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Journal Office and address for communications: Dr. P.Ramachandran, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

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CRITICAL CARE - II

PRACTICAL APPROACH TO ELECTROLYTE DISTURBANCES

***Thangavelu S**
****Ratnakumari TL**

Abstract: *With the advent of emergency and critical care units, electrolyte disturbances are being recognized in every hospital more often than before. They are commonly associated with critical illness of any etiology. Amongst the sodium and potassium disturbances hyponatremia is commonly encountered among the hospitalized children, next common being hypokalemia and hyperkalemia. Common manifestations of hypo- and hypernatremia are convulsions and irritability secondary to osmolar disturbances. Potassium being the electrolyte responsible for biological electricity, disturbances in this cation results in cardiac arrhythmia and weakness. Knowledge on electrolyte disturbances is mandatory for any pediatrician managing hospitalized children.*

Keywords: *Electrolyte disturbances, Hyponatremia, Hypernatremia, Hypokalemia, Hyperkalemia, Children*

Water and electrolytes make up most of the bulk of the human body. In critical care units, electrolyte disturbances constitute a common problem, either as presenting problem or as the consequence of illness. Electrolyte estimation becomes a priority in critically ill children because the clinical features of electrolyte disturbances are non-specific during critical illness such as respiratory distress or failure or shock or altered level of consciousness. They also play a great role in survival and mortality.[1] They have to be estimated routinely since they reflect the internal milieu and their disturbances need to be recognized early. Hence importance of electrolyte estimation is second only to vital signs.

* Former Reader in Pediatrics, PICU,
Institute of Child Health, Madras Medical College, Chennai.
Currently Head, Department of Pediatrics,
Mehta Children Hospital, Chennai.

** Former Professor of Pediatrics & Neonatology
Institute of Child Health, Madras Medical College, Chennai.
Currently Professor of Pediatrics,
PGIMSR-ESIC, Chennai.

Sodium disturbances

Both water and sodium play an equal role in the maintenance of osmolar homeostasis. Hyponatremia means serum sodium is relatively lower than the water content. Aldosterone is the key factor which is responsible for sodium concentration of body fluids whereas antidiuretic hormone and thirst directly regulate water homeostasis. Whenever there is loss of sodium or water, interaction of these factors corrects the imbalance. Failure of these mechanisms may lead to dysnatremia.

Hyponatremia

Case scenario

A five years old child presented with meningitis. On the third day of hospital stay, his GCS worsened and he developed seizures. Repeat brain CT was the same and no new findings seen. Repeat CSF analysis showed improvement, but serum sodium was 118 mEq/L (Previous sodium 138mEq/L, 24 hrs earlier) and he was on maintenance IV fluid D5 NS. Repeat sodium: 111.mEq/L. Possible causes: SIADH or Cerebral Salt Wasting syndrome. If there is no dehydration or edema, urine output is low, serum uric acid is low and urine sodium is > 20-40mEq/L, it is more likely SIADH. If the child is dehydrated, urine output is high, and urine sodium is > 90mEq/L it is more likely to be Cerebral Salt Wasting Syndrome. In this scenario the child needs further investigations to differentiate whether it is due to SIADH or Cerebral Salt Wasting Syndrome.

Initial assessment: Hyponatremia causing encephalopathy and seizures, either due to SIADH or cerebral salt wasting syndrome.

Hyponatremia is the most common electrolyte abnormality seen approximately in 25% of the hospitalized children.[2]

Definition: A serum sodium level of 135 mEq/L is considered as hyponatremia.[3]

Pathophysiology: Whenever the serum sodium is low, intracellular sodium cannot move out of the cell to correct low sodium in the ECF. Instead water is freely permitted to move across cell membrane. This leads to shifting of the

excess water from ECF to ICF which can lead to cell swelling. In a watertight compartment like brain, any swelling of neuronal cells leads to deleterious complications and cerebral edema leading to seizures and other neurological symptoms. These are decided by two factors. Severity of hyponatremia and rapidity of fall in serum sodium.[1] For example, a level of 110 mEq/L may be asymptomatic if it is chronic, but a level of 120 mEq/L may cause convulsions if it develops rapidly. Any hyponatremia lasting longer than 48 hrs is considered as chronic. A duration of less than 24-48 hrs is considered as acute. This is based on the time taken by the cells for adaptation. Brain cells are given the power of self-adaptation to prevent cell swelling in the presence of hyponatremia. Neurons can decrease or increase the cell size to normal by extrusion of electrolytes, idiogenic osmoles and osmotically active substances or vice versa which prevents further increase in cell size. This adaptation takes about 48 hours and similarly dissipation of these adaptive changes also will take 48 hours. This is precisely the reason that one corrects the serum sodium levels slowly not exceeding the rate of 12 mEq/L day to give time for the dissipation of adaptive mechanisms. If hyponatremia is corrected rapidly this adaptation does not happen and because of the relative hypo-osmolarity of ICF water movement occurs in the reverse direction from ICF to ECF causing cellular dehydration and leads to the syndrome of central pontine myelinolysis or osmotic disequilibrium syndrome.

Etiology

It is easier to categorize the causes based on total body water (TBW) or volume status of the individual, which can be clinically recognized. In every child with hyponatremia, the possibility of pseudohyponatremia should be thought of and excluded.

Pseudohyponatremia: In pseudohyponatremia serum osmolality is normal or high unlike in true hyponatremia,where it is always low.[3] Falsely low serum sodium occurs in the following situations.

1. *Improper sample:* blood obtained from a vein proximal to an infusion of hypotonic saline.
2. *Factitious hyponatremia:* (present but artificial than natural) occurs in hyperglycemia and in mannitol therapy, causing shifting of intracellular water to ECF to dilute serum sodium. Every 60 mg rise in blood sugar will decrease serum sodium by 1.0mEq/L Hyponatremia associated with hyperglycemia generally resolves as hyperglycemia is corrected. In hyperglycemia the serum osmolality is high.
3. *Pseudohyponatremia:* This is a laboratory artefact seen in hyperlipidemia and hyperproteinemia where the serum osmolarity is normal. This situation is seen when the lab uses old technology such as flame photometry and does not occur when ion selective electrode is used. Hyperlipidemia is suspected when serum is lipemic. Hyperproteinemia is very rare in children.

True hyponatremia: In true hyponatremia, serum osmolality is low and this can be classified into 3 categories[3]: hypovolemic hyponatremia, isovolemic hyponatremia and hypervolemic hyponatremia. Various etiological factors are shown in Table I. Even though SIADH is categorized in isovolemic hyponatremia, there is subtle expansion of intravascular volume and there will be an attempt by the kidneys to increase the sodium excretion.

Clinical evaluation

If true hyponatremia is suspected, the volume status needs to be evaluated based on history and physical examination to categorize the illness.

History: Should be elucidated for diarrhea, vomiting, polyuria, oliguria, edema, breathlessness, altered level of consciousness or convulsions, any surgical procedure done, drugs and IV fluids administered.

Physical examination: Look for signs of dehydration, features of shock, respiratory distress, tachycardia, S3 gallop, ascites, edema, pigmentation, stigmata of liver or renal disease and bony deformities suggestive of rickets. Genital examination is mandatory to identify congenital adrenal hyperplasia (CAH).

Thus with history and physical examination, three clinical groups of hyponatremia can be recognized (Table I).

1. Hypovolemic hyponatremia (Hyponatremia with dehydration)
2. Hypervolemic hyponatremia (Hyponatremia with edema)
3. Euvolemic hyponatremia (Hyponatremia with no dehydration and no edema)

Clinical manifestation

The clinical features can fall into any of the three groups. (i). Signs of systemic illness: Hyponatremia is never an isolated disorder; it is always present as a part of systemic illness. Hence, the features of underlying illness such as diarrhea, septic shock, meningitis, or congenital

Table I. Comparison of features among various causes of hyponatremia

Hypovolemic hyponatremia	Euvolemic hyponatremia	Hypervolemic hyponatremia
Dehydration present	No dehydration, no edema	Edema present
Causes	**Causes**	**Causes**
1.Extra renal loss: Vomiting, Diarrhea and replacing this loss with electrolyte free solution	1.Water intoxication (Use of 5% dextrose in post-operative period.)	1. Renal failure 2. Nephrotic syndrome 3. Congestive heart failure 4. Protein energy malnutrition 5. Cirrhosis of liver
Third space loss as in dengue with capillary leak, sepsis, acute pancreatitis, anaphylaxis and intestinal obstruction	2. Psychogenic water drinking	
2. Renal loss: Renal tubular acidosis (RTA), osmotic diuresis (Diabetic ketoacidosis), diuretic therapy, adrenal insufficiency, CAH	**3. SIADH: Respiratory:** bronchiolitis, pneumonia, mechanical ventilation	
3. Cerebral salt wasting syndrome	**Neurological disorders:** traumatic brain injury, CNS infections	
Investigation	**Medications:** Cyclophosphamide, vincristine, carbamezepine and sodium valproate	
Urine Na >20 mEq/L–renal	**Investigation**	**Investigation**
Urine Na <20 mEq / L–non-renal	Urine Na > 20 mEq/L – SIADH	Urine Na > 20 mEq/L – renal failure
↓Na ↓K ↑Cl – RTA	Urine Na< 20 mEq/L – water intoxication	Urine Na < 20 mEq – all others
↓Na ↑K ↓ glucose – Adrenal insufficiency	Psychogenic water drinking	

adrenal hyperplasia will be present. (ii). Non-specific symptoms such as lethargy or vomiting and (iii). Neurological signs: In severe hyponatremia and following rapid fall of serum sodium, neurological features like convulsions or irritability appear.

Investigations

The most useful investigations are, serum electrolytes, blood glucose, blood urea, serum creatinine, serum uric acid, X-ray chest, serum osmolarity, urine osmolarity and urine sodium and potassium are the most useful investigations.

Urine Na <20 mEq / L indicates non renal loss

Urine Na > 20 mEq / L indicates renal loss

Urinary potassium if it is high may indicate Bartter's syndrome and if low indicates CAH.

Management: Management of hyponatremia depends on factors such as volume status, whether the child has neurological symptoms and on the nature of underlying illness. One would answer the following questions in a stepwise manner for proper management of hyponatremia (Fig.1).

Step 1: Is it true hyponatremia? First step is to establish the fact that the hyponatremia is real (after excluding the causes of pseudo hyponatremia).

Step 2: Is the child symptomatic or asymptomatic? if symptomatic, whether the child has neurological symptoms like seizures, irritability or altered level of consciousness?

Step 3: If asymptomatic, categorize them according to the volume status: a) Hypovolemic hyponatremia b) Isovolemic hyponatremia c) Hypervolemic hyponatremia (Table I).

Step 1 *True hyponatremia:* First step in the treatment is to confirm whether hyponatremia is true or false. Usually true hyponatremia is associated with hypo-osmolaerity. In pseudo hyponatremia serum osmolality will be normal or high. When facility to test the serum osmolality is available this is easier. If this facility is not available, or cannot be determined, decision should be based on clinical situations. Exclusion of pseudohyponatremia is straight forward once blood glucose is checked and found to be normal, the serum sample is not found to be lipemic and if the sample is taken in right manner.

Step 2 Development of neurological symptoms depends on the severity of hyponatremia as well as the rapidity of its evolution. Treatment of symptomatic hyponatremia: Management is common in all children with hyponatremia and neurological symptoms, irrespective of the category. If the child develops seizures or irritability or altered level of consciousness, serum sodium level has to be raised quickly by at least 5 mEq/L.[4,5] This can be done by giving 6 mL/kg of 3% saline over 30 min to 1 hour through peripheral line and this will be enough to tide over the crisis, irrespective of serum sodium level. One mL/kg of 3% saline will raise the serum sodium level by 0.8 mEq/L. Further management is as for an asymptomatic child. This crisis management is common for all three categories when the child displays neurological symptoms. In general, all calculations and equations cannot replace meticulous clinical and frequent biochemical monitoring, because they do not take into consideration the effects of added solutes and water and presume that there is no ongoing loss. It is also impossible to give precise recommendation for every situation, and it is individualized based on repeated monitoring. Hypertonic saline also reduces ICP by promoting water movement from ICF to intravascular space.

Step 3 If the child has hyponatremia, but does not have seizures or other CNS symptoms, here management based on volume status. In hypovolemic hyponatremia treatment is replacement of salt and water, isovolemic hyponatremia needs water restriction and in hypervolemic hypernatremia, both sodium and water has to be restricted.

1. Treatment of hypovolemic hyponatremia: Calculate the degree of dehydration and correct the deficit using normal saline or ringer lactate. This will correct both dehydration and hyponatremia. This can be done by one of the two methods.

For example, one year old weighing 10 kg moderately dehydrated, no seizures, neurological status normal.

Three phase correction: Deficit 10 x 60 = 600 mL. This has to be given over a period of 6 hrs. Phase 1: In the first hour 20 mL/kg of NS (0–1 hour 200 mL) is given over one hour for rapid deficit correction and in the phase 2 (i.e., 1–6 hrs), the rest of 400 mL of NS can be given over 5 hours. This is followed by Phase 3,where maintenance fluid for 7–24 hrs as 1000 mL of ½ GNS is given. Serum sodium has to be rechecked after 12 hrs after dehydration correction to ensure that serum sodium level is returned to normal (Table II).

Two phase correction: E.g. deficit correction is 600 mL and maintenance fluid is 1000 mL with a total of 1600 mL. Phase 1 : 200 mL in the first hour; rest (1400 mL) is given over 1-24 hrs (Table III).

