deprivation before seeking medical attention. The classical clinical picture of well-established disease is unmistakable but the detection of the disorder in the newborn and young infants, where symptoms and signs are often non-specific, poses problems. Less than 5% of the newborns detected on screening can be diagnosed clinically. In the newborns and in early infancy symptoms predominate over signs. Growth retardation which is so characteristic of this disorder in postnatal life is not noted at birth. Clinical signs become more obvious over the following weeks. Older children may present with usual symptoms and signs of hypothyroidism but failure to grow or short stature, disorders of pubertal development and obesity are occasional presentations.

Diagnosis

Radioimmunoassays for thyroid hormones and TSH have simplified early diagnosis of congenital hypothyroidism. Serum TSH is the most discriminatory for the diagnosis of primary hypothyroidism. In compensated hypothyroidism when serum T4 is not subnormal but in the lower normal range, TSH values may be elevated and help in the diagnosis. Presence of serum thyroglobulin indicates presence of some amount of functioning thyroid tissue as with thyroid ectopia or dyshormonogenesis while undetectable levels may signify thyroid aplasia or agenesis. Radioactive iodine uptake (RAIU) gives a direct measure of thyroid function and technetium scintiscans or ultrasonography help to locate the size, site and nodularity. The demonstration of high titres of thyroid antibodies, antimitochondrial (AMA) and antithyroglobulin (ATG) specially the former, help in the diagnosis of autoimmune thyroiditis. Free T4 and free T3 estimations which are now available may not be routinely advocated but are useful when thyroid hormone reports are borderline or for other specific reasons. Demonstration of delayed skeletal maturation is helpful in diagnosis and in dating the approximate age of onset of the disorder. Epiphyseal

dysgenesis (stippled appearance) may also be encountered occasionally.

Therapeutic approach

Counselling: Once the diagnosis of hypothyroidism is confirmed it is essential for the attending physician to explain the nature of the disorder, the importance of thyroid hormones for physical and mental growth as well as maturation in children and adolescents, and their role in all normal subjects for the maintenance of various body functions all throughout life. The need for life long therapy should be emphasized. We can expect a great deal of parental co-operation once the parents and guardians understand the nature of the problem and the need for continued regular and adequate treatment, as well as follow up. Adequate rapport with the parents and the patient is an essential part of management and will ensure good follow up. It is worthwhile inquiring about the health and growth of other siblings if the patient has goitrous hypothyroidism due to environmental causes or dyshormonogenesis where the inheritance is autosomal recessive. Other siblings also should be examined. Information on risk of recurrence in subsequent pregnancies should also be conveyed. Recurrence risk for thyroid dysgenesis is minimal unless it is due to the recently described genetic abnormalities related to thyroid transcription factors (TTF-1, TTF-2) or PAX 8 gene defect. In patients with hypothyroidism due to autoimmune thyroiditis (AITD) family history of thyroid disorders in other members of family – female relatives in particular – may be obtained, and occasionally other siblings may also be affected.

Treatment: The goal of therapy is to normalize the T4 level as quickly as possible during infancy and to maintain the circulating serum total T4 values in the upper normal range upto 10 µg/dl or above (10-16 µg/dl) in neonates, and normalize the elevated TSH levels. If free T4 concentration is being measured it should be maintained in the upper half of the normal infant range. The preferred preparation is sodium-levothyroxine because of its uniform potency, reliable absorption and greater bioavailability. As discussed earlier it is also most rational and physiological to provide T4, which can be effectively converted into T3 according to the biological needs of the body. Most controversies centre around the dose to be administered to newborns detected on neonatal screening so as to improve the ultimate neuropsychologic outcome and IQ. In newborns detected on screening, to rapidly normalize the serum T4 concentration, 10 to 15µg/kg has been recommended[3,9,10]. Babies with compensated hypothyroidism may be started on a lower dose, whereas those with severe CH having T4 < 5µg/dl often having thyroid agenesis should be started on higher dose. Imaging studies help to decide the underlying cause but need not delay the initiation of treatment. In the newborn period full replacement therapy with 37.5 µg to 50 µg daily can be initiated promptly in full term newborns[10]. Thyroxine tablets have to be crushed and administered with juice or milk taking care that all the medicine is swallowed. In long standing thyroid deprivation whether due to thyroid hypoplasia or ectopia or AITD, when the diagnosis is delayed for months or occasionally for years, a quarter or one third of the calculated daily dose (100 µg/m^2) can be administered initially and stepped up gradually at weekly or 2 to 3 weekly intervals till full replacement dose can be offered within 3 to 6 weeks or longer, depending on the age at presentation. Based on our studies we recommend a dose of 10 µg/kg of levothyroxine during infancy, 6 to 8 µg/kg in the preschool age group, 4 to 6 µg/kg in older children and 2 to 3 µg/kg in the adolescent age group[11]. Our recommendations also conform to those of others[12,13]. The per kg dose declines with age. The daily requirement rarely exceeds 0.15 to

0.2 mg or 150 to 200 µg/day in older children and adolescents. The required dose is administered as one single dose, preferably at a convenient fixed time during the day and on empty stomach hence early morning, to maximize absorption. Iron, soya or fibre interferes with absorption. Many babies learn to chew the tablets even before the teeth have erupted. Regular therapy is extremely important irrespective of any acute or chronic illness. The tablets should be stored in a place away from direct sunlight.

In a placebo controlled double blind trial of T4 treatment, 8 µg/kg per day for 6 weeks was carried out in 200 infants less than 30 weeks gestation. Though overall no difference in cognitive outcome was found, there was an 18 point increase in the Bayley mental development score in the subgroup < 27 weeks gestation but a 10 point decrease in mental score in infants > 27 weeks[14]. Further studies are essential. For the present it may be reasonable to treat any premature infant with a low T4 and elevated TSH and to consider treatment of any infant < 27 weeks with a low T4 whether or not the TSH is elevated. A dose of 8µg/kg/day is recommended[14].

Therapeutic monitoring: Clinical evaluation and growth monitoring during therapy are important and indicators of therapeutic adequacy. Hormone estimations which relate more to the immediate or present time, and do not always reflect the adequacy of therapy during the interim period between two blood collections. Serum T4 concentration normalizes in a week and the TSH usually within a month. Estimation of T4 and TSH will usually suffice for therapeutic monitoring after initial stabilization. Serum T3 estimation is not very helpful except in occasional patients with suspected inadequate or excess therapy but not required for routine therapeutic evaluation. Occasionally, in young infants even with adequate dose, the serum TSH concentration may remain inappropriately elevated, usually not more than

15 to 20µU/ml with a serum T4 well within the upper normal range for age. This elevation of TSH is usually noted in first few months of initiating therapy but can persist through the second decade of life in about 10% of patients[15,16]. Normalization of TSH concentration is delayed because of relative pituitary resistance. Noncompliance should be excluded. In this situation estimation of free T4 or TSH response to TRH can be utilized as a guide for therapy. If serum T4 is already high, in the age related upper normal range, the dose of levothyroxine should not be stepped up. The T4 value is used to titrate the dose. Thus T4 and free T4 concentrations are important parameters of adequate thyroid hormone replacement at this age[10]. The elevated serum TSH level relative to T4 concentration in CH infants is caused by resetting of the feedback threshold for T4 suppression of TSH release in infants with CH[16]. The mechanism of this resetting which occurs in utero is unknown. Individualization of therapy by monitoring serum thyroid levels and TSH is ideal. An inadequate dose may affect the neuropsychologic outcome and IQ adversely, whereas excessive replacement dose given for long time may lead to craniostenosis, advanced bone age, hyperactivity and brain dysfunction as well as possible osteoporosis[8]. Careful monitoring of patients with dose adjustment is hence imperative.