Table II. Three phase dehydration correction[6]

0–1 hr	1–6 hrs	7–24 hrs
Rapid restoration of intravascular volume (20 mL/kg) 200 mL over one hr (NS/RL)	Deficit correction: Rest of 40 mL/Kg) 400 mL over 5 hrs (NS/RL)	Maintenance + replacement of ongoing losses 1000 mL G5 ½ NS with K 20 mEq/L

Table III. Two phase dehydration correction

0–1 hr	1–24 hrs
Rapid restoration of Intravascular volume (20 mL/kg) 200 mL over one hr (NS/RL)	**Deficit correction** + Maintenance 400 + 1000 mL = 1400 mL over1- 24 hrs (G5 ½ NS + K 20 mEq/L) 0-8 hrs: 700 mL; 9-24 hrs: 700 mL

2. Isovolemic hyponatremia: Here there is a subtle increase in water and that leads to hyponatremia. Restriction of water will raise the serum sodium level. Usually in normovolemic individuals, water retention and resultant fall in tonicity suppresses ADH release. Two appropriate stimuli for ADH release are increase in osmolarity or fall in effective plasma volume. But in SIADH, despite falling tonicity, ADH secretion continues which is inappropriate. Inappropriate stimuli in this situation are certain clinical

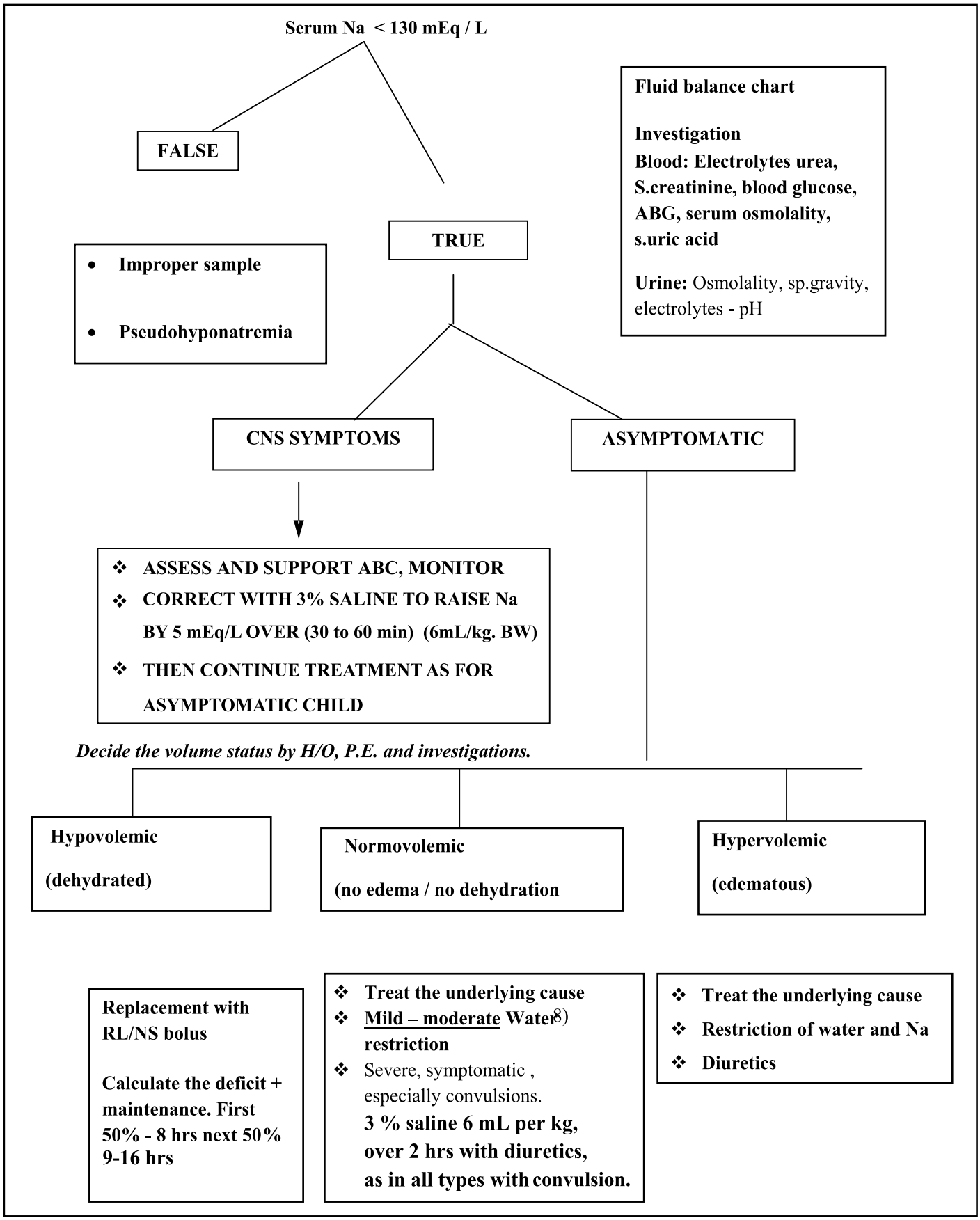

Fig.1. Hyponatremia-Management

conditions such as stress, pain and anxiety. Treatment is restricting the fluid intake to 2/3 maintenance and type of fluid should be normal saline.

3. Hypervolemic hyponatremia: This category of hyponatremia occurs when hypervolemia (increased total body water, clinically manifested as edema) is associated with reduced effective circulating volume (ECV). Reduced ECV leads to ADH release causing water retention and fall in serum sodium. Conditions in this category are nephrotic syndrome, cirrhosis liver, cardiac failure and renal failure. Management is restriction of both water and sodium, as both are in excess. This includes restriction of salt and water less than that of urine output, diuretic therapy and management of the underlying disease such as dialysis in renal failure.

Hypernatremia

A sodium concentration > 145 mEql/L is defined as hypernatremia.[3] Hypernatremia is relatively less common than hyponatremia.[1]

Brief case scenario: A seven months old girl suffering from acute watery diarrhea for which she was given readymade ORS solution in a tetra pack. On the 4th day of illness, she developed sleepiness and refusal of feeds. Last voided urine 3 hours prior. Electrolytes done: Two hours ago, Sodium 175 mEq/L, Potassium 4.2 mEql/L, urea 65 mg/dL, Creatinine 0.5 mg/dL and CBG 90 mg/dL. There was no seizures on arrival to Emergency Room, she was pain responsive and irritable. Mildly dehydrated. No loss of skin turgor, no doughy feel of skin. Anterior fontannel normal, pupils reacting. HR 130/mt, pulses well felt; respiratory rate normal.

Initial assessment: CNS symptoms like drowsiness indicate i) Dehydration with hypo or hypernatremia ii) Other metabolic encephalopathy such as hypoglycemia and iii) CNS infection.

Causes of hypernatremia

There are two important defence mechanisms which maintain osmolality and serum sodium at optimum levels in a healthy state, thirst and vasopressin. Most vulnerable subjects are young infants who cannot express nor have free access to water and child with depressed level of consciousness.[7] Hypernatremia is caused by relative deficit of water in relation to body's sodium stores which can result from excessive electrolyte-free water loss as in Diabetes Insipidus (DI) and disproportionately more water loss than sodium as in diarrhea (more common) or sodium gain as in salt poisoning (rare).[8]

1) Hypotonic fluid loss: (disproportionately more water loss than electrolyte): (i) Diarrheal dehydration with predominant vomiting or reduced intake of water because of vomiting or lack of access to water (ii) Diarrhea in a child with obstructive uropathy and renal tubular dysfunction (iii) Common in infants, because of increased body surface area relative to body weight and renal immaturity.

2) Sodium excess: (i) Improperly mixed (concentrated) formula feeds or oral rehydration solution (ii) Excessive sodium bicarbonate usage during resuscitation (iii) Salt poisoning either intentional or unintentional where salt is substituted for sugar by mistake and iv) Mineralocorticoid excess like hyperaldosteronism.

3) Electrolyte free water loss: In diabetes insipidus, hypernatremia develops in the following situations: reduced access to water as in infants, retarded children or those with depressed level of consciousness or defective thirst mechanism.

Hypernatremia in neonates is a marker for reduced breast milk intake and lactation failure. It is associated with high sodium content in breast milk of some mothers.

Pathophysiology:[5] Alteration in intracellular tonicity and osmolality in the neuronal cells subsequent to increase in the sodium content in ECF leads to movement of water from ICF to ECF. This results in shrinking of cells referred to as cellular dehydration.[9] This leads to disturbances of consciousness and in extreme situations causes tearing of the blood vessels and intracranial bleed. Neurons have the inherent capacity to prevent cell shrinking. They produce osmotically active substances called "idiogenic osmoles". which are now identified as taurine and other aminoacids. This protective mechanism may take few hours to evolve as well as to resolve. That is why treatment guidelines prescribe gradual reduction or elevation of serum sodium at not more than 0.5 mEq/L per hour. Whereas if there is rapid reduction in serum sodium in the presence of undisposed idiogenic osmoles, it causes reversal of movement of water into the cells from ECF, leading to the development of cerebral edema during therapy. If it is done slowly or gradually as per the guidelines, this complication is avoided.

Clinical features[6]

- Predominant clinical presentation of hypernatremia is neurological symptoms such as lethargy, restlessness, high pitched cry, convulsions and loss of consciousness. This includes features of intracranial bleed. Signs of dehydration such as loss of skin turgor will be absent except in severe volume loss. This is because of

hypertonicity, which preserves ECF volume. The child may exhibit a doughy feel of skin.

- History should include the frequency of diarrhea, whether ORS was used, how diluted and how much given. Any history of polyuria, polydipsia or bed wetting? Was there any likelihood that salt was mistakenly substituted for sugar while preparing feed? What was the IV fluid used in the hospital for resuscitation?

Laboratory Investigations

- It is mandatory to check electrolyte, urea, creatinine, CBC, urine electrolytes, arterial blood gas analysis, etc, which will be able to identify the associated abnormalities like hypokalemia (hyperaldosteronism), hypocalcemia and hyperglycemia which are two common associated problems. Fractional excretion of sodium will be useful to differentiate salt poisoning from hypernatremic dehydration. It is elevated in salt poisoning and low in the latter.[3] Neuroimaging is done, only if warranted and will identify hemorrhage or any other cause for altered consciousness and seizures.

Management

Management is done in four phases.

1. Stabilizing the child: Control of seizures with benzodiazepines, oxygen, assessing the need for ventilatory support and cardiopulmonary monitoring.

2. Correction of shock if present: Correct the shock with normal saline 20 mL/kg irrespective of serum sodium level and repeat if needed. Only normal saline is used and ringer lactate should not be used because it is relatively hypotonic in the presence of hypernatremia.[3]

3. Hypernatremia correction: After the correction of shock, hypernatremia is managed by administration of one half normal saline at a rate of 25%–50% more than maintenance (which includes deficit correction + maintenance). This management is practiced in hypernatremia with dehydration (hypovolemic and isovolemic hypernatremia), but not applicable for hypernatremia with edema (salt excess leading to hypervolemic hypernatremia). Most important component of therapy is estimation of serum sodium 4-6 hrly and adjust the fluid rate or sodium concentration of IV fluid.

4. Treatment of the underlying illness: Identifying the underlying cause such as diabetes inspidus or salt poisoning and also associated problems like hypocalcemia or hyperglycemia.

Management of hypernatremia with dehydration (hypovolemic or normovolemic) (Fig.2) Having understood the background of loss of fluid and also sodium, (hypernatremia does not mean there is no sodium loss), we need to know the issues to be addressed.

Eg. One year child weighing 10 kg and serum sodium is 160 mEq/L. Moderately dehydrated (6%-10%).

Total fluid deficit = 10 x 100 = 1000 mL; Maintenance is 1000 mL; Total (deficit + maintenance) deficit is 2000 mL. This also includes electrolyte free water loss. Concept of free water deficit and sample fluid calculation are included in the annexure for further clarification (Annexure 1 and 2).

1. How much is the electrolyte free water deficit? There are two formulas available for estimation of free water.

Formula 1. Free water deficit = 4 x body wt. x sodium excess above140 mEq

= 4 x 10 x (160–140) = 800 mL needed.

Formula 2. Free water deficit in litres = Current total body water (TBW) (10 x 0.6 = 6) x [current plasma Na/ 140] - 1

6 (1.14-1.0) = 6 X 0.14 =0.84 L = 840 mL. Both the formula derive nearly the same value.

2. Duration of replacement of electrolyte free water deficit? Time to be taken for the correction based on initial serum Na level, because of rate of correction should not exceed 0.5 mEq/L per hour (Table IV). One must take care of this rate of correction to avoid rapid change in osmolality and resultant complications.[10]

Here the deficit should be replaced over 48 hrs, as 800 = 400 mL/day

Table IV. Time taken for correction based on serum sodium

Serum Na (mEq /L)	Time taken (hrs)
140–157	24
158–170	48
171–183	72
184–196	84

3. How to replace fluid after shock correction or when the child presents without shock? Total fluid

replacement include the maintenance fluid, isotonic (solute) fluid losses, and electrolyte free water loss.

4. A rule of thumb for practicing pediatrician:[3] Infusing 1/2 normal saline at the rate of 1.25 to 1.5 times maintenance (which includes isotonic deficit + free water def. + maintenance) over every 24 hrs for 48 hrs, with careful 4-6 hrly monitoring is the right treatment. Dextrose content and addition of potassium of this fluid depends on serum glucose and K. If serum glucose and potassium are normal, D5 ½ NS with potassium 20 mEq/L is the appropriate solution at the rate 60 mL/hr (i.e 1.5 times the rate of maintenance). In fact most of the calculations in electrolyte disturbances including hypernatremia do not take into account the ongoing losses and other biochemical or endocrine interactions. All these calculations are useful for initial decision and further titration is mainly based on clinical and monitoring of serum sodium frequently i.e., every 4-8 hrs depending on the level of care.

5. How to monitor the rate of fall of serum sodium? Because of the above said reasons, frequent monitoring of serum sodium every 3–4 hrly and adjusting the type of fluid is the only way to fine tune the rate of fall, as per the following plan. (Table V).

- Half NS is available as commercially prepared solution
- D5 1/3 NS is commercially available. In case of non-availability this can be prepared by mixing 175 ml of D5 NS with 325 ml of D5 in a sterile manner.
- D5 1/4 NS can be prepared by mixing 125 ml of D5 NS with 375 ml of D5 in a sterile manner. It is also available as commercial preparation.
- If there is rapid fall in sodium > 0.5 mEq/L/hr increase the sodium concentration. Fluid is chosen in the ascending order: 1/4 Ns to1/3NS to ½ NS to RL.
- If the fall is < 0.5 mEq/L/hr decrease the sodium concentration. Fluid is chosen in the descending order.
- If the fall is appropriate i.e., 0.5 mEq/hr same fluid is continued.

Sodium content of various fluids

NS with 5% Dextrose (154 mEq/L)

RL and 5% Dextrose (130 mEq/L)

½ NS and 5% Dextrose (75 mEql/L)

1/3 NS And 5% Dextrose (50 mEq/L)

1/4 NS And 5% Dextrose (37 mEq/L)

6. Oral replacement of free water Once the child improves, i.e. on second or third day free water deficit also can be replaced as plain water orally or by nasogastric feeding in a young child in addition to maintenance IV fluid.

7. Management of hyperglycemia and hypocalcemia: Hyperglycemia does not require correction. Hyperglycemia will be a buffer in reducing the osmolality fluctuations happening when serum sodium level falls.[8] So either D 2.5% ½ NS or ½ NS can be used. Hypocalcemia has to be corrected by calcium infusion.[8]

8. If seizures occur during treatment of hypernatremia: It is usually due to rapid fall in sodium level, 3% Nacl is infused at the rate of 5 mL / kg over one hour. This will raise sodium by 5 mEq/L.

Management (hypervolemic) hypernatremia with edema due to salt excess:

Here both water and sodium are in excess. Hence child needs less volume of fluid and less sodium or hypotonic fluid. But in management of isovolemic or hypovolemic hypernatremia, more volume of fluid but less sodium is needed. Salt excess or salt poisoning leads to hypervolemic hypernatremia. So the plan is to give diuretics and then replace the volume by volume of urine by hypotonic fluid such as ¼ NS. If primary problem is treatable, treat the primary cause. Eg. Dialysis in renal failure.

- Monitor hydration, urine output, electrolytes, Glucose and calcium 6th hourly and modify the therapy.
- Correct hypocalcemia.
- Do not go for routine hyperglycemia correction unless it is persistent.
- Attempt to identify the cause.
- If there is renal failure or multiple electrolyte disturbances exists or refractory, decide on dialysis.
- Use vasopressin, if the cause is diabetes insipidus.

Table V. Serial monitoring of serum sodium and titration of the fluid[3]

Rapid fall > 0.5 mEq/hr	Optimum fall 0.5 mEq/hr	Slow fall <0.5 mEq/hr
• Increase Na concentration. From ½ NS to ¾ NS or RL	• Continue the same fluid at same rate	• Decrease Na concentration ½ NS to 1/3 to 1/4 NS

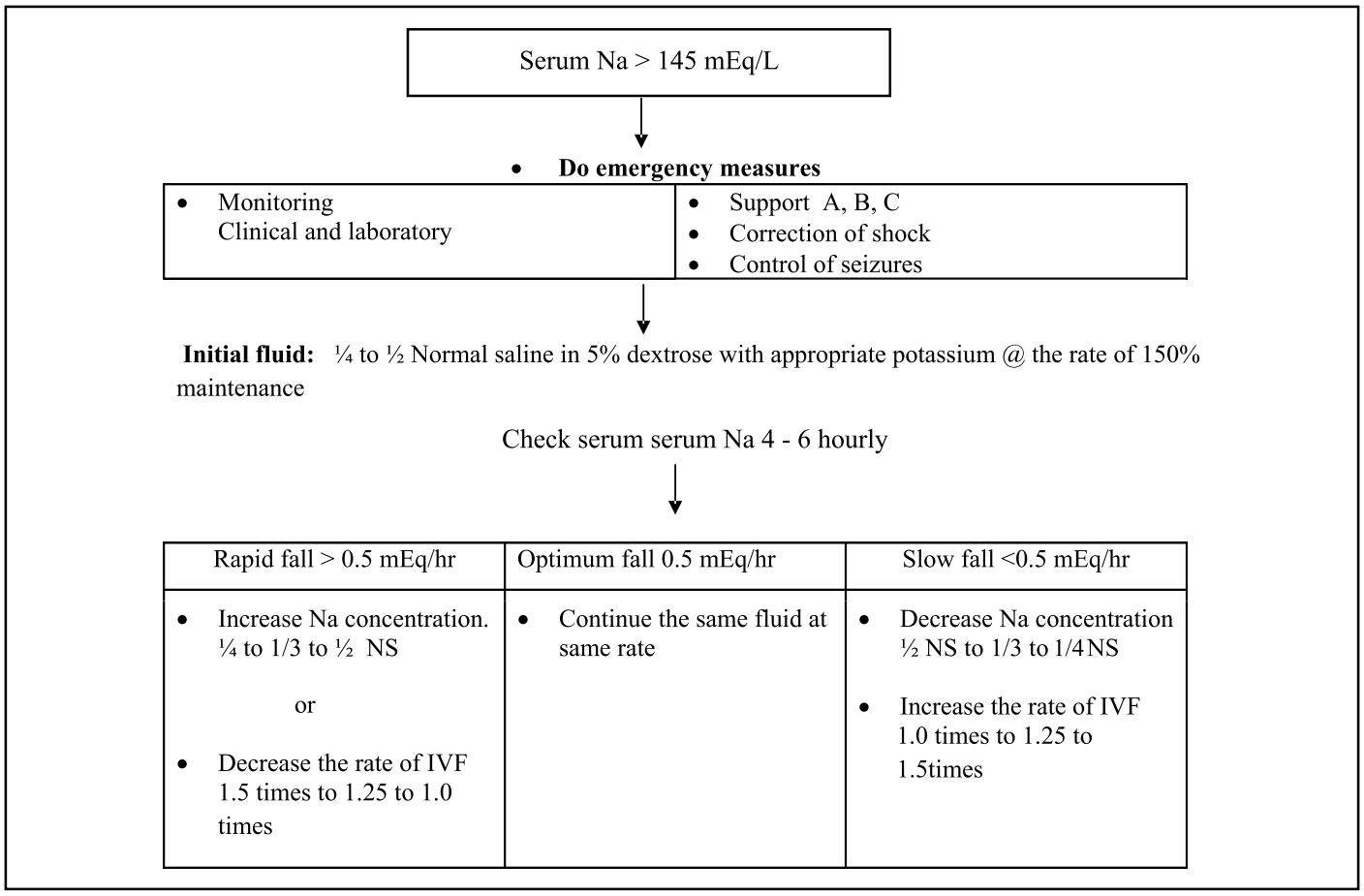

Fig.2. Hypernatremia-Management[3]

Potassium disturbances

It is surprising to know that only 1 % of the potassium content of the body stays in ECF but when there is some disturbance, that decides all the clinical features and risks.[11] The concentration of potassium in ICF is about 40 times higher than that in plasma. (150 mEq/L in ICF and 3.5-4.5 mEq/L in ECF). This gradient is maintained by sodium potassium ATPase pump, which pumps sodium out of cell and retains potassium inside. This gradient forms the basis for resting membrane potential which is the vital factor for cardiac rhythm, nerve conduction and muscle conduction. Hence potassium represents biological electricity. Both hypo and hyperkalemia are associated with lethal complications. Unlike sodium disturbances, potassium disturbances affect both vital functions like cardiac rhythm and neuromuscular function.[12] Hypokalemia is the most common and life threatening abnormality noted in sick children. Hyper-kalemia occurs commonly in renal disorders where as hypokalemia is equally common in non-renal disorders too.

Hypokalemia

Normal serum level is 3.5 to 4.5 mEq/L and a level < 3.5 is defined as hypokalemia.

Causes of hypokalemia

1. *Reduced intake:* This is a rare cause of hypokalemia and is often iatrogenic, when a child is receiving potassium free IV fluid for a few days without any oral intake or in the presence of malnutrition.[13]
2. *Transcellular shifts:* Following are the clinical conditions where intracellular shift of potassium leads to hypokalemia. Usually they are not associated with acid-base disturbances.
   a) Insulin therapy during management of DKA.
   b) Use of β2 agonists such as salbutamol and terbutaline in the management of asthma.
   c) When bicarbonate is used in the correction of metabolic acidosis.
   d) Familial hypokalemic periodic paralysis.
   e) In rodenticide poisoning, barium salt present in the insecticide prevents normal efflux of potassium from to cell to ECF leading to hypokalemia.
3. *Loss of potassium*

a) *Gastrointestinal loss:* Vomiting, diarrhea and laxative

abuse lead to hypokalemia. Pyloric stenosis is associated with metabolic alkalosis and hypokalemia

b) *Renal loss*

- Metabolic acidosis coexists with hypokalemia in proximal and distal renal tubular acidosis as well as in diarrheal disorders.
- Metabolic alkalosis: Three groups of hypokalemia occur in metabolic alkalosis. (i). Polyuria and dehydration is observed in Bartter's syndrome, Gitelman syndrome and in diuretic therapy. (ii). Hypokalemia and hypertension in renal artery stenosis, hyperaldosteronism and (iii). Hypomagnesemia is a prominent feature in Gitelman and in Liddle's syndrome it is associated with hypertension.
- Diuretic therapy

Case scenario: A one year old child developed diarrhea in the form of watery stools passed more than 10 times. When he was brought to emergency room, he was moderately dehydrated, lethargic and also had head lag and hypotonia of limbs. Deep tendon jerks were sluggish. Heart rate was 120/min and regular. Hypokalemia was suspected and his serum potassium level was 2.8 mEq/L. ECG was normal.

Clinical features

Clinical features of hypokalemia are due to lower or more negative influence on resting membrane potential (RMP) across cell membrane. Thus symptoms and signs involve abnormal function of heart, skeletal muscle, gastrointestinal tract and renal system.[12]

1. In mild hypokalemia symptoms are non-specific such as fatigue and myalgia.
2. Severe hypokalemia manifests with weakness of skeletal and smooth muscle function. Neuromuscular features include hypotonia, proximal muscle weakness, lower limb weakness than upper limbs, causing head lag and frog leg posturing, rarely respiratory paralysis. Cranial musculature is usually spared. Rhabdomyolysis, myoglobinuria, ascending paralysis also occur in severe hypokalemia.
3. Gastrointestinal manifestation is abdominal distension due to paralytic ileus and phantom hernia.
4. Severe life threatening hypokalemia leads to bradycardia and cardiac arrhythmia. Increased incidence of arrhythmia is observed in the presence of underlying heart disease. Hypokalemia also increases the potential for digoxin toxicity.[12] Common ECG changes are prolonged PR interval, reduction in T wave amplitude or flattening or inversion, ST depression and appearance of U waves. In general, there is poor correlation between serum level of potassium and ECG changes.[12]
5. Persistent hypokalemia also leads to reduced concentrating ability in the kidney and persistent alkalosis by causing increased excretion of chloride. However on most occasions diagnosis is made by the laboratory report when child presents with systemic illness that is likely to cause hypokalemia.

Evaluation of underlying etiology

Decision can be made in pediatric clinic without renal investigations, by asking three questions.

1. Any predisposing conditions? Diarrhea and oliguria indicating gastrointestinal loss or polyuria indicating renal diseases or other polyuric states leading to renal loss.

Table VI. Laboratory approach to the cause of hypokalemia

Lab abnormality	Diagnosis
• Metabolic acidosis with hypokalemia	GI loss-diarrhea Renal-RTA
• Urine anion gap > 20 mEq	favours distal RTA
• Metabolic alkalosis and urine Cl < 20 mEq/L	GI loss-vomiting
• Metabolic alkalosis and urine Cl > 20 mEq/L	Renal loss-Bartter's syndrome

2. Any predisposing clinical situation or drugs? Insulin therapy in DKA, salbutamol or terbutalin in asthma (transcellular shift), diuretic therapy (urinary loss), amphotericin B is likely to cause hypokalemia (Table VII).
3. Any acid base disturbances? (Table VI)
4. Check blood pressure, if BP is low and child is in shock or dehydration, loss through gastrointestinal or renal route is likely. High BP in the background of hypokalemia indicates hyperaldosteronism

Further work up with nephrology assistance: Additional investigations such as serum sodium, chloride, bicarbonate, calcium, magnesium, creatinine, glucose and blood gases are essential. Urine potassium, urine chloride will be useful to narrow down the etiology further (Table VI). In diarrhea urine potassium will be <20 mEq/L and > 20 mEq/L in renal losses such as RTA. Estimation of renin and aldosterone levels will be helpful in recognizing the endocrine causes such as hyperaldosteronism particularly when hypertension is present. Hypomagnesemia is a common problem seen in association with hypokalemia and hypokalemia cannot be corrected fully without correcting magnesium deficit.[11]

Management

Hypokalemia never occurs alone and is always part of a systemic illness. Initial management includes stabilization of airway, breathing as they may present with respiratory failure or shock. Specific management and correction of potassium deficit depends on the severity of deficit and presence of cardiac symptoms. In practice, there are three clinical situations seen in hypokalemia based on serum level.