The serum half life of T4 approximates upto 5 days in the newborn and 6 days thereafter[9]. Thus blood samples for thyroid hormones and TSH estimation can be obtained 4 weeks after initiating therapy in the newborn or 5 to 6 weeks after reaching the final calculated dose in older infants and children, preferably 12 to 24 hours after the last T4 dose is administered. TSH normalization preferably should be achieved in 45 days[3,10]. During early infancy and in newborns, therapeutic monitoring is recommended with blood samples obtained at 2 to 4 weeks after

initiation of treatment, at 2 months intervals during first year, at 2 to 3 months intervals during 1 and 3 years and every 3 to 12 months till growth is completed. It is advisable to obtain repeat blood samples about 6 to 8 weeks after any change in dosage schedule. In hypothyroid babies where the diagnosis is in doubt at birth or where transient disease is suspected and therapy initiated, a trial of replacement therapy can be initiated after 3 years of age, when most thyroid hormone dependent brain maturation has occurred.

As opposed to congenital hypothyroidism, in children with acquired hypothyroidism following thyroiditis, after the initial 2 to 3 years of replacement therapy the treatment can be stopped for a brief period of 4 to 6 weeks and the thyroid functions retested. In case the functional ability of the thyroid gland is restored to normal, therapy may be discontinued but periodic monitoring is advisable for initial 1 or 2 years and at a later age during adolescence. In majority of instances however thyroid functions do not return to normal when the initial TSH elevation has been significant. Life long therapy may then be needed.

Physical growth and development of infants with CH are usually normalized by early adequate therapy[17]. IQ values alongwith mental and motor development also are normalized in most infants with CH detected on screening with early initiation of treatment[3,18]. Occasionally low IQ values have been reported in a small subset of CH children detected on screening with very low serum T4 and delayed bone maturation at birth inspite of prompt therapy[19]. In this country in the absence of neonatal screening a high index of clinical suspicion, significant early diagnosis (preferably within the first three months), prompt institution of optimal therapy and periodic laboratory and growth monitoring and careful clinical surveillance will contribute a great deal towards improved prognosis and near normal intellectual outcome.

Points to remember

- *CH is the most important preventable cause of mental retardation.*

- *A high index of clinical suspicion, and confirmation of diagnosis in neonatal period or within first 8 to 10 weeks of life with prompt implementation of optimal treatment can help prevent future mental consequences.*

- *Regular, adequate treatment and periodic therapeutic monitoring with appropriate modification of the dose of levothyroxine sodium in infancy are equally important for optimal outcome.*

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NEWS AND NOTES

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ACUTE LIVER FAILURE IN CHILDREN

* Ashish Bavdekar
** Madhumati Otiv

Abstract *: Acute liver failure (ALF) is uncommon in children. However when it occurs, has a high mortality with medical therapy alone. There are many causative factors which differ between children and adults and often from region to region. Most cases in India are due to Hepatitis A and /or Hepatitis E virus. Treatment of children with ALF is supportive, aimed at preventing and managing associated complications until the native liver recovers. Liver transplantation is the only therapeutic option for severe ALF, but is associated with risks, shortage of organs and at present not available in most centres in the country.*

Key Words *: Liver failure, management, transplantation*

Definition

Acute liver failure (ALF) is better described as a clinical syndrome rather than a specific disorder. It is a multi-system disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a child with no previous recognised underlying chronic liver disease[1].

Causes of ALF

The common causes of ALF are given in Table 1. Unlike older children, the common causes of ALF in infants are usually non-hepatotropic viruses and metabolic disorders. In India, Hepatitis A alone or in combination with Hepatitis E is the commonest cause of ALF in older children[2,3].

Warning signals of ALF

In a child with acute hepatitis, presence of one or more of the "red flag signs" listed in Table 2 should be viewed with concern as they could herald the onset of liver failure[4].

Aims of Managment

In ALF, management is largely supportive while trying to identify a treatable etiology. It is aimed at maintaining fluid electrolyte, acid base and glucose balance; supporting cardiovascular, respiratory and renal systems and monitoring CNS function. Intensive monitoring to prevent and manage complications is of paramount importance.

History

A detailed history to find out the probable cause is necessary. This includes history of hepatitis A and B vaccination, intravenous injections, needle stick injury, infusions of blood products, contact with jaundiced patients, liver disease in family, hepatotoxic medications, poisons (e.g. mushrooms), etc.

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Table 1 : Causes of acute liver failure in children

INFANTS	OLDER CHILDREN
Metabolic disorders Galactosemia, tyrosinemia, neonatal hemochromatosis, fructose intolerance, mitochondrial hepatopathy	**Infections** Hepatitis A, B, E, non A-E, EBV, parvovirus, adenovirus
Infections Hepatitis B, adenovirus, parvovirus, Herpes, sepsis, non A-E hepatitis	**Drugs** Valproate, Paracetamol, INH, Phenytoin
Drugs Valproate, INH, paracetamol	**Metabolic disorders** Wilson's Disease
Others Severe asphyxia, congenital heart disease, malignancy, giant cell hepatitis with hemolytic anemia	**Others** Autoimmune disease, Budd Chiari syndrome malignancy, mitochondrial hepatopathy

Examination

Initial clinical examination should assess vital functions, hemodynamics, and encephalopathy grading. This includes assessment of protective airway reflexes (cough, swallow), respiratory distress (respiratory rate and use of accessory muscles), oxygen saturation, perfusion (heart rate, blood pressure, capillary refill) and degree of encephalopathy (Table 3). Dehydration is common at the time of admission. Identification of evidence of spontaneous bleeding – GI, skin, nose bleeds points towards abnormality of synthetic function. A firm and sharp liver, splenomegaly and ascites point towards chronicity of the liver disease. It is useful to mark the liver span with a waterproof marker in order to monitor the liver size accurately during the subsequent course of the illness.