Situation 1 (Severe hypokalemia): Serum level <2.5mEql/L or presence of paralysis or cardiac arrhythmia or ECG changes Urgent correction is needed using intravenous potassium. Rapid correction is done only in a PICU environment, infusing potassium in the dose of 0.3-0.5 mEq/L/kg over a period of 2-3 hours under cardio respiratory monitoring. Potassium is diluted in normal saline as dextrose solution will further drop the potassium level because of transcellular shift. Ideally a concentration more than 40 mEq/L, should be given through central vein. Hyperkalemia can occur, following therapy and hence monitoring should be done frequently.

Situation 2 (Moderate hypokalemia): Serum level is more than 2.5 and less than 3.0 mEq/L, no cardiac arrhythmia or bradycardia or paralysis Correction can be done less aggressively. On most occasions as these children are sick and may not tolerate oral replacement, intravenous maintenance fluid potassium should be raised to 40 mEq/L. Serum potassium can be repeated after 8-12 hrs. Adding 5 mL of potassium chloride in 500 mL of maintenance fluid (D5 ½ NS) will make the concentration 20 mEq/L and addition of 10 mL will make a concentration of 40 mEq/L. Serum level should be checked every 12 hrs and replacement should be titrated.

Situation 3: (Mild hypokalemia) Serum level is > 3.0-<3.5 mEq/L, no cardiac arrhythmia or bradycardia or paralysis When oral intake is possible, correction can be done less aggressively with oral potassium chloride solution or dietary supplements such as orange juice or coconut water. If dietary supplements fail to correct hypokalemia, oral potassium chloride solution should be used. Standard oral potassium chloride solution 15 mL will give 20 mEq. Potassium citrate solution is used when acidosis is associated with hypokalemia.

If possible, offending drug should be stopped if the primary illness permits. Management of the primary disease such as control of diarrhea, treatment strategy for RTA or Bartter's syndrome should be employed. Once the serum level is raised to > 3.0, and the child can retain oral intake, oral potassium supplements can be started.

General rules to be followed in the potassium replacement therapy:

- Oral replacement is always superior in the absence of paralysis or arrhythmia and the child is ready to take oral preparation.
- Intravenous potassium chloride should never be infused as bolus or undiluted. It should be used as infusion with clear prescription by physician mentioning the concentration of solution, volume, dilution and duration.
- Extra potassium chloride should not be added to premixed potassium containing solutions. It should not be mixed with half emptied bottle with rough estimation of the volume of the fluid. It should be always mixed in a full 500 mL bottle.
- Hyperkalemia can follow IV replacement particularly in higher doses; hence frequent estimation of serum level (6-8 hrly or immediately after higher doses) is needed. Diluting fluid should be normal saline as dextrose will stimulate insulin secretion and worsen hypokalemia.
- Correction of hypocalcemia or hyperglycemia or metabolic acidosis can worsen hypokalemia. If possible correction of these should be postponed till safer level

of 3 mEq/L is reached or simultaneously both issues are addressed till serum levels are raised to safe limits.[13]

- In refractory hypokalemia anticipate and correct hypomagnesemia or alkalosis.
- Potassium replacement up to a concentration of 40 mEq/L can be administered through peripheral vein. Beyond a concentration of 40 mEq/L, it should be given through central venous access.[15]
- When KCl stock solution is added to the intravenous fluid for infusion, bottle or bag should be inverted at least 10 times to ensure that it is thoroughly mixed and or to avoid unequal distribution leading to iatrogenic complications.[15] Adding KCl should be done only by an experienced nurse or doctor who is familiar with the risks associated. This drug should be properly kept in a separate container where scheduled drugs are stored.

Table VII. Mechanism of hypokalemia caused by drugs

Drug	Mechanism causing hypokalemia
Diuretics, amphotericin B	Increased renal loss of potassium
Insulin therapy in DKA, Beta 2 agonists	Transcellular potassium loss
Chronic use of purgatives	Increased stool loss

Hyperkalemia

Potassium plays a major role in the regulation of biological electrical activity and creation of resting membrane potential. Hence hyperkalemia can cause life threatening arrhythmia and is less well tolerated than hypokalemia[12] Serum potassium level more than 5.5-6.0 mEq/L is considered as hyperkalemia.

Case Scenario: A five years old child with chronic kidney disease has presented with fever, fast breathing and one episode of seizures. His BP is 160/100mm of Hg. He is already on antihypertensive medications. He had posterior urethral valve with obstructive uropathy, was operated and is being followed by pediatric nephrologist and urologist. He has effortless tachypnea, no edema and is drowsy. Serum electrolytes Na 132 mEq/L, K 6.7 mEq/L, HCO_3 10 mEq/L. Urea 130 mg/dL, creatinine 3.0 mg/dL. ABG shows uncompensated metabolic acidosis. Complete blood count showed Hb 6.0 gm/dL, lecocytosis and neutrophilia. In this case scenario, the diagnosis is obvious: chronic renal failure with hyperkalemia.

Causes: Cause of hyperkalemia is often multifactorial contributed by renal failure and some medications. In the absence of known predisposing conditions, clinical or ECG changes with normal renal function, consider the possibility of spurious hyperkalemia strongly. During clot formation, potassium is released into the serum after sample collection. This phenomenon is exaggerated in the presence of leucocytosis and thrombocytosis. Hence high potassium will be seen in the serum sample and not in the patient. Estimation of potassium in plasma sample will be normal[12] (Table VIII).

Table VIII. Causes of hyperkalemia

1. Spurious hyperkalemia: Prolonged tourniquet application, squeezing the limb, leucocytosis, thrombocytosis.
2. True hyperkalemia
   a) Accidental iatrogenic hyperkalemia. Change IV fluid to potassium free fluid to give the benefit of doubt
   b) Increased release of potassium: E.g. Acute hemolysis, trauma to muscle and rhabdomyolysis, tumor lysis syndrome
   c) Transcellular shift from ICF to ECF: Acidosis, familial hyperkalemic periodic paralysis (AD), non-oliguric hyperkalemia of prematurity
   d) Decreased excretion: Acute or chronic renal failure, primary hypoaldosteronism, secondary hypoaldosteronism, pseudo hypoaldosteronism and congenital adrenal hyperplasia
   e) Drugs: Potassium sparing diuretics, ACE inhibitors, NSAID, use of trimethoprim and pentamidine contribute to hyperkalemia in patients with HIV infection and pneumocystis jiroveci

Clinical features

In general, presenting features are usually non-specific and will be that of the underlying illness such as renal failure. History of underlying drug intake should be elicited. As the resting membrane potential depends on the gradient between ICF and ECF prolonged depolarization occurs in the presence of hyperkalemia. This leads to flaccid paralysis, respiratory failure and cardiotoxicity and final event will be ventricular fibrillation and asystole. Early ECG changes are tall, peaked T wave i.e., T wave height is more than half the size of preceding Q wave, prolonged PR interval, loss

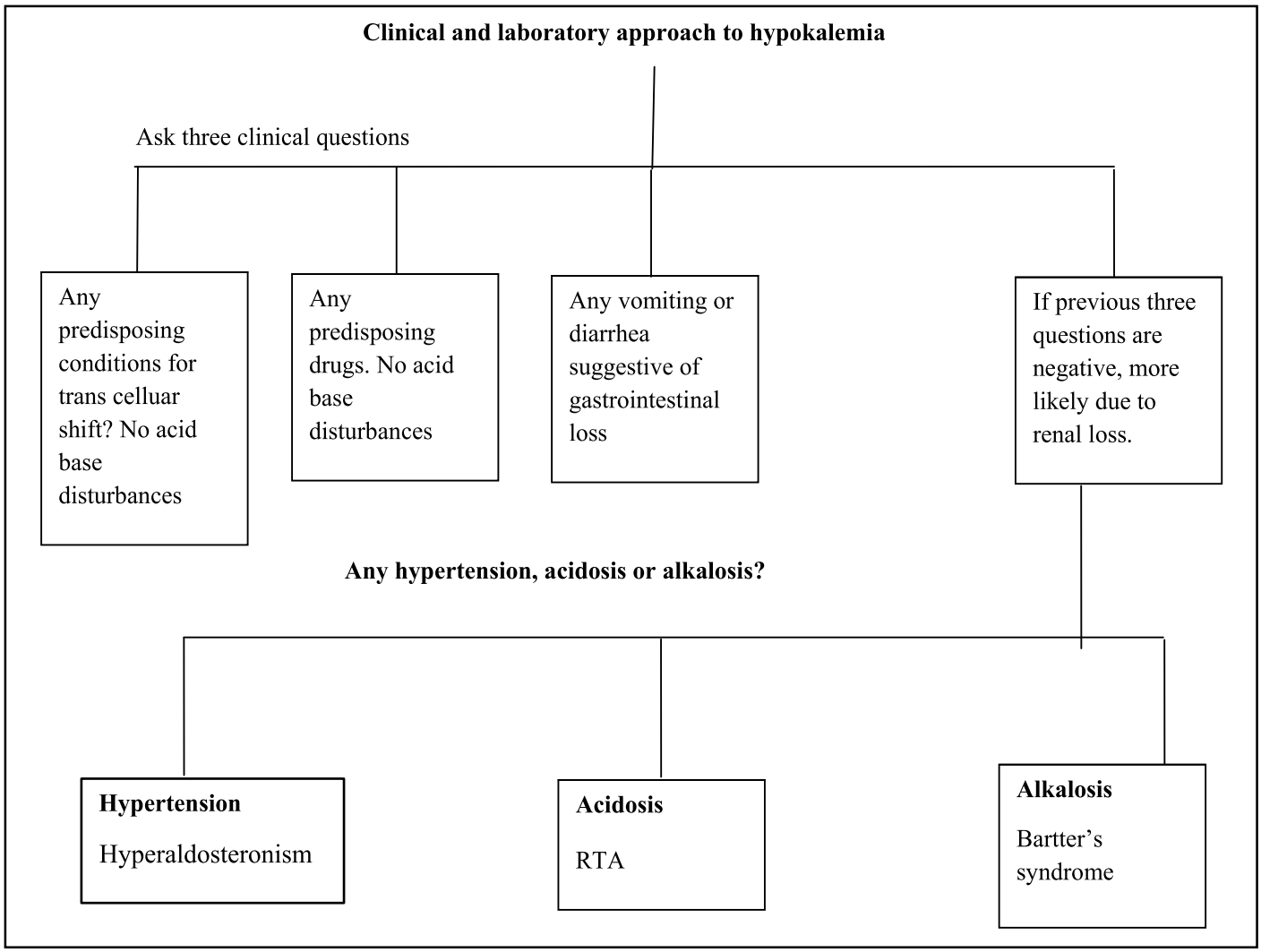

Fig.3. Hypokalemia clinical and laboratory approach

Table IX. Time schedule of drugs used in the management hyperkalemia[12]

Drug/Intervention	Time onset	Duration of action	Caution and comments
• IV calcium gluconate	1–3 min	30–60 minutes	Given as infusion over10–20 min Monitor HR
• IV sodium bicarbonate 7.5%	20–30 min	2 hrs	Flush the line with saline between these infusions
• Insulin and glucose	20–30 min	2–4 hrs	Monitor capillary blood glucose
• Nebulized salbutamol	30 min	4–6 hrs	
• Na/K exchange resins	4 hrs	6–8 hrs	Oral or rectal

of P wave, prolonged QRS ending with sine wave pattern. Brisk rise of potassium, digitalis toxicity, renal failure, hyponatremia are considered as risk factors for hyperkalemia.

Differential diagnosis

In asymptomatic children, causes of spurious hyperkalemia should be sought and excluded. Renal function

test will lead to diagnosis of cause. In neonates and in young infants a possibility of CAH is considered.

Management

If the serum potassium level is > 6.0 mEq/L or between 5.5-6.0 mEq/L with risk factors like renal failure, following treatment is started when there are predisposing factors. This is a medical emergency; hence treatment should not be delayed for investigation or to exclude spurious causes. Management of hyperkalemia has three components (i) Stabilizing membrane and managing cardiotoxicity (ii) Promoting shift of potassium ECF to ICF (iii) Elimination of potassium from the body[12] (Table IX).