Investigations

Investigations are aimed at finding the etiology, severity of ALF, precipitating cause and complications. The initial work up should include hemogram, platelet count, serum bilirubin, SGPT, serum proteins (albumin, globulin), PT, GGT,

Table 2 : Red flag signs of ALF

CLINICAL	LABORATORY
Persistent anorexia	PT > 5 secs difference inspite of Vit. K
Deepening jaundice	Persistent hypoglycemia
Relapse of jaundice	Low serum albumin
Shrinking liver size	Raised SGPT > 3000 IU/L
Ascites	Serum bilirubin > 20mg/dL
Spontaneous bleeds	

Table 3 : Clinical stages of hepatic encephalopathy

Grade I	Mild drowsiness, impaired cognition, concentration or psychomotor functions, altered sleep–awake cycle
Grade II	More drowsy, confused, inappropriate behaviour, mood swings, but capable of conversation
Grade III	Marked drowsiness but arousable, unresponsive to verbal commands, delirious, hyperreflexia, positive Babinski's sign
Grade IV	Unconscious, decerebrate or decorticate posture, response to pain present (IV A) or absent (IV B)

glucose, ammonia, urea, creatinine, electrolytes, blood culture, urine routine, viral markers (Anti-HAV IgM, Anti-HEV IgM, HbsAg) and USG abdomen. Blood grouping and cross matching should be done and blood bank should be requested to keep FFP (fresh frozen plasma) and packed red cells reserved. If indicated, a chest X ray will be useful to rule out associated pneumonia and effusions. A cranial CT could be considered, if intracranial bleed or encephalitis needs to be excluded. On suspicion of chronic liver disease, copper studies for Wilson's disease (Ceruloplasmin, 24 hr urinary Cu, serum Cu), autoimmune markers for autoimmune Chronic Active Hepatitis (CAH) (ANA, anti LKM, anti SMA) are indicated. Rare metabolic diseases can be confirmed by studies like GALT enzyme, urine succinylacetone, etc.

Treatment

All patients should be managed in an intensive care setting and be **treated as potentially infectious.**

Table 4 : Criteria for liver transplantation in patients with acute liver failure

Acetaminophen patients	Non-Acetaminophen patients
pH < 7.3 (regardless of grade of encephalopathy)	PT > 100 sec (INR > 6.5) (regardless of the grade of encephalopathy)
Or	Or
All of the following present at the same time:	Any 3 of the following (regardless of the grade of encephalopathy)
PT > 100 sec (INR> 6.5)	Age < 10 years
Serum Creatinine > 3.4 mg/dL	Jaundice to encephalopathy duration of > 7 days
Encephalopathy Grade III or IV	Etiology : Non A to E hepatitis, halothane hepatitis, idiosyncratic drug reactions
	PT > 50 sec (INR > 3.5)
	Serum bilirubin > 17.5 mg/dL

General measures: Treatment priorities in ALF are to ensure airway protection, maintain cerebral perfusion presure (CPP), to reduce raised intracranial pressure and to remove precipitating events. Children with ALF should be nursed head up at 30 degrees. A nasogastric tube should be passed to detect and remove GI haemorrhage. In order to maintain strict input /output, catheterise bladder. CVP line placement should be considered to guide fluid therapy. All hepatotoxic agents should be stopped. Elective ventilation must be considered if there is impaired airway protection, respiratory failure, shock, severe agitated behaviour or grade III / IV encephalopathy.

Fluid and electrolytes : Fluid therapy should strike a careful balance between maintenance of hydration with adequate urine output and prevention of cerebral edema. Recommended fluids in ALF are 75-100% of maintenance requirement; sodium is 1-2 mEq/kg/day; potassium is 3-5mEq/kg/day and dextrose is adjusted to maintain blood sugar between 60-100mg%. This can be usually achieved by giving 10% Dextrose in 0.2 N Saline and appropriate addition of potassium chloride while monitoring serum electrolytes. Urine output should be maintained (>1ml/kg/hour) using colloid / plasma. If necessary, frusemide (1-3 mg/kg 6hrly) may be added and a low dose dopamine may be used to improve renal perfusion (2-5μg/kg/day). The goal of fluid therapy should be to maintain mean arterial pressure > 60 mmHg in order to prevent fall of CPP below 45-50 mm of Hg. If needed packed cell transfusion should be considered to keep Hb above 10 gm/dL to ensure good oxygen carrying capacity.

Antibiotics : Infections are invariably associated with ALF and prophylactic antibiotics – IV Cloxacillin / ampicillin and cefotaxime / ceftazidime are indicated routinely. Nephrotoxic drugs are tp ne avoided .

Prevention of GI haemorrhage: GI haemorrhage is usually secondary to associated gastritis, stress ulcers or part of coagulopathy which worsens the encephalopathy. Routine use of IV Vitamin K (<1 year 2.5mg/day, >1 year 5mg/day, >5 years 10mg/day), IV Ranitidine - 1-3mg/kg/dose 12 hourly, Sucralfate orally- 1-2 gm 4 hourly is recommended.

Management of encephalopathy : Management is aimed at reducing intake and absorption of ammonia which is achieved by following strategies. Proteins must be stopped because they are ammoniagenic. Instead, if indicated vegetable proteins (less ammoniagenic) - rich in branch chain amino acids (metabolised in muscle, not liver) could be used. Reintroduction of proteins is advisable slowly (0.5-1 gm/kg/day) during recovery. Evacuation of colonic contents with 50% magnesium sulphate enema / bowel washes with acidic fluid twice daily helps in reducing ammoniagenic bacterial flora. Lactulose when given in 0.5ml/kg/dose orally every 6 hrs to produce 2-3 semi-loose stools daily acts as a cathartic, acidifies colonic contents and alters bacterial flora. It can also be given by enema. Neomycin (50-100mg/kg/day) although controversial reduces bacterial ureases and proteases responsible for ammonia production. Mechanical ventilation helps in decreasing raised ICP. Benzodiazepines should be avoided.

Management of Complications

1. Raised intracranial pressure: Sustained rise of ICP > 30 mmHg is indicative of raised intracranial pressure. Cerebral edema occurs between Stages II and III. Clinical signs include abnormally reacting pupils, increased muscular tone, decerebrate posturing, abnormal reflexes, focal seizures, loss of brain stem reflexes, bradycardia and increased BP. Treatment of cerebral edema is unsatisfactory and all efforts should be taken to prevent it.

Strategies to prevent cerebral edema include avoidance of excessive handling, stimulation, unnecessary suctioning, (prevent coughing , vomiting). Raise head end of bed to 30 degrees, avoid neck flexion. It is wise to restrict fluids to 60-75% of maintenance while ensuring good cerebral perfusion pressure (mean arterial pressure *minus* intracranial pressure). Use of mannitol should be considered if the child in stage II or more in a dose of 0.5g/kg over 5 mins and may be repeated every 4-6 hours for a maximum of period of 48 hours. Ensure adequate urine output while on mannitol because its use can be dangerous in presence of inadequate urine output. It is also desirable to monitor and keep serum osmolarity below 320mOsmol /kg. while on mannitol. Elective ventilation is indicated if cerebral edema is suspected. Hyperventilation to maintain pCO2 between 25-35 mmHg may be effective in reducing raised ICP, but it's effect is short lasting. Mild hypothermia (32-33° C) using a cold blanket has been reported to reduce ICP. Ensure that hypothermia is maintained continuously as wide swings in body temperature may be deleterious. Some centres use intracranial pressure (ICP) monitoring devices to measure ICP but it's use is controversial as it has its' own risks and does not appear to influence the overall outcome. Steroids have no role in the management of raised ICP in ALF and may be detrimental[5]

2. Convulsions : Convulsions can be controlled by bolus of Phenytoin 10mg/kg IV slowly followed by maintenance dose of 5-8mg/kg/day. Phenytoin can be repeated if there is no response to initial dose. If convulsions persist, administer phenobarbitone 10-15mg/kg slowly and wait upto 20 minutes for a response. Maintenance dose is 5mg/kg/day in two divided doses. If seizures still persist use IV Thiopentone. Child should be mechanically ventilated and watched for hypotension.

3. Hemorrhage : Hemorrhages are due to decreased hepatic synthesis of coagulation factors, reduced platelet number and function or associated DIC. Prothrombin time is a sensitive indicator of synthetic function of liver. If an abnormal PT is less than 30 secs, FFP transfusion is indicated only for invasive procedures but if PT is more than 30 secs, FFP transfusion should be given 10ml/kg every 6-8 hrs. If there is associated severe bleeding, FFP transfusion should be given 10-20 ml/kg every 6-8 hrs and platelet transfusions to maintain the counts above 50,000/cmm. If fluid balance becomes a consideration, double volume exchange transfusion may be of temporary use as also hemofiltration.

3. Renal Failure : Renal failure may be due to hepatorenal syndrome, dehydration, or acute tubular necrosis. Aim of therapy should be to maintain urine output above 0.5ml/kg/hour. A colloid challenge of 10ml/kg may be helpful in bringing up the urine output. Repeat if no response. CVP is a useful guide to fluid management and if it is high (> 8mm), start renal dose of dopamine 2-5µg/kg/min. If no response, add Frusemide 1-2mg/kg stat. In case of established renal failure -Frusemide infusion (0.25mg/kg/hr) is indicated. Established renal failure requires dialysis.

4. Sepsis : Subtle signs like rise in heart rate or core-toe temperature gradient, fall in blood pressure or urine output, hypoglycemia, hypo-thermia, deterioration in mental state, fits, acidosis may be present. Common organisms are gram negative bacteria, staphylococci and occasionally fungal infections. A full septic screen except lumber puncture and suprapubic puncture is indicated in a child with ALF. Routinely broad-spectrum antibiotics like IV Cloxacillin / Ampicillin combined with IV Cefotaxime / Ceftazidime should be started. Antifungals and metronidazole may be added if no response in 48-72 hours. Avoid aminoglycosides as far as possible.

5. Electrolyte and acid base balance : In presence of electrolyte and acid base abnormality consider hypovolaemia, hypoxia, sepsis, and renal failure. Hypokalemia, hypocalcemia and hypomagnesemia are very common and should be corrected. Respiratory acidosis will require ventilation while metabolic acidosis could be corrected by NaHCO3.

Therapy in specific situations

1. Paracetamol ingestion: Gastric lavage and forced diuresis are indicated in case of paracetamol toxicity. Specific therapy includes administration of N- acetylcysteine in a dose of 140mg/kg initially followed by 70 mg/kg 4hourly. It should be started within 24 hours of drug ingestion and continued till liver failure resolves.

2. Metabolic disorders : Stopping lactose feeds in galactosemia; n-acetylcysteine (100 mg/kg/day), selenium (3 mg/kg/hr), desferioxamine (30 mg/kg/day), and oral alpha-tocoferol (25 U/kg/day) for neonatal hemochromatosis.

Liver Transplantation (LT)

Liver transplantation, where available, should be considered in all children with Stage III or IV encephalopathy. It is usually appropriate for all the common causes of ALF except those with multisystemic disorders, uncontrolled sepsis, mitochondrial hepatopathies, etc. The King's College Criteria has been most widely applied since their introduction in 1989, (Table 3)[6]. Survival rates after LT for children with ALF are 60-70%. In India, LT is available in only a few centres, and even then mainly for chronic liver disease. Auxiliary liver transplantation, where part of the native liver is removed, and replaced with either the respective left or right lobe of a reduced graft could prove to be useful for ALF. The advantage of this procedure is that the native liver is retained, and if sufficient hepatic regeneration were to occur, immunosuppression could be withdrawn and the liver graft allowed to atrophy or be surgically removed[7].

Artificial hepatic support systems like Molecular Adsorbent Recycling system (MARS), bioartificial livers (Extrahepatic Liver Assist Device) have been successfully used as a bridge prior to transplantation[8].

Points to remember

1. *Non-hepatotropic viruses and metabolic liver diseases are the commonest causes of ALF in infants while Hepatitis A and / or Hepatitis E virus are common in older children*

2. *The major causes of death include cerebral edema, hemorrhage, renal failure and sepsis. Overall mortality is high (70%).*

3. *Management is directed at life support, prevention and management of complications and allowing time for native liver to recover.*

4. *Liver transplantation is the only option that offers a good chance of survival but is not easily available and expensive in India.*

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NEWS AND NOTES

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GATROENTEROLOGY

PROBIOTICS IN CHILDREN

*** Anitha Srilakshmi R**
**** John Matthai**

Abstract: Probiotics are live microbial food supplements that act by improving the endogenous host flora. By modifying the intestinal flora, they alter the functional mucosal barrier of an individual. Lactobacillus GG and Saccharomyces boulardii are the most widely studied strains. They have been proven beneficial in antibiotic associated diarrhea, rota viral diarrhea and in recurrent Clostridium difficile diarrhea. The other strains of Lactobacilli need evaluation with large controlled trials, before they can be recommended for use. Probiotics are generally safe. The role of curds in prevention of intestinal illnesses is a promising area for research.

Keywords: Probiotics, Lactobacilli, Saccharomyces, Diarrhea

The human gastrointestinal tract has an extensive surface area (200 sq. meter) and it is colonized by a large number of bacteria (10^{14} bacteria). These bacteria (the endogenous bacterial flora) constantly interact with the ingested pathogenic bacteria and also with the intestinal mucosal cells. The mucosal cells are

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part of the "functional intestinal barrier" which plays a crucial role in the prevention of various intestinal disorders. The integrity of the functional barrier is dependent on the endogenous bacterial flora. A healthy flora is necessary to maintain the health of the intestine. Probiotics modify the intestinal flora and thus influence the functional mucosal barrier of an individual.

What are Probiotics?

Probiotics are live microbial food supplements that have a beneficial influence on humans by "improving" the endogenous microbial flora.

Probiotic Strains
  - Lactobacillus (many strains)
  - Bifidobacterium
  - Streptococcus thermophilus
  - Saccharomyces boulardii

Mechanisms of action

Various mechanisms have been proposed to explain the beneficial effects of probiotics. They include

1. Production of inhibitory substances (Bacteriocins)

2. Competitive inhibition of the adhesion of pathogens.

3. Competition for nutrients required for the growth of pathogens.

4. Modification of toxins or toxin receptors.

5. Trophic effect on the intestinal mucosa

6. Immune modulation (increasing IgA levels)

7. Inducing changes in the intestinal permeability

8. Increasing anti-inflammatory cytokines

9. Acidification of the intestinal lumen

It is possible that in a given setting several different mechanisms are operative, depending on the specific probiotic being used as well as the properties of the enteric pathogen targeted.

Probiotics in antibiotic associated diarrhea

Diarrhea is a well known complication of antibiotic treatment, especially with broad spectrum antibiotics. The prevalence ranges from 8-30 % in children. The clinical spectrum may vary from a mild self -limiting diarrhea to severe life threatening pseudo-membranous colitis[1]. It is postulated that antibiotics produce alterations in the normal intestinal microflora and result in colonization by antibiotic resistant bacteria. Since probiotics can beneficially modify the intestinal flora, they have been used to prevent and treat antibiotic associated diarrhea.