1) **Intravenous calcium gluconate** 0.5-1.0 mL/kg of 10% solution, diluted with equal quantity of 5% dextrose and given as a slow IV for over 10 min. Monitoring with ECG or manually checking the heart rate is essential. If the child develops bradycardia, calcium. injection is stopped. Calcium therapy will not alter the serum 'K' level, but protects myocardium from the toxic effects of hyperkalemia and its action is immediate. This can be repeated in 5-10 minutes if ECG changes persist.
2) **Intravenous sodium bicarbonate** (7.5%) 1-2 mL/kg IV, over 10 min diluted with equal volume of 5% dextrose. Between the calcium and bicarbonate infusions, flush the IV line with normal saline to avoid precipitation. Both should never be mixed in syringe or in infusion
3) **Nebulised salbutamol** is given in the usual dose as for asthma. This can be repeated hourly. Salbutamol respiratory solution 1.25 mg for less than 1 year, 2.5 mg between 1-5 years, 5 mg above 5 years.
4) **Insulin and dextrose** The combination of insulin and glucose works within 30 min. Add 6 units of short acting insulin (Actrapid) to 100 mL of 25% dextrose. Infuse this in the dose of 2mL/kg as a slow IV for over one hour. Monitor blood glucose every 15 min while the insulin glucose infusion is given.
5) **Frusemide** is given at the dose of 1-2 mg/kg IV if renal function is normal and perfusion is adequate.
6) **Kayexalate** (potassium exchange resin) can be given in the dose of 1gm/kg/dose orally or rectally. About 1-2 mmol/kg can be reduced by this intervention. This can be repeated 6-12 hourly. Kayexalate is very useful, but expensive.
7) **Dialysis** if all these measures fail or potassium is rapidly raising or it is caused by renal failure.

Only the last three measures (5) (6) and (7) facilitate excretion of potassium.

8) If hyperkalemia is part of adrenal insufficiency, hydrocortizone 10mg/kg/IV should be started.
9) When serum 'K' level is between 5.5 and 6.0 mEq/L it is better to treat the cause and just discontinue the administration of potassium containing solutions (even the pediatric maintenance solution) and potassium free IV fluids are started. Drugs containing potassium or those leading on to hyperkalemia should be discontinued. One should continue to monitor ECG and serum potassium levels and act accordingly.

Points to Remember

- ***It is mandatory to check serum electrolytes in hospitalized children, particularly those on intravenous fluid therapy.***
- ***Hospital acquired hyponatremia is being increasingly reported and hypotonic intravenous fluid is to be avoided in maintenance therapy.***
- ***Though concept on hypernatremia management appears complex, management guidelines for hypernatremia are simple by using half normal saline at 1.25-1.5 times maintenance, with frequent monitoring of serum sodium level.***
- ***Potassium as a drug has to be handled with caution and practised as per the guidelines and by experienced medical or paramedical personnel.***
- ***Hyperkalemia is a medical emergency and should be managed stepwise, simultaneously evaluating for the underlying cause.***
- ***Every pediatric practitioner managing hospitalised children should update their knowledge on fluid electrolyte therapy, because IV fluid is the commonest drug used in hospital.***

Acknowledgment

Dr. Niranjan Vijayakumar for drawing the figure.4.

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ANNEXURE I

Concept of electrolyte free water deficit and its impact on hypernatremic dehydration

Water loss occurs from the body in two forms 1. Water mixed with solute. 2. Electrolyte or solute free water. Loss of this free water either evaporative or renal loss will change the serum osmolality and leads to water shift. This is equivalent of boiling off water from the soup, making it thicker and salty. This is similar to hypernatremic dehydration secondary to free water loss. (Refer Fig.1) calculation of the water deficit is already decreased in the management of hypernatremia.

One liter of various fluids	Sodium content	Free water content in one Litre	Free water content in 100 mL
Normal Saline	(154 mEq/L)	No electrolyte free water	Nil
Ringer Lactate	(130 mEq/L)	160 mL	16 ml
1/2 Normal Saline	(75 mEq/L)	500 mL	50mL
1/3 Normal Saline	(50 mEq/L)	670 mL	67mL
1/4 Normal Saline	(37 mEq/L)	750 mL	75mL
5 % Dextrose	Nil	1000 mLl	100 mL

ANNEXURE II

Sample calculation of fluid replacement in hypernatremic dehydration

Refer Fig 1.

Fluid replacement in isonatremic dehydration is straight forward, as the fluid loss is uniform as isotonic fluid loss. But in hypernatremic dehydration there are two types of fluid losses ie isotonic and electrolyte free water.

Eg. One year old child weighing 10 kg and serum sodium is 160 mEq/L. Moderately dehydrated (10%)

- Total fluid replacement in hypernatremic dehydration = Deficit correction (Isotonic fluid deficit +Electrolyte free water deficit) + maintenance fluid.
- Total fluid deficit = wt x % of dehydration = 10 x 100 = 1000 mL.
- Electrolyte free water deficit = 4 x Sodium excess (160-140=20) x Body wt 10 kg = 800 ml.
- Solute fluid deficit (Isotonic deficit) = 1000-800=200 mL.
- Total fluid replacement in hypernatremic dehydration = Deficit correction (Isotonic or solute fluid deficit + Electrolyte free water deficit) + maintenance fluid.
- = 200 ml + (Electrolyte free water def /2 days i.e 800/2=400 mL) + 1000 mL = 1600 mL.
- Free water deficit is to be replaced over 48 hours.
- Sodium deficit = Isotonic deficit 28 mEq/L in 200 mL (14 mmol in 100 mL) + FW deficit no sodium in 400 mL fluid + maintenance 40 mEq/L in 1000 ml fluid.
- = Sodium (28+0+40=68 mEq/L) in (200+400+1000=1600 mL fluid). (This is equivalent to ¼ NS - 40 mEq/L)
- So replacement fluid is 1600 mL containing 68 mEq/L; among this free water deficit should be 400 ml.
- Ideally this fluid is equivalent to one third to one half NS containing approximately 50-75 m.Eq/L of sodium.

What are the options available to replace this fluid?

Hence to deliver 1600 ml fluid including 400 ml free water and 68 mEq/L of sodium in the first 24 hours.

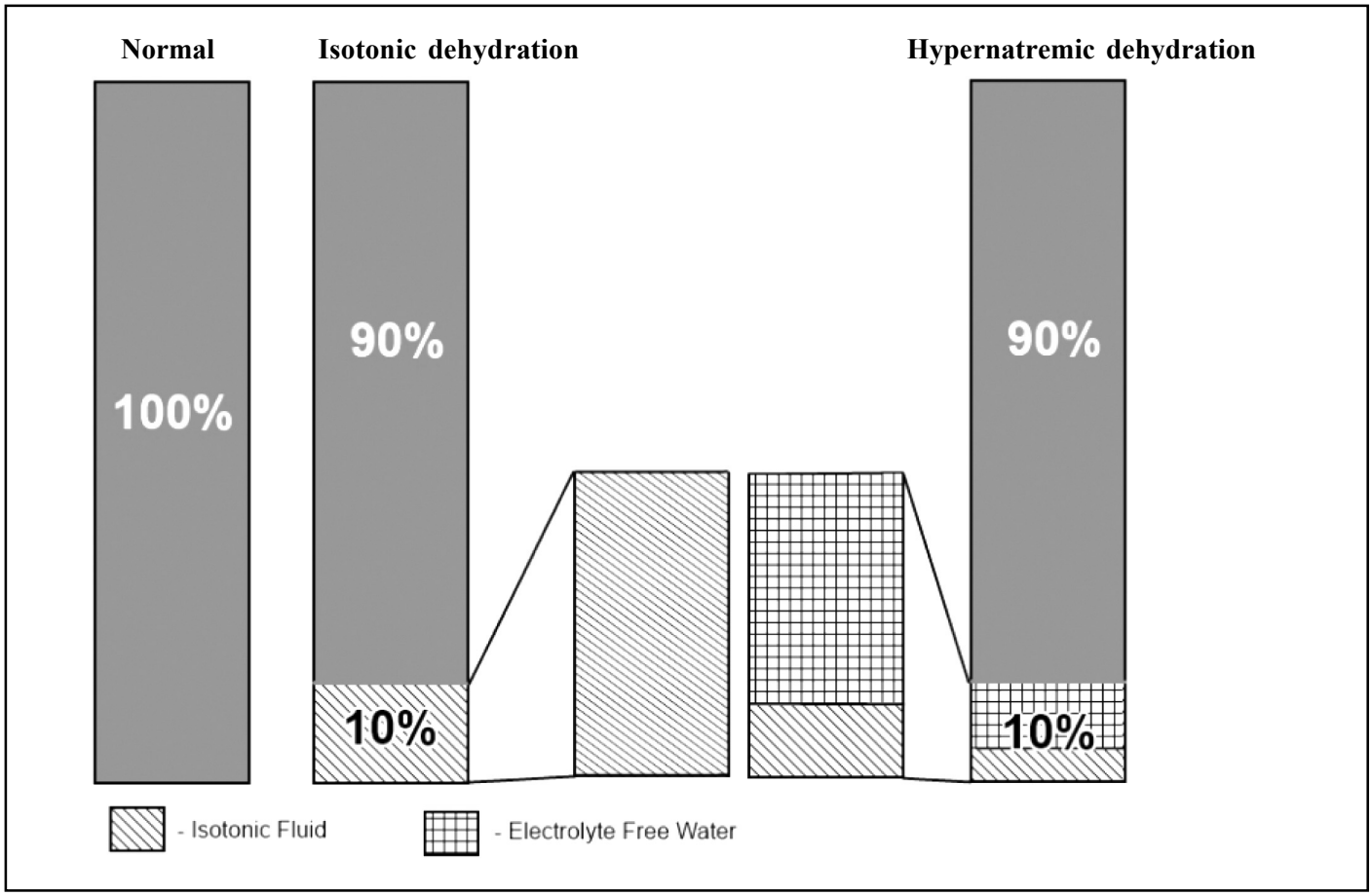

Fig.4. Type of fluid loss in hypernatremic dehydration

Option 1

Fluid	Volume	Sodium in the fluid in mEq/L	Free water
1/2 NS	800 mL	60	400 mL
NS	800 mL	120	No free water

As sodium supplied is high (180 m.Eq in 1600 m) this is not ideal. Other options follow

Option	Fluid used	Free water delivered	Sodium delivered
Option 2.	1500 mL of ¼ NS over 24 hours (ie 150% of maintenance rate)	1125 mL	60
Option 3.	1500 mL of 1/3 NS over 24 hours (ie 150% of maintenance rate)	1000 mL	75
Option 4.	1500 mL of 1/2 NS over 24 hours (ie 150% of maintenance rate)	750 mL	112

So initial fluid of choice is any one of the above fluids option 2, 3 or 4 after correction of shock. Most commonly practiced is option 4. i.e using ½ NS in 150 % maintenance (which includes isotonic deficit + Free water deficit + maintenance fluid).

Serial monitoring: All these formulas are for initial calculation and further titration of fluids is calculated by serial monitoring of sodium level.

CRITICAL CARE - II

METABOLIC ACIDOSIS IN PICU

Indira Jayakumar

Abstract: *Disorders of acid–base equilibrium are common in critically ill and injured patients. The presence of these disorders often signals severe underlying pathophysiology and particularly metabolic acidosis, is a significant marker of adverse outcome. Metabolic acidosis is a clinical disturbance characterized by an increase in plasma acidity. Accumulating evidence suggests that a significant proportion of these disturbances in pediatric intensive care unit (PICU) patients can result from therapy too. So, it is essential that clinicians understand why they occur and how to avoid them.*

Keywords: *Acid base disorder, Metabolic acidosis, Anion gap, Delta gap.*

Acid–base homeostasis in body

In body fluids, the concentration of hydrogen ions ($[H^+]$) is maintained within very narrow limits, with the normal physiologic concentration being 40 nEq/L. The concentration of HCO_3^- (24 mEq/L) is 600,000 times that of $[H^+]$. The tight regulation of $[H^+]$ at this low concentration is crucial for normal cellular activities because H^+ at higher concentrations can bind strongly to negatively charged proteins, including enzymes and impair their function.

Buffers: Buffers work as first-line of defence. Intracellular buffer system are comprised of phosphates and proteins, extracellular buffer system are comprised of hemoglobin and bicarbonate. Carbonates in bone and hemoglobin may be more important in chronic metabolic acidosis, when the extracellular HCO_3^- level is low.

Alveolar ventilation (Respiratory compensation): Medullary chemoreceptors compensate for metabolic acidosis through increases in alveolar ventilation. The resulting tachypnea and hyperpnea (alveolar hyperventilation) reduce the $PaCO_2$ in an attempt to increase the pH back towards normal. Those in metabolic acidosis may exhibit deep, rapid breathing called 'Kussmaul respirations'. Over compensation via respiratory alkalosis to form an alkalemia does not occur.

Renal acid handling: To maintain normal pH, the kidneys perform two physiologic functions. Reabsorbing all the filtered HCO_3^- (proximal tubule) and excreting the daily H^+ load (collecting duct). Phosphate, ammonia, uric acid and creatinine are important renal buffers.[1]

Pathophysiology of metabolic acidosis

A fall in pH is termed acidemia and the underlying disorders that lead to acidemia is acidosis. A primary metabolic acidosis is a pathophysiologic state characterized by an arterial pH of less than 7.35 (acidemia) in the absence of an elevated $PaCO_2$. It is created by one of 3 mechanisms, a) increased production of acids, b) decreased excretion of acids or c) loss of alkali.

$PaCO_2$ falls by 1 mm Hg for every 1 mEq/L fall in serum HCO_3^- concentration (a compensatory response that can occur fairly quickly). Compensation is always on the same side as the primary variable. If the change in $PaCO_2$ is not within this range, then a mixed acid-base disturbance is present. For example, if the $PaCO_2$ is higher than the expected fall, a primary respiratory acidosis is also present. The development of normocapnia or hypercapnia when a severe metabolic acidosis is present often signals respiratory muscle fatigue, impending respiratory failure and the possible need for initiating mechanical ventilation. Rarely, metabolic acidosis can be part of a mixed or complex acid–base disturbance in which two or more separate metabolic or respiratory derangements occur together. In these instances, pH may not be reduced or the HCO_3^- concentration may not be low.

The traditional Henderson-Hasselbalch theory: This states that there exists an equilibrium as given in the formula $[H^+] = 24 \times PaCO_2/[HCO_3^-]$. A change in either HCO_3^- or $PaCO_2$ changes the other variable in the same direction (compensation) in an attempt to maintain near-normal pH but within certain limits. However, this theory is inadequate to establish the underlying mechanism of acid-

* ER and PICU Consultant, Apollo Children's Hsopital, Chennai.

base disturbances in the body and emphasizes simple data interpretation rather than pathophysiology. Limitations of this approach is that it does not give information about any acid other than carbonic acid. Though it does show the change that occurs in $PaCO_2$ and HCO_3 it does not necessarily state that they are the cause of the underlying acid base abnormality, and the role of plasma proteins, specifically albumin, in acid-base balance is neglected.

The modern Stewart approach: The modern physical-chemical approach introduced in 1980 by Peter Stewart gives better insight to acid–base balance and has significantly enhanced our understanding of these problems and simplified clinical application. It states that there are only 3 independent variables controlling H^+ concentration and that changes in HCO_3 and $PaCO_2$ are the consequence of these in an attempt to maintain pH in the normal range most of the times. $PaCO_{2-}$ considered as a cause as well as consequence.

SID-Strong Ion Difference (Strong cations - Strong anions) (Na+K+Ca+ Mg) - (Cl+lactate), normal value is 40 mmol/L (Na:sodium, K:potassium, Mg:magnesium, Cl: chloride) Narrowing of SID causes acidosis and widening of SID alkalosis.

Total acid (Atot) - weak acids (albumin, phosphate) Albumin and phosphate act as weak acids, the latter contributing to acidosis in renal failure. Hypoproteinemia causes a base excess.

Metabolic alkalosis seen with severe emesis or nasogastric losses is because of chloride loss, widening of SID and replacement with saline, not bicarbonate, corrects the abnormality. Metabolic acidosis occurring with large volume saline administration is because of excess chloride administration and narrowing of SID. When large volumes of saline are administered it has a proportionally greater effect on total body chloride than on sodium.

Low albumin: In hypoalbuminemia, as is commonly seen in critically ill patients a correction factor of 3 must be multiplied to every 1g/dL reduction of albumin below 4 g/dL and this sum added to anion gap (AG) to get the true anion gap. Eg, albumin-1.6 and anion gap-12, the corrected (True) AG=(4 - 1.6) 3 + AG = 7.2 +12= 19.2. When the anion gap is not corrected in hypoalbuminemic patients, as much as 50% of abnormally elevated anion gaps could be missed.

Effects of metabolic acidosis[2]

Untreated, severe metabolic acidosis can lead to myocardial depression, seizures, shock and multiorgan failure. Outcome depends on etiology of shock that is the underlying disease which influences the survival, and also it has been shown that serum lactate levels greater than 8 mmol/L are associated with mortality rate of 80% more. The clinical manifestations of a metabolic acidosis are related to the degree of acidemia: they are mostly cardiovascular, as peripheral vasodilatation, reduced contractility and low cardiac output. As the serum pH continues to fall below 7.2, myocardial depression occurs because hydrogen ions act as a negative inotrope and cardiovascular response to endogenous and exogenous catecholamines can decrease as well. Acidosis can increase the incidence of arrhythmia and increased pulmonary vascular resistance, with increase in right ventricular after load and right ventricular dysfunction.

The other manifestations are reduced hepatic and renal blood flow, respiratory muscle fatigue, and metabolic changes like insulin resistance, inhibition of glycolysis with reduced ATP production and hyperkalemia. For every decrease in the serum pH by 0.1, a concomitant increase in the serum potassium level by 0.5 mEq occurs.

Hematological consequences are right shift of Hb O_2 curve, decreasing hemoglobin's affinity for oxygen and thus promoting its release into body tissues. There will also be a decrease in clotting factor function, increased blood viscosity, increased cerebral blood flow and raised intracranial pressure and coma.

Etiology of metabolic acidosis[3]

Anion gap (AG)

Calculation of the AG is helpful in the differential diagnosis of metabolic acidosis. To achieve electrochemical balance, ionic elements in the extracellular fluid must equal a net charge of zero and therefore, the sum of negatively charged ions (anions) should equal the sum of positively charged ions (cations). Anions (measured) are chloride and bicarbonate. Unmeasured anions are phosphates, sulfates and proteins (eg, albumin). Cations (measured) are sodium, potassium, calcium and magnesium . Under typical conditions, unmeasured anions exceed unmeasured cations and this is referred to as the anion gap.

The equation is derived is as given below:

(Chloride + Bicarbonate) + Unmeasured Anions = Sodium + Unmeasured Cations

Unmeasured Anions - Unmeasured Cations equals Sodium - (Chloride + Bicarbonate), which is nothing but the Anion Gap.

Hence Anion Gap is (Sodium) - (Chloride + Bicarbonate).

A metabolic acidosis is divided into processes that are associated with a normal anion gap (8-12 mEq/L) or an elevated anion gap (>12 mEq/L). A normal anion gap metabolic acidosis or non-anion gap acidosis involves no gain of unmeasured anions; however, because of the need for electrical neutrality, serum chloride replaces the depleted bicarbonate, and hyper chloremia develops. In contrast, an elevated anion gap metabolic acidosis is caused when extra unmeasured anions are added to the blood.

Non-Anion Gap Acidosis: Non-AG metabolic acidosis is characterized by hyperchloremia and is sometimes referred to as hyperchloremic acidosis. Some of the mechanisms that result in a non-AG metabolic acidosis are the following (Fig.1).

They are addition of Cl to body fluids (normal saline, TPN) or loss of HCO_3^- from the kidneys or GI tract (diarrhea, renal tubular acidosis). In renal failure (acute) hydrogen ions cannot be secreted. Early to moderate stages of kidney disease are associated with a normal AG (hyperchloremic acidosis) and advanced renal failure is associated with a high AG acidosis. In ureteroenterostomy, and use of carbonic anhydrase inhibitors can result in non AG acidosis.

High AG acidosis : Several mnemonics (none totally comprehensive) are used to help recall the differential diagnosis of high anion gap acidosis. One such is MUDPILES: M-methanol, U-uremia; D-DKA, Poisoning, I- IEM, iron, isoniazid, L-lactic acidosis, E-ethylene glycol, S-salicylates).

Classification of lactic acidosis by Cohen & Woods

There are two types of lactic acidosis as described by the basis of pathophysiology:

TYPE A

It occurs in hypoperfusion and hypoxia.

Tissue hypoxia is seen in carbon monoxide poisoning, severe asthma and severe anemia. Hypoperfusion occurs in state of shock (cardiogenic, hemorrhagic, septic, regional such as mesentric, and limb ischemia) and cardiac arrest.

TYPE B

It occurs when there is no clinical evidence of hypoperfusion. The latter is further subdivided into 3 subtypes:

B1: Acquired diseases: Diabetes mellitus, seizures, ARDS, septicemia, malignancies, pheochromocytoma, post cardiopulmonary bypass, renal failure, thiamine deficiency, thyroid storm (all causing increased production) hepatic failure, (decreased clearance) etc.

B2: Medications and toxins: Acetaminophen, epinephrine, isoniazid, lactulose, nitroprusside, antiretroviral therapy, terbutaline, theophyline etc.

B3: Inborn errors of metabolism

Point of interest is that laboratory assays estimate only L- lactic acidosis. D-lactic acidosis is rare and is caused by d-stereo isomer of lactic acid which is synthesized by pathological gut flora.

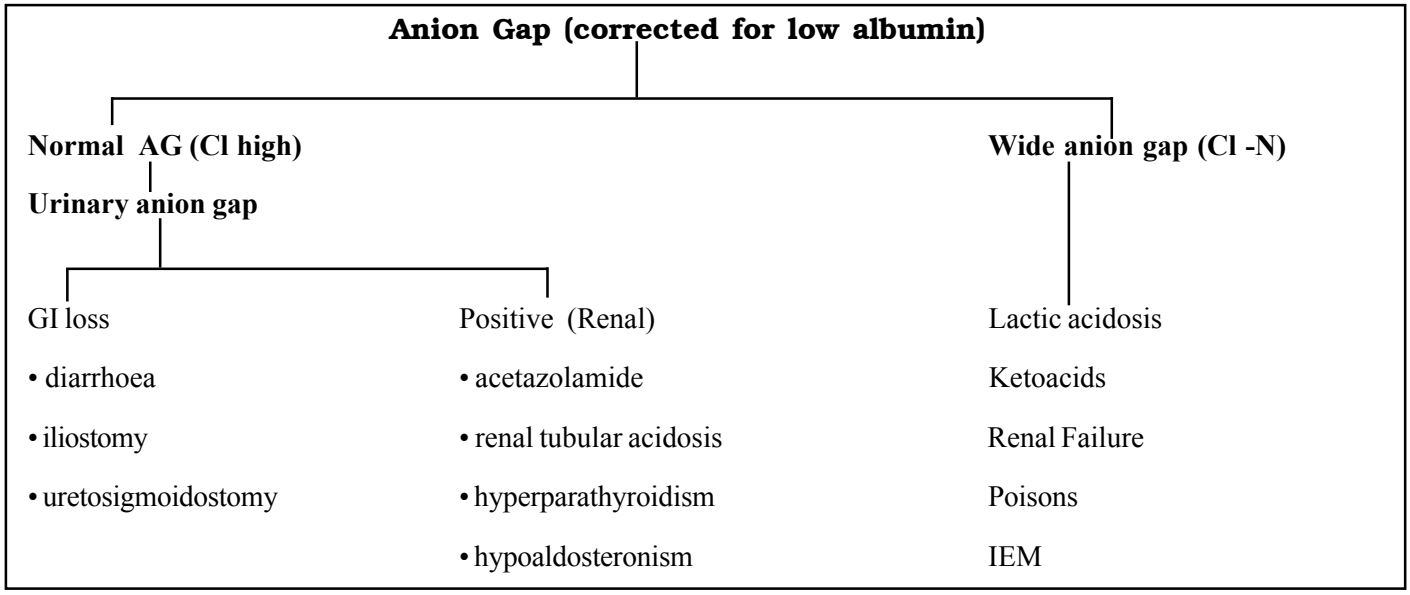

Fig.1. Metabolic acidosis[4,5]

Investigating metabolic acidosis

An arterial blood gas (ABG) measurement is a must for the diagnosis which would reveal the acidemia. A low serum HCO_3^- and a pH of less than 7.40 in ABG analysis confirm metabolic acidosis. However, a decreased serum [HCO_3^-] level can be observed as a compensatory response to respiratory alkalosis. A [HCO_3^-] level of less than 15 mEq/L, however, almost always is due (at least in part) to metabolic acidosis.

1) Also do serum electrolytes.
2) Calculate corrected anion gap (Na + K – Cl) (correct for hypo albuminemia)
3) Estimate serum Lactate (L -lactate)
4) Analyse delta gap - even if anion gap is increased check for coexisting disorders - Metabolic alkalosis or non anion gap acidosis. Delta ratio is Change in anion gap / Decrease in bicarbonate. Delta ratio of <1 strongly suggests a normal anion gap acidosis. Ratio of >2 suggests coexistent metabolic alkalosis.
5) Analyse osmolar gap: If anion gap is increased check for osmolar gap – difference between measured serum osmolality and calculated osmolality (Normal - 10) - seen high in methanol and ethylene glycol poisoning (rare in children).
6) Include renal and liver function tests
7) Urinalysis is mandatory

Urine pH obtained on a fresh sample >5.3 in the face of severe acidemia indicates distal renal tubular acidosis (RTA). Urine AG is urinary (Na + K) Cl^-. Urine anion gap is positive in RTA (reduced relative ammonia excretion) and negative in diarrhea (increased ammonia excretion along with chloride). Urine Ketones are present in diabetic ketoacidosis and inborn errors of metabolism. Urine transtubular potassium gradient (TTKG) is useful in determining the etiology of hyperkalemia or hypokalemia associated with metabolic acidosis.

A stepwise approach to interpretation of ABG is given in Fig.2. Other related investigations are ultrasound which may show nephrocalcinosis and CT abdomen which may show mesenteric ischemia.

Special tests are plasma renin/plasma aldosterone levels which are useful in determining the etiology of the hyperkalemia and hypokalemia that accompany metabolic acidosis.

Treatment of metabolic acidosis

Always treat the underlying cause.

Shock: Restore perfusion with fluid and ensure adequate tissue oxygenation / ventilation. Vasoactive agents (dopamine, noradrenaline) should be added only with/ after volume replacement as they can worsen the acidosis.

Sepsis: Early antibiotic treatment and source control (surgical debridement, central line removal , ischemic gut) will help.

Status asthmaticus (improving): High dose of β2 agonist should be tapered to reduce lactate levels.

Changing from normal saline to Ringer Lactate or balanced solutions to reduce chloride administration will help correct normal anion gap acidosis. Normal saline-contains Na- 154 mEq/l and Cl- 154mEq/L while Ringer Lactate contains Na-130 mEq/L and Cl-110 mEq/L. Septic shock patients receiving large volumes of saline can have both wide anion and normal anion gap acidosis .

Antidotes for toxins, drugs (paracetamol even in normal doses can be toxic in hepatic dysfunction).