Randomized controlled trials have shown that concurrent use of probiotics, result in a modest reduction in the incidence of diarrhea (from 26% to 8%), reduction in the stool frequency as well as improvement in the consistency of stool.[2,3] Only Lactobacillus GG has been proven definitely beneficial in various studies. Other strains of lactobacillus have not been adequately studied. There are no large scale randomized controlled trials with Saccharomyces boulardii.

It is important to realize that in most children, antibiotic associated diarrhea is self-limiting and does not result in dehydration. However, it is an annoying symptom and most parents are anxious about it. Available evidence suggests that it may be cost effective and prudent to use probiotics with antibiotics in malnourished children, children with past history of severe antibiotic associated diarrhea and prolonged use of broad spectrum antibiotics.

Probiotics in infectious diarrhea

Two major meta-analyses of studies done in children regarding probiotics in infectious diarrhea arrived at the following conclusions.[4-7]

1. There is a clinically significant benefit in the treatment of acute infectious diarrhea in infants and children, particularly in rotaviral gastroenteritis. There was a reduction in stool frequency and the duration of the diarrhea.

2. Lactobacillus GG showed the most consistent effect, although other strains may be effective.

3. The beneficial effects of probiotics are strain and dose dependent.

4. They are ineffective in invasive bacterial diarrhea.

5. Beneficial effects are more evident when they are started early in the course of the disease

The role of probiotics in prevention of diarrhea is not proven. Studies suggest that long term use of Lactobacillus GG may reduce the incidence of diarrhea in malnourished children in the community[8]. No benefit has been observed in breast fed infants. Other strains of Lactobacillus have not been evaluated.

Probiotics have also been evaluated in the prevention of nosocomial diarrhea.[9] While some studies reported benefit, others did not. More trials are needed before drawing conclusions.

Probiotics in Clostridum difficile diarrhea

In adults, the combination of a standard antibiotic and Saccharomyces boulardii was shown to be an effective and safe therapy for patients with recurrent Clostridium difficile diarrhea.[10] However no benefit was observed in

those with the first episode of Clostridium difficile diarrhea. Eventhough data in children is limited, it seems prudent to recommend their use. Other probiotics have not been proven effective even in adults.

Probiotics and lactose digestion

A number of microorganisms specifically Lactobacillus bulgaricus, Streptococcus thermophilus and Lactobacillus acidophilus can exert their lactase activity in vivo following ingestion. Thus the activity of these micro-organisms in the intestine can facilitate the digestion of lactose and its subsequent absorption with the amelioration of the clinical signs of lactose intolerance.

Yoghurt is effective in reducing symptoms of lactose intolerance. Yoghurt has a lower lactose concentration when compared to milk, because organisms use lactose as a substrate during fermentation. The micro-organisms present in yoghurt also have high lactase activity.[11-13] In the Indian setting, Curd (contains several strains of lactobacilli mainly L.bulgaricus) is an alternative to yoghurt. Very few studies have assessed their efficacy scientifically. In a study from Delhi on 100 children aged 2 – 5 years given curds regularly for 6 months, there was decreased incidence of diarrhea as well as better weight gain during the study period.[14] Whether the beneficial effects are sustained on a long term is not known.

Probiotics in inflammatory bowel disease

The gut immune system and the microbial flora play an important role in the pathogenesis of inflammatory bowel disease. Hence probiotics may have a role in the management of inflammatory bowel disease.

In adult studies probiotics show promise as an adjunct to standard therapy. They are still under evaluation in children. In a recent placebo controlled study in children with Crohn's disease in remission, Lactobacillus GG was not proven beneficial in maintaining remission, when added to the standard maintenance therapy.[15]

Very recently, Lactococcus lactis was engineered to secrete IL-10 (anti-inflammatory cytokine) in the colon, to reduce the local inflammation (Turbo –Probiotic). In animal models, the results were promising.

Probiotics and atopic dermatitis

In one study it was noted that the incidence of atopic eczema in susceptible infants was reduced by 50% (compared to placebo), when probiotics were given prenatally to expectant mothers for a month and then to their infants for 6 months.[16] This has led to questions whether early colonization of the gut with "bad bacteria" predispose to atopy. The gut flora might be a hitherto unexplained source of natural immune modulators for the prevention of atopic disease. More research is needed before conclusions can be drawn.

Safety of probiotics

Probiotics are generally considered safe. There have been isolated case reports of systemic fungemia after use of Saccharomyces boulardii in adult patients in intensive care units. There have also been case reports of lactobacillus bacteremia in immuno-compromised children.[17]

Probiotics in India

Lactobacillus GG is the most potent among the lactobacillus strains. However it is very costly and not available. Lactobacillus acidophilus and lactobacillus sporogenes are cheap and readily available in India. However, they are not as potent as Lactobacillus GG. The viability and survival of these strains in commercial

preparations is another problem. Large controlled trials need to be done using these organisms before they are recommended for specific use. Saccharomyces boulardii is now available in India.

Dosage

Lactobacillus: The minimum dose of lactobacillus required is 10^8 organisms. This varies with the strain being used and the indication for use. The benefits reported are dose related.

Sacharomyces Boulardi: Dosage is 500 mg once daily or 250mg twice daily for at least 5 days.

Probiotics in children – current status

The current status of probiotics (Lactobacillus GG and Saccharomyces Boulardii) can be summarized as follows.

Definitive role : Antibiotic associated diarrhea, Recurrent clostridium difficile diarrhea, Rota virus diarrhea

Possible role : Prevention of diarrhoea in non breast-fed infants, lactose intolerance

Experimental role : Prevention of atopic disease in infants, inflammatory bowel disease

Key messages

1. *Among the many probiotics, only Lactobacillus GG and Saccharomyces boulardii have been adequately evaluated. The former is costly and not available in India now.*

2. *Probiotics are of proven benefit in antibiotic associated diarrhea, recurrent Clostridium difficile diarrhea and rota virus diarrhea.*

3. *Though probiotics are considered safe, indiscriminate use without scientific basis is not justified.*

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NEWS AND NOTES

PALS Karamsad 2005, Gujarat

Date: March 5-6, 2005

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National Hematology Update-IV, New Delhi

Date: February 26-27, 2005

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RADIOLOGIST TALKS TO YOU

JAUNDICE (Contd.)

* *Vijayalakshmi G*
** *Natarajan B*
*** *Ramalingam A*

This article is a continuation of the topic 'Hepatitis and fever' of the last issue. High-resolution real-time ultrasonography serves as an important tool for differentiation of obstructive and non-obstructive causes of jaundice in infants and children. This non-invasive, non-ionising modality is independent of liver function. If the US does not show features of obstruction in a child with jaundice, surgical conditions can be excluded. In obstruction, abnormality will be seen as dilatations of the pathways of bile. These include the intrahepatic biliary radicles, the common bile duct and the gall bladder with the cystic duct. The normal common bile duct is hardly seen in a child. It is less than 4 mm in the young child and should not exceed 7 mm in the adolescent or adult. The intrahepatic biliary radicles are also not normally visualised. The gallbladder is a smooth oval cystic structure with a varying volume, depending on the timing of the previous meal.