Institute dialysis early in renal failure for persistent acidosis

Role for sodium bicarbonate: Alkali therapy is theoretically appealing but should be avoided in view of undesirable effects like hypernatremia, hyperosmolality (osmolality of sodium bicarbonate is 2,000 mOsm/L), volume overload, cardiac dysfunction, rebound or 'overshoot' alkalosis, hypokalemia and impaired oxygen unloading due to left shift of the oxyhaemoglobin dissociation curve which can compound matters in shock.

If tissue hypoxia is present bicarbonate can cause acceleration of lactate production by removal of acidotic inhibition of glycolysis and by increasing the activity of rate limiting enzyme phospho fructokinase. It can also can result in hypercapnia with paradoxical intracellular and CNS acidosis and ventilation must be adequate to eliminate the CO_2 produced from bicarbonate. It can also can cause ionized hypocalcemia (due to alkalosis) which can decrease myocardial contractility.

Adverse effects of bicarbonate can be reduced by giving slow infusions in preference to rapid boluses, by correcting hypocalcemia and ensuring adequate ventilation. Correction of acidosis with bicarbonate may be warranted in patients of myocardial dysfunction as acidosis increases the risk of major arrhythmias due to lowering of the myocardial threshold and can cause catecholamine refractoriness. In these patients bicarbonate infusion to keep pH above 7.10 can be justified. In all other circumstances when acidosis is accompanying shock,

In ABG the measured values are pH, $paCO_2$, paO_2, tCO_2 and calculated values are HCO_3, BE, SBE

Stepwise approach to interpreting the arterial blood gas.

1. **History and physical examination:** Gives an idea about the acid base disorder which might be present

2. **Look at the pH**
   - If pH < 7.35, denotes acidemia
   - If pH > 7.45, denotes alkalemia
   - pH may be normal in the presence of a mixed acid base disorder, particularly if other parameters of the ABG (PCO_2, HCO_3)are abnormal.

3. **Look at PCO_2, HCO_3**
   - What is the acid base process (alkalosis vs acidosis) leading to the abnormal pH? Are both values normal or abnormal?
   - One abnormal value will be the initial change (side of the pH change) and the other will be the compensatory response.
   - The direction of compensatory variable is on the same side as the primary variable.
   - Remember compensation never overshoots the pH.

Acid base disorder	Primary change	Compensation
Respiratory acidosis	↑ PCO_2	↑ HCO_3^-
Respiratory alkalosis	↓ PCO_2	↓ HCO_3^-
Metabolic acidosis	↓ HCO_3^-	↓ PCO_2
Metabolic alkalosis	↑ HCO_3^-	↑ PCO_2

4. **If it is respiratory process, is it acute or chronic?**
   - To assess if acute or chronic, determine the **extent** of compensation.

   10 mmHg change in $PaCO_2$ – Bicarbonate changes by 1 (Acute)

   10 mmHg change in $PaCO_2$ – Bicarbonate changes by 4 (Chronic)

5. **If it is metabolic process, is degree of compensation adequate**?
   - Calculate the estimated PCO_2, this will help to determine if a separate respiratory disorder is present. In a primary metabolic acidosis, the degree of acute respiratory compensation (PCO_2 rise) can be predicted by the following relationship:

   Expected $PaCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$ (Winters formula)

   If the measured $PaCO_2$ is higher than the expected $PaCO_2$, a concomitant respiratory acidosis is also present. Another formula for the same derivation is:

   For 1 mEq/L change in HCO_3 $PaCO_2$ changes by 1 (Acute)

   For 1 mEq/L change in HCO_3 $PaCO_2$ changes by 4 (Chronic)

6. **If metabolic acidosis, then look at the Anion Gap.**
   - If elevated (> 12), then acidosis due to. (Ketoacidosis, Uremia, Lactic acidosis, Toxins).
   - If anion gap is normal, then acidosis likely due to diarrhea, RTA, saline excess

7. **If anion gap is elevated, then calculate the Delta-Ratio (△/△) to assess for other simultaneous disorders.**
   - △/△ compares the change in the anion gap to the change in bicarbonate.
   - If the ratio is between 1 and 2, it denotes wide anion gap acidosis
   - If <1, then there is a coexistent Normal anion gap acidosis
   - If >2, then there is a coexistent Metabolic alkalosis present (or rarely a compensated chronic respiratory acidosis).

8. If normal anion gap and cause is unknown, then calculate the urine anion gap (UAG).
   - In RTA, UAG is positive.
   - In diarrhea and other causes of metabolic acidosis, the UAG is negative.

Fig.2. ABG analysis

cardiopulmonary arrest, seizures, and diabetic ketoacidosis, bicarbonate therapy is not recommended .

THAM (Trishydroxy methyl aminomethane) is a more effective buffer and supplements the buffering action of sodium bicarbonate by decreasing partial pressure of carbon dioxide and does not require an open system to eliminate carbon dioxide. Side effects include respiratory depression and hypoglycemia.[5]

The preferred management of metabolic acidosis is to make aggressive efforts to determine, correct the primary cause and use specific treatment. Metabolic acidosis is a common problem in critically ill patients and is associated with poor outcome. Although it remains uncertain whether there is a true cause-effect relation between acidosis and adverse clinical outcomes, acidosis is a powerful marker of poor prognosis in critically ill patient.

Points to Remember

- ***pH derangement is a canary (heralds trouble). Be aggressive in ascertaining cause of acidosis and treating it rather than administering bicarbonate to artificially correct pH.***
- ***Check the anion gap (correct for albumin) even if there is no apparent acid-base disturbance.***
- ***Check for delta gap for concealed acidosis or alkalosis . Both wide anion and normal anion gap acidosis can coexist.***
- ***Avoid large quantities of saline (use balanced solutions containing low chloride) to prevent hyper chloremic acidosis.***

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CRITICAL CARE - II

RESPIRATORY FAILURE - RECOGNITION AND INITIAL MANAGEMENT

***Ramachandran P**
****Dinesh M**

Abstract: *Respiratory disorders in children can present as emergencies. Early recognition and prompt management are required as they have a potential to deteriorate to cardiac arrest. The causes can be related to airway, lung parenchyma or neurological problems. A systematic clinical approach based on Pediatric Advanced Life Support (PALS) helps to categorize the severity as well as the type of problem. This approach helps to initiate the immediate measures and escalate the treatment if required. This article outlines the pathophysiology, categorization and initial management of respiratory failure in children.*

Keywords: *Respiratory failure, Respiratory distress, PALS, Initial management, Ventilation.*

Respiratory problems in children may manifest as respiratory distress or respiratory failure. Respiratory failure can also occur due to non-respiratory causes such as central nervous system(CNS) problems. Respiratory distress is a common emergency in children and accounts for 10% of emergency department visits and 20% of hospitalizations.[1] Respiratory failure is commonly encountered in pediatric intensive care units (PICUs). Nearly two-thirds of PICU patients will be admitted with a diagnosis of respiratory failure.[2] Respiratory distress in children, particularly neonates and infants must be promptly recognized and aggressively treated as they may decompensate rapidly. Prompt recognition and management are fundamental to pediatric advanced life support (PALS) as respiratory problems are a major cause of cardiac arrest in infants and children.[3] The unique anatomic and physiologic characteristics of respiratory tract in infants and young children make them vulnerable to respiratory failure. Initial rapid assessment to identify the severity and type of problem helps in initiating necessary measures to stabilize the child irrespective of the etiology. Knowledge of common respiratory emergencies and further evaluation help in specific management.

* Professor of Pediatrics,
Sri Ramachandra Medical College & Research Institute,
Chennai.

** Fellow in Pediatric Critical Care
Sri Ramachandra Medical College & Research Institute,
Chennai.

Pathophysiology

Respiratory failure represents a common end point to multiple pathologic processes categorized as hypoxemic, hypercapnic or mixed. Inadequate oxygenation of blood results in hypoxemia leading onto tissue hypoxia. The child may initially compensate by increasing the respiratory rate and effort to improve arterial oxygenation and by increasing the heart rate to improve cardiac output and tissue oxygen delivery. As tissue hypoxia worsens clinical signs of respiratory distress become more severe and child may tire out. Inadequate ventilation from decreased respiratory effort may occur due to progressive airway or parenchymal disease of the lung or due to disordered control of breathing. This results in respiratory failure with carbon-dioxide (CO_2) retention (hypercarbia) and respiratory acidosis. It is necessary to understand the anatomic and physiologic differences in airways and breathing in children, who are in fact, not like adults. The factors contributing to respiratory failure in children include smaller airways, increased metabolic demands, decreased respiratory reserves and inadequate compensatory mechanisms as compared to adults.[4] Infants and young children have lower percentage of efficient, slow twitch skeletal muscle fibres (Type 1) in their muscles compared to older children.[5] Further collateral ventilation through pores of Kohn and Lambert in the alveoli are not well developed early in life making the young children more vulnerable to alveolar collapse.[6]

Changes in breathing in respiratory failure: Normal breathing involves minimal work. In respiratory distress, the work of breathing (WOB) increases with increased use of respiratory muscles. This may be due to increased airway resistance or decreased lung compliance. Breathing efforts may also be less due to decreased strength of respiratory muscles and the altered control of breathing due to CNSdisrders.

Increased airway resistance may be caused by decreased airway size as in edema, broncho-constriction,

secretions, etc., or airway turbulence as in crying and agitation. When airflow is laminar as in quiet breathing, airway resistance is inversely proportional to the fourth power of airway radius. When airflow becomes turbulent airway resistance is inversely proportional to the fifth power of airway radius.

Compliance refers to the distensibility (stiffness) of the lung, chest wall or both. Decreased lung compliance is seen in lung conditions such as pneumonia, acute respiratory distress syndrome (ARDS), pneumothorax or pleural effusion. In these children increased work of breathing reduces the intra-pleural pressure well below the atmospheric pressure to create airflow into the lung. Thus in respiratory disorders with increased airway resistance or decreased lung compliance accessory muscles are used to produce inspiratory air flow. But in infants and young children the chest wall is compliant resulting in marked inspiratory refraction of chest wall limiting lung expansion. This results in inadequate tidal volume even with maximal inspiratory effort. Children with neuromuscular disorders have a weak chest wall resulting in ineffective cough and seesaw breathing.

The normal diaphragm is domeshaped and it contracts most forcefully when in this shape. When diaphragm is flattened as in hyperinflation or its movement is impeded due to abdominal distension its contraction is less forceful and respiration is compromised.

Breathing is controlled by CNS especially the brain stem respiratory centre. Infection of CNS, traumatic brain

Table I. Causes of acute respiratory failure in children[6]

Location	Causes
UAW obstruction	• Infection (croup, bacterial tracheitis) • Foreign body • Anaphylaxis
LAW obstruction	• Asthma • Bronchiolitis • Cystic fibrosis
Parenchymal disease	• Pneumonia • Pulmonary edema • ARDS • Pleural effusion
CNS disorder	• CNS infection (Encephalitis, meningitis) • Intracranial bleed • Toxins • Metabolic encephalopathy
Peripheral nervous system and muscle disorders	• Guillian Barre syndrome • Spinal cord injury • Toxins (organophosphates) • Snake bite (cobra, krait) • Muscular dystrophy

injury and drug overdose can impair the central respiratory drive and can cause hypoventilation or apnea.[7]

Classification of respiratory problems

Respiratory problems can be classified as per severity or type.

Categorization as per severity

Respiratory distress is a clinical state characterized by increased respiratory rate and effort such as use of accessory muscles of respiration or retraction. It can be associated with changes in airway sounds, skin colour and mental status.

Respiratory failure is a clinical state of inadequate oxygenation, ventilation or both and is often the end stage of respiratory distress. When the child has an impaired CNS control of breathing she may develop respiratory failure without any respiratory distress.

Categorization as per type

Respiratory distress or failure can be classified based on the underlying mechanism as upper airway (UAW) obstruction, lower airway (LAW) obstruction, lung parenchymal disease and disordered control of breathing. Sometimes more than one type may be seen.

Categorization as per arterial blood gas (ABG)

Type I respiratory failure (oxygenation failure / arterial hypoxemia): This is is characterized by low partial pressure of oxygen (O_2) in arterial blood (Pa O_2 < 60mm Hg in room air). It is the most common form of respiratory failure. Factors affecting Pa O_2 are: i) Partial pressure of O_2 in inspired air ii) Minute ventilation iii) Pulmonary blood flow iv) Oxygen saturation of hemoglobin in pulmonary blood v) Diffusion across alveolar membrane vi) Ventilation perfusion ratio.

Type II respiratory failure (ventilator failure/arterial hypercapnia): In type II failure partial pressure of CO_2 in arterial blood (Pa CO_2) is increased (>46 mm Hg) and is accompanied by fall in Pa O_2. Pa CO_2 level reflects the efficiency wash out of the CO_2.

Type III respiratory failure (combined oxygenation and ventilator failure): Both arterial hypoxemia and hypercapnia are seen.

Causes of acute respiratory compromise

Common causes of acute respiratory distress or failure are shown in table I. Any of these conditions causing respiratory distress can become life-threatening by compromising oxygenation and/or ventilation and hence require early recognition and appropriate management.

Initial evaluation

The evaluation of a child with respiratory problem includes assessing the severity as well as determining the the underlying cause. Features of the history and physical examination will help in localizing the source and etiology and guide initial management. The initial rapid assessment of pediatric assessment triangle (PAT) is based on quick evaluation of appearance, breathing and circulation in any acutely ill child to identify conditions requiring immediate intervention.[3]

The rapid cardiopulmonary assessment as per PALS also helps in identifying whether the respiratory distress is due to respiratory, cardiac or metabolic causes.