The extent of biliary dilatation points to the level of obstruction. To observe dilatation, the portal vein is first identified. The common bile duct, if dilated, is seen anterior to it as another tube (Fig 1). This is sometimes referred to as the 'two tubes' sign or the 'double duct' sign. The dilated intrahepatic biliary radicles will be seen as dilated tubes running along with the intrahepatic portal radicles within the liver. In fact this is one of the first signs of biliary obstruction that catches the attention of the sonologist on seeing the liver. There are 'too many tubes' in the liver (Fig 2). Next, the gall bladder is identifed. It is either distended or not, depending on whether the block is proximal or distal to the junction of the cystic duct with the common duct.

Biliary obstruction resulting in jaundice may be related to neoplasms, benign strictures (rare in children), or gallstone disease.

Neoplasms of the biliary duct are extremely rare in the child. The cause is rhabdomyosarcoma of the CBD. We have seen only one such case in the last ten years. This is a highly infiltrative tumor and runs a hopeless course. The tumor is seen as an ill-defined solid mass near the porta hepatis. Proximally there is dilation of the biliary tree. Other tumors of the liver present with a palpable mass and only rarely with jaundice. There was one case of endodermal sinus tumor in the pelvis with hepatic secondaries and jaundice.

There are many reports to suggest that common bile duct lithiasis should be considered among the causes of cholestatic jaundice in children. Some of the gallbladder calculi seen in older children might have resulted from a lithogenic process that occurred during fetal life or shortly after birth. We have seen one newborn

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Fig. 1 Double duct sign. The CBD is seen anterior and parallel to the portal vein.
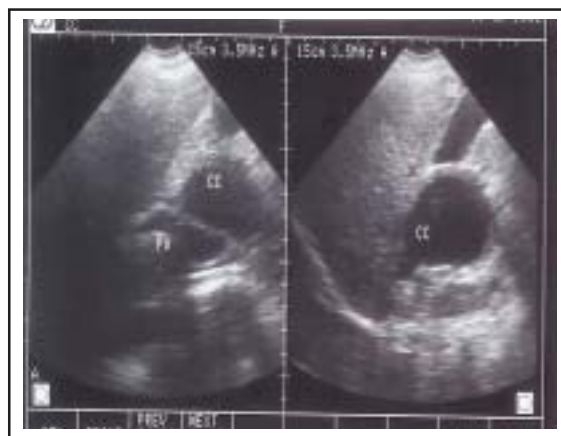

Fig. 2 Dilated intrahepatic biliary radicles.

Fig. 3 Newborn with a stone in distal CBD C-Calculus. Note the after shadow.

Fig. 4 Stone in distal CBD in an adolescent.   P-Pancreas.

Fig. 5 Narrowing at the lower end of the CBD with sludge in a case of pancreatitis.

Fig. 6 Choledochal cyst (CC) PV-portal vein.

with a mildly dilated common bile duct and a small stone at the lower end. This disappeared in about two weeks (Fig.3). There has been one long-term study from France[1], which showed that the gall bladder calculi can undergo spontaneous dissolution. They can also produce jaundice, abdominal pain or sepsis. CBD stones definitely require treatment and interventional radiological procedures are increasingly being used.

However, isolated gallstones remain a rare diagnosis in children. Gallstones may be secondary to obstructive congenital anomalies of the biliary tract, total parenteral nutrition, furosemide treatment, phototherapy, dehydration, infection and hemolytic anemia. Jaundice in infants and children can also be seen in cirrhosis or benign strictures.

The commonly seen congenital anomaly of the biliary tree is the choledochal cyst which we have discussed earlier. This is sometimes an incidental finding. Asymptomatic small choledochal cysts are not be accompanied by dilated intrahepatic biliary radicles (Fig 6) or there is very minimal dilation. This indicates that there is no significant obstruction to bile flow. So dilatation of intrahepatic biliary radicles is an important finding that is easy to appreciate and also a pointer to active obstruction. Following cholecystectomy the bile duct alone is mildly dilated, but this should not be mistaken for obstruction.

In the next issue we will be discussing imaging in neonatal jaundice.

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NEWS AND NOTES

CME on Common Cardiac Disorder in Children,

Date: March 20, 2005

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NEWS AND NOTES

Call for Nominations for FIAP-2005 - Last date extended

Nominations on prescsribed form are invited duly proposed and seconded by the members of the Indian Academy of Pediatrics for the year 2005. It is open to the members of the society to propose the name of any scientist who may not necesarily be a member of the society for award of FIAP. The FIAP Nomination form could be obtained from the Central IAP Office on request. The nomination for FIAP should be submitted in SIX copies. The last date for submission of nomination for 2005 to the Central IAP Office is 31st March 2005.

CASE STUDY

SUPRASELLAR ARACHNOID CYST PRESENTING WITH PRECOCIOUS PUBERTY

* *Seenivasan V*
** *Ravisekar CV*
** *Venkataraman P*
*** *Sundararaman PG*
**** *Vasantha Mallika TK*

Arachnoid cysts are intra arachnoidal collections of cerebrospinal fluid and are commonly of congenital origion. Suprasellar arachnoid cysts are uncommon lesions, accounting for 9% of all intracranial arachnoid cysts. They are usually asymptomatic and discovered incidentally. Endocrine dysfunction can occur in the form of precocious puberty, developmental delay, skeletal growth retardation and hypothalamic disturbances[1,2]. A seven-year-old girl child presenting with precocious puberty secondary to suprasellar arachnoid cyst is reported along with review of literature.

Case report

A seven-year old girl child, second born to non-consanguineous parents, presented with complaints of progressive enlargement of both breasts of two years duration, white discharge and spotting per vaginum of six-months duration.

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The child had one episode of seizure in the form of upward deviation of eyes with loss of consciousness at the age of six. The child also gave history of transient attacks of headache and giddiness on and off over the previous two years. There was no history of visual disturbances, birth asphyxia, developmental delay, head trauma or CNS infection.

Clinical examination revealed breast development at Tanner stage III and pubic hair development at Tanner stage II – III with absent axillary hair. The height was falling just above the 50th percentile, while the weight was above the 90th percentile. The head circumference was appropriate for the age. Clinically, there was no neurological deficit and optic fundi were normal. With this clinical picture, a working diagnosis of GnRH dependent precocious puberty was made.

Endocrinological investigations revealed increased levels of LH (11.54 mIU/L), FSH (5.9 mIU/L) and 17-beta estradiol (20 pg/ml) and normal levels of prolactin (14.6 ng/ml) and cortisol (8:00 am level – 14.2 micro gram / L). The child had normal thyroid profile and growth hormone dynamic test.