Appearance: Restlessness, anxiety or combativeness suggest hypoxia. Lethargy or sleepiness may indicate severe hypoxia, hypercarbia or both.

Table II. Respiratory insufficiency–categorization by severity by clinical features

Distress	Failure
• Tachypnea	• (Early) marked tachypnea / tachycardia
• Tachycardia	• (Late) Bradypnea / apnea / bradycardia
• Increased respiratory effort	• Increased / decreased / no respiratory effort
• Abnormal airway sounds	• Cyanosis
• Pale, cool skin	• Stupor / coma
• Changes in mental status	

Breathing: Any increased or decreased or absent respiratory effort or abnormal sounds are noted.

Circulation: Pallor, ashen colour and cyanosis can occur not only shock but also in hypoxemia.

Severity assessment

Clinical features helpful in identifying respiratory distress and respiratory failure are classified in Table II. The initial response to respiratory compromise is tachypnea and tachycardia. A simple, but reliable way to identify rapid breathing in different age groups based on WHO guidelines is given in Table III. Besides tachypnea and tachycardia abnormal airway sounds such as stridor or wheeze and increased use of accessory muscles of respiration (intercostals, subcostals, sternal, suprasternals and supraclaviculars) with chest refraction indicate respiratory distress. Mild chest refractions may be normal in neonates and young infants. Severe chest indrawing indicates significant distress.[9] Significant refraction of more than one muscle group also indicates significant hypoxia. Nasal flaring is often observed in infants with respiratory distress. Head bobbing (extension of head and neck during inhalation and falling forward of head during exhalation also indicates severe respiratory distress. As the severity increases child may become fatigued and respiratory rate and effort decrease, with irregular respirations and changes in level of consciousness. These are danger signs and if not intervened immediately, respiratory arrest can occur. Thus respiratory failure which is often the end stage of respiratory distress requires immediate intervention to prevent respiratory arrest and later cardiac arrest.[10]

Table III. Cut-off rate for fast breathing[8]

Age	Rate
• Upto 2 months age	• ≥ 60 breaths/min
• 2 mo–upto 12 mo	• ≥ 50 breaths/min
• 12 mo–upto 5 years	• ≥ 40 breaths/min

Cyanosis is a late finding in children with hypoxemia. Severely anemic patients may not show cyanosis despite severe hypoxemia.

Bradypnea and apnea in young infants are usually the result of respiratory muscle fatigue. In young infants apnea may also be the initial manifestation of bronchiolitis or pertussis. Other causes of apnea may be head trauma or poisoning. Bradycardia in a hypoxic child is a late and ominous sign indicating impending cardiac arrest.

Classification of respiratory problems by type[7]

Besides the general features of respiratory distress, the following specific features may be helpful to identify the type of respiratory distress/failure.

Upper airway (UAW) obstruction : Specific features like hoarseness of voice, barking cough, predominantly inspiratory stridor and suprasternal and supraclavicular refractions are seen. To maximize the airway patency a child with UAW obstruction may sit upright and assume a 'sniffing' position with neck flexed and head mildly extended. Drooling and dysphagia may be seen in oropharyngeal obstruction.

Lower airway (LAW) obstruction : Expiratory wheeze and prolonged expiratory phase of respiration are the characteristics in LAW obstruction. The child may assume a 'tripod position' with sitting up and learning forward on outstretched hands.

Parenchymal disease of lung : Clinical signs such as grunting, crackles and diminished breath sounds are seen. Grunting is typically a sign of moderate to severe respiratory distress in young infants with conditions such as pneumonia or pulmonary edema.

Disordered control of breathing : Inadequate and variable respiratory rate and / or effort are seen. If it is due to CNS causes, altered level of consciousness is usually associated. Thoraco abdominal dissociation or paradoxical breathing (see-saw respiration) in which the chest collapses on inspiration while the abdomen protrudes, is a sign of severe respiratory fatigue or muscle weakness due to neuromuscular causes.

Based on the assessment of severity and type respiratory insufficiency is classified as respiratory distress or failure and UAW obstruction, LAW obstruction, parenchymal disease or disordered control of breathing to decide the type of management.

Pulse oximetry

This non-invasive technique is now considered an invaluable vital sign. It helps to assess the oxygen saturation (SpO_2) status of arterial blood. A resting room air SpO_2 of less than 97% is abnormal in infants and children. Oxygen saturation should be monitored continuously till the child is stabilized. Small changes in oxygen saturation reflect much larger changes in PaO_2. SpO_2 of 98% correlates with a PaO_2 of approximately 100mm Hg, 95% with 80 mm Hg and 90% with 60 mm Hg, a level which represents

significant hypoxia.Pulse oximetry should be assessed with other clinical findings.[12] Technical difficulties like improper placement of sensor or movement artifacts can make the readings unreliable. Low perfusion states and anemia also can result in inaccurate readings. It available, the other non-invasive bedside technique to measure end tidal CO_2 (ET CO_2) helps in quickly identifying inadequate ventilation.

Arterial/venous blood gas

Accurate information regarding a critically ill child's oxygenation, ventilation and acid base status is essential for further optimum management. Blood gas is especially useful to assess ventilator status when $ETCO_2$ measurement is not available and to measure PaO_2 and $PaCO_2$ when non-invasive measurements may not be accurate. Venous pH generally correlates well with arterial pH. The correlation between venous and arterial PCO_2 and PO_2 is not sufficiently accurate for assessment of ventilation and oxygenation in critically ill patients.[13]

Initial management

The initial treatment of respiratory distress/failure is to ensure adequate oxygenation and ventilation. Once oxygenation and ventilation are established, identifying the cause of respiratory dysfunction will facilitate targeted intervention.[13]

Children with abnormalities identified in cardio-pulmonary assessment require stabilization of airway, breathing and circulation.

Airway: The airway is supported by allowing the child to assume position of comfort. When the child deteriorates or is in respiratory failure or has altered level of consciousness, airway maneuvers such as head tilt-chin lift is performed to open the airway. Airway is cleared of secretions by gentle suction of the nose and mouth as necessary. If the tongue tends to fall back an artificial airway can be inserted. Oropharyngeal airway can be used only in an unconscious child with absent gag reflex. For a semi-conscious child nasopharyngeal airway is preferred to keep the airway patent.

Breathing: Supplemental oxygen: supplemental oxygen should be administered to any child presenting with respiratory distress. For spontaneously breathing children oxygen can be administered by blow-by, nasal prongs, simple face mask or in infants, head box. To deliver high concentration of oxygen a non-rebreathing mask with reservoir is used.

Oxygen should be administered in a non-threatening manner with the child on mother's lap as separating from the mother may make the child cry and aggravate the hypoxia due to turbulent air flow. Oxygen saturation should be monitored by pulse oximetry for any child requiring supplemental oxygen.

Assisted ventilation : Children with apnea or bradypnea require assisted ventilation. Children categorized with respiratory failure are also candidates for ventilatory support if they do not show anticipated improvement with initial management. Assisted ventilation should initially be provided with bag-mask ventilation (BMV). Endotracheal intubation and ventilation are needed for those who are not expected to improve quickly.

Circulation : Continuous cardiac monitoring for heart rate and rhythm is necessary as hypoxia frequently causes tachycardia and the improvement in oxygenation status will bring about a reduction in heart rate along with improvement in other clinical parameters. Vascular access is established to administer fluids as there is a risk of aspiration with oral feeding and also to administer drugs if required.

Specific management of different types of respiratory dysfunction is carried out after the initial stablilizations.

UAW obstruction

The most important aspect in management of UAW obstruction is to allow the child to assume a position of comfort and to avoid unnecessary agitation which may worsen the obstruction. A gentle suctioning of nose and mouth may be done cautiously as even this procedure may cause vagal stimulation and bradycardia in an unstable child. Nebulized epinephrine along with inhaled or systemic corticosteroid may be helpful in conditions such as croup. Help from an experienced colleague skulled in airway procedure should be sought early if UAW obstruction is severe. Failure to treat an UAW obstruction aggressively may lead to complete airway obstructions and cardiac arrest.[14]

LAW obstruction

Common causes are bronchiolitis and bronchial asthma. For bronchial asthma specific measures like inhaled â2 agonists and systemic steroids are given along with close monitoring. In the rare event of need for assisted ventilation, BMV at a relatively slow rate is done to allow more time for expiration and to prevent air trapping.

Lung parenchymal disease

These are a heterogeneous group of clinical conditions such as pneumonia, pulmonary edema, ARDS, pulmonary contusion due to trauma etc. Specific management in these

disorders includes use of CPAP, BIPAP in spontaneously breathing children with respiratory distress. Assisted ventilation with high PEEP is employed when the hypoxemia is refractory to high concentration oxygen administration with CPAP and there are other features of respiratory failure. Cardiac output and tissue perfusion are supported besides antimicrobial therapy for pneumonia.

Disordered control of breathing

These are CNS disorders or neuromuscular disorders resulting in inadequate minute ventilation (Type II failure). These conditions require appropriate airway management and ventilatory support besides management of underlying CNS problems like increased intracranial pressure or infection. In neuromuscular diseases, non-invasive positive pressure ventilation may be adequate to improve ventilation and comfort and decrease hospitalizations.

Conclusion

Respiratory problems in children may present as emergency. Initial cardiopulmonary, assessment based on PALS guidelines helps in categorizing the severity and type of problem and to initiate steps to stabilize the child and provide the appropriate initial management for the underlying condition. Such an emergent approach is essential as unrecognized and untreated respiratory problems are a major cause of cardiac arrest in infants and young children.

Points To Remember

- ***Children with respiratory problems may present with respiratory distress or respiratory failure***
- ***In early stages, the child may attempt to increase oxygenation and ventilation by increasing the respiratory rate, heart rate and work of breathing and when these fail, may show features of respiratory failure***
- ***Children with neurological problems may directly present as respiratory failure without taking 'respiratory distress' route***
- ***A systematic PALS-based approach helps in categorizing the severity as well as the type of respiratory distress/failure and guide in initial stabilization measures***
- ***When improvement is not seen with initial measures or the child has respiratory failure on presentation itself, non-invasive ventilation with CPAP or invasive ventilation has to be carried out.***

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CRITICAL CARE - II

ACUTE RESPIRATORY DISTRESS SYNDROME

***Manivachagan MN**
****Kala R Inbaraj**

Abstract: *The acute respiratory distress syndrome (ARDS) is an important cause of acute respiratory failure which is often associated with multiple organ failure. Disruption of the alveolar capillary membrane by direct or indirect injury with increased permeability, followed by accumulation of inflammatory cells, dysregulated inflammation and uncontrolled activation of coagulation pathway are the central pathophysiological events of ARDS. Overall therapeutic approach is on lung protective ventilation with low tidal volume with the use of optimal PEEP, prevention of secondary complications such as ventilator induced lung injury (VILI) and noscomial infections. New insights into the pathophysiology offer new therapeutic options. New therapeutic modalities refer to corticosteroid, surfactant and inhaled nitrous oxide (NO). High frequency oscillatory ventilation (HFOV), prone ventilation and airway pressure release ventilation (APRV) are used as rescue measures.*

Keywords: *Acute respiratory distress syndrome, Lung protective ventilation , High frequency oscillatory ventilation, Inhaled nitric oxide, Surfactant.*

In 1981 Laennec described a new syndrome with respiratory distress due to pulmonary edema and without heart failure.[1] Earlier to this there are descriptions of patients who had presented with refractory hypoxemia due to non-thoracic injuries, massive transfusion, sepsis and various other conditions during the World War I. In 1967, Ausbaugh et al.,[2] described this condition as Adult respiratory distress syndrome(ARDS) in 12 patients who had presented with bilateral diffuse infiltrates, refractory hypoxemia and respiratory failure.

* Associate Professor,
** Professor,
Pediatric Intensive Care Unit,
Christian Medical College,
Vellore

Multiple definitions existed until 1994, when the American–European Consensus Committee (A-ECC) formulated a clear definition for ARDS (Table I).[3]

The wide acceptance of the A-ECC definition by physicians and clinical researchers improved the care of children with ARDS. However, the A-ECC definition had drawbacks: lack of definite criteria for defining acute onset, poor reliability of chest radiograph criterion, difficulty in differentiating the cause of hydrostatic edema and the failure to incorporate the effect of different ventilator settings, PEEP in particular, on PaO_2/ FiO_2 ratio. For these reasons and the need to revise any definition with increasing knowledge of disease process periodically, the European society of intensive care medicine with endorsement from the American thoracic society and the society of critical care medicine revised the definition of ARDS in Berlin 2012[4] (Table II).

Epidemiology

The incidence of pediatric ARDS varies from 8.5 to 27 per 1000 pediatric intensive care unit (PICU) admissions.[5] A case series from All India Institue of Medical Sciences, New Delhi showed an incidence of 20.1 per 1000 PICU admissions.[6] The incidence of acute lung injury (ALI) in Australia / Newland PICU is reported to be 2.2% of all PICU admissions. In a population based study from Germany, prevalence of pediatric ARDS was 5.5 cases per 100,000 population the incidence being 3.2 cases per 100,000 population. The study also showed that the incidence increases progressively.[7]

Although the overall incidence in pediatric population is low, the mortality is higher ranging from 22% to 35 %. The cause of death in a majority of patients is more due to sepsis and multiorgan failure (MOF) than due to primary disease. Failure to improve at the end of first week is poor prognostic indicator. Although MOF is the leading cause of death in ARDS, the pathophysiological link between ARDS and MOF is not well established.

Etiology

Table III gives the various causes of ARDS. ALI