Ultrasonogram of the pelvis revealed uterine length of 4 cm, which was well above the upper pre-pubertal limit (3.5 cm). Both the ovaries were enlarged. Two follicles, each measuring 0.9 cm in diameter were observed in right ovary. The child was found to have an advanced bone age of 11-12 years as against the chronological age of seven years. Cone view of sella showed enlarged sella.
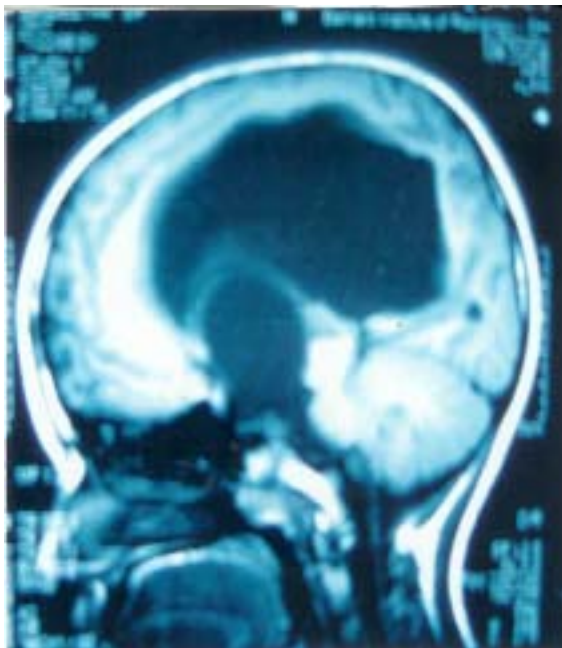
Fig 1. MRI of Brain showing the arachroid cyst (c)

MRI brain showed a large well-defined lesion, isointense to the CSF in all sequences. It was noticed anterior to the brain stem and extending superiorly indenting the lateral ventricles and displacing the third ventricle posteriorly. The mass was extending across the midline at the level of ventricular body. The hypothalamus appeared thinned out and bowed anteriorly by the lesion. The lateral ventricles were dilated. The corpus callosum was stretched and thinned out.

With the above investigations, a final diagnosis of suprasellar arachnoid cyst resulting in isosexual precocious puberty was arrived.

Discussion

GnRH dependent (central or true) precocious puberty occurs as a result of the premature release of Gonadotropin Releasing Hormone from the hypothalamus, which stimulates the secretion of pituitary gonadotropins, which in turn stimulate the secretion of gonadal sex steroids[3,4].

Up to 75% of boys and 10% if girls with isosexual precocious puberty have structural neurological abnormalities. The most common lesion being hypothalamic hamartoma and suprasellar arachnoid cyst is a rare cause. Suprasellar arachnoid cyst causes disorder of growth, puberty and hypothalamic-pituitary function due to its proximity to hypothalamic pituitary area[5].

Arachnoid cysts account for 1% of all intracranial space occupying lesions. They are intra arachnoidal collections of cerebrospinal fluid. Hyperplastic arachnoid cells and dense connective tissue with collagen, line the cysts[6]. The fluid collection inside the cyst may be either due to secretion by arachnoidal cells or due to ball valve communication between the cyst and the surrounding CSF[2]. If they enlarge, they become usually symptomatic in the first two decades of life. They are most commonly located in the anterior and middle organised fossa extending along the sylvian fissure. Only 10% of them lie in the supra and parasellar region[7].

The advent of wider use and higher resolution of cranial MRI has identified previously undiagnosed intracranial pathology as a possible aetiology for GnRH dependent precocious puberty. The use of MRI in children with GnRH dependent precocious puberty has been shown to increase the detection rate of abnormalities in the hypothalamic-pituitary region, which might have been missed by previous techniques[8,9,10].

The pathogenesis of precocious puberty in suprasellar arachnoid cysts is debatable. It is known that tumours and pathological processes involving the hypothalamus frequently modify sexual development. These lesions may destroy the posterior hypothalamus, leaving the anterior

hypothalamus intact, which in the absence of inhibitory influences leads to increased pituitary function. According to Styme, inhibitory tone develops with in the central nervous system after birth, which reduces the gonadotropin levels, preventing early pubertal development[11]. It is postulated that suprasellar arachnoid cysts may interrupt this neural inhibition, leading on to precocious puberty.

This case is reported because of its rarity and also to stress the importance of neuro imaging in the evaluation of all children with GnRH dependent precocious puberty.

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NEWS AND NOTES

Postgraduate Clinics in Gastroenterology 2005

Date: April 1-2, 2005

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CASE STUDY

HYPERNATREMIC DEHYDRATION IN A NEWBORN WITH INADEQUATE LACTATION

Ratnakumari TL
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**Prakash V*
***Meer Mustafa Hussain K*

Abstract: Hypernatremic dehydration is an uncommon entity increasingly being recognised in the context of exclusively breast fed babies with mother having inadequate lactation insufficient lactation. This results in dehydration and a slow process of malnutrition sets in. Consequent to inadequate lactation the breast milk sodium content increases with resulting hypernatremia which might already exist in dehydration. If one is not aware of this entity, the treatment becomes difficult because the cause of hypernatremia is not identified fully in these babies.

Ketwords: Hypernatremia, breast milk sodium.

Hypernatremic dehydration with increased breast milk sodium has been reported in the literature in the past widely[1-4]. Inadequate support to the lactating mother and poor feeding predisposes to this condition and adequate

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technical and psychological support to the breast feeding mother would prevent this silent malnutrition in babies.

Case report

Twenty one day old male baby presented to our nursery with lethargy, poor weight gain, decreased urine output noted by the mother since 7th day of life. Baby was delivered full term in another city hospital with a birth weight of 2.5 Kg with history suggestive of birth asphyxia and was admitted to the nursery. Baby was discharged on day 6 and was on exclusive breast feeds since then. Mother had noticed progressive weight loss and decreased urine output after discharge. There was no history of vomiting or loose stools. On admission baby was pale, lethargic, weighing 1.75Kg (weight loss of 750Gm), severely dehydrated, with a doughy skin and shock. Other systems examination were not contributory. Shock was corrected with initial Normal Saline boluses. Dehydration was corrected as per WHO protocol. Serum electrolytes on admission revealed hypernatremia (160 mEq/L) with elevated renal parameters. Baby was managed with ¼ isotonic saline and a gradual fall of sodium was achieved over 72 hours. There was a parallel fall in the elevated renal parameters. Sodium, urea and creatinine values are shown in the chart below. Septic work up on admission was negative. At the same time mother (on day 22 postpartum)was subjected to breast milk sodium analysis which revealed a 10 fold increase in the sodium content i.e., 99mEq/l(Normal 7-12mEq/L). The breast milk sodium content came down to 36mEq/L after 72 hours. Baby's condition improved with adequate lactation. Serum sodium
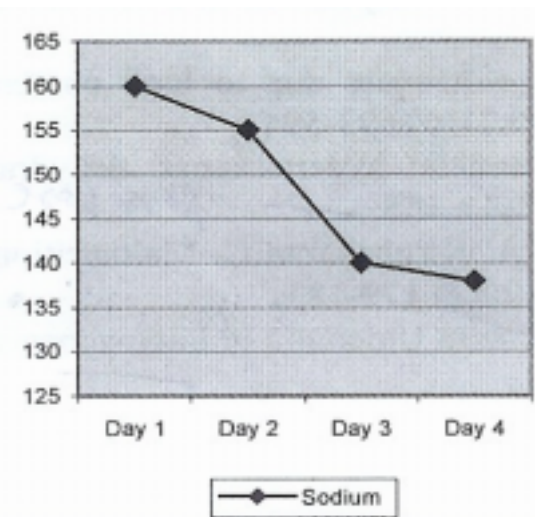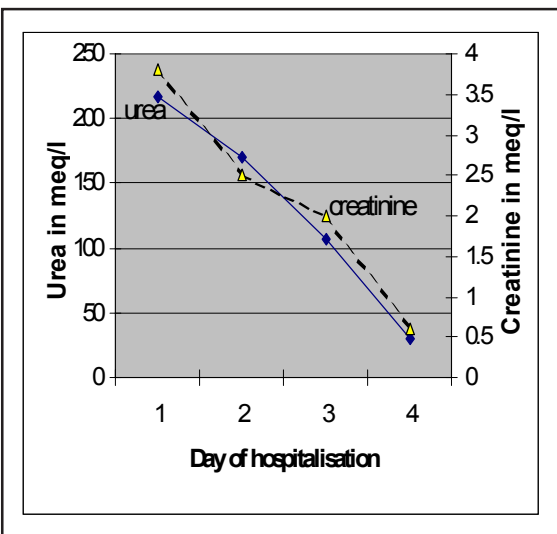
Fig 1 : Serum Sodium values

Fig 2 : Blood urea and creatinine values

was normal from the third day of correction and remained so until the very last. During the course of stay in the NICU baby developed Klebsiella sepsis and died at 46 days of life.

Discussion

In a neonate who is exclusively breastfed, yet not fed adequately, results in dehydration and malnutrition. Inadequate feeding and increased sodium content of the breast milk leads to hypernatremic dehydration[5-7]. This entity of increased sodium content of the breast milk is the result of inadequate lactation with inadequate emptying[8,9]. This results in increased pressure in the breast with prolactin inhibition which opens the tight junctions of the epithelial cells lining the ducts causing sodium leak across the tight junctions and thereby increasing the sodium content of the breast milk[10]. This coupled with inadequate feeding results in hypernatremic dehydration and malnutrition due to lack of psychological and technical lactation support. Normally the sodium content of the breast milk falls from 20-40 mEq/L at birth to 8-12 mEq/L by 3-5 days postpartum. But in abnormal

situations the levels remain persistently high beyond the expected time of fall. If adequate lactation is not established hypernatremic dehydration results in the baby. This is worsened by the increased sodium content of the breast milk.

Breast milk sodium can also be increased in conditions like pregnancy, preterm labour, mastitis and uterine involution apart form lactational failure[10]. Management of this entity is by adequate fluid resuscitation, hydration and establishment of adequate lactation. It is important to ensure a gradual fall of sodium at a rate not more than 0.5 mEq/L/hour. This is a preventable neonatal illness and this can be prevented by initiating breast feeding in the delivery room and continuing the same adequately with adequate emptying during the hospital stay and the emphasis on this message is maintained during the follow up and at every point of contact the mother has with the health care provider.

Key message

In an exclusively breast fed neonate with failure to thrive and hypernatremic

dehydration, one should always exclude inadequate lactation, by assessment of breast feeding and analysis of breast milk sodium content.

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NEWS AND NOTES

Course on Medical Genetics & Genetics counseling

Date: April 11-23, 2005

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ERRATA

We regret for the omission of names, Dr.Rakesh Jora and Dr.N.P.Chhangani, the co-authors of the article titled "Splenic infarct and splenic abscess with falciparum malaria" published in IJPP 2004;6(4): pp 342-344 and mentioning "Dr.Ujjal Poddar" as "Dr.Ujjal Podar", the author of the article titled "Approach to constipation in children", published in IJPP 2004;6(4): pp 322-327.

QUESTION AND ANSWER

Q.No.1. In dog bite, is scratch by nail of the animal taken as exposure and does this need antirabies vaccination / immunoglobulin?

Dr. B.Rajsekhar
Visakhapatnam, A.P.

A.No.1. This is a very important question and needs careful answering.

Whether transdermal bite / scratch, it should be remembered that it is only the infected saliva of the animal that is responsible for the transfer of the rabies virus. It is possible that by virtue of their natural habits dogs do scratch their mouth with their fore limbs and other body parts with hind limbs. Hence the nails getting contaminated by infected saliva is quite possible and hence even such transdermal scratches need post exposure prophylaxis with a full 5 doses course with any of the modern cell culture vaccines.

Rabies Immunoglobulin (RIG) is reserved only for multiple, deep wounds of category III type. Transdermal nail scratch needs no RIG.

Prof. A.Parthasarathy
Former Senior Clinical Professor of Pediatrics, Madras Medical College & Institute of Child health and Hospital for Children, Chennai

Q No.2: Is Nitazoxanide useful in children with protozoal and helminthic infections? what is the safety profile?

Dr. Pradyut Mondal,
Burdwan, WB.

A No.2.: Nitazoxanide was first introduced in 1980s as an effective human cestoidal drug against T.saginata and H.nana. In 1994 it gained importance after its broad spectrum activity was recognized against common emerging and resistant intestinal protozoa and intestinal helminths.

Nitazoxanide, a 2 acetelyloxy-N(5-nitro-2-thiazolyl)benzamide is well absorbed from the GIT. It interferes with pyruvate ferredoxin oxidoreductase(PFOR) enzyme dependent electron transfer reaction which is important for anaerobic glucose energy metabolism. This results in cell swelling,membrane damage and vacuole injury of the trophozoites ,resulting in dysfunction of the parasite. The drug is metabolized to the main active metabolite desacetyl nitazoxanide(tizoxanide). Excretion of the drug occurs in urine,bile and faeces.

The spectrum of activity includes protozoal infections C.parvum, G.lamblia, I.belli, E.histolytica, T.vaginalis and helminthic infections such as A.lumbricoides, A.duodenale, T.trichura, T.saginata, H.nana and Fasciola .hepatica .It is also effective against bacteroides,H.pylori and Clostridium spp.

A study comparing the efficacy of a 5 day metronidazole with a 3 day nitazoxanide therapy in children with diarrhoea caused by Giardia lamblia was conducted in Peru. The response rate was 90% and 83% in the nitazoxanide and metronidazole group respectively[1]. A 3 day course is also effective against cryptosporidiasis in HIV negative children as documented in the Zambian study[2]. In 2002 this drug was approved by FDA for children aged 1-11 years with giardiasis and cryptosporidiosis. It is also being evaluated for

HIV positive children with cryptosporidiosis, the duration of therapy however is longer for 32 weeks. Its efficacy as an antihelminthic compared to the single dose albendazole was not statistically significant in the study done in Mexico city[3]. In this study side effects was seen in 26.5% of children compared to 7.4% in the albendazole group. It is therefore not recommended in the mass prophylactic programmes against helminthic infections.

The adverse effects reported are abdominal pain,diarrhoea,vomiting,headache,flatulence, fever, malaise, rhinitis, discolouration of urine, increased transaminases and creatinine.The recommended dosage in children 12 to 47 months of age is 100 mg twice a day for 3 days and 200 mg twice a day for 3 days in children 4-11 years.It is prescribed with food to decrease the GI effects.The efficacy of the drug in children less than 1 year has not been evaluated.Thus at present this drug can be prescribed for children above the age of one year with giardiasis or cryptosporidiasis

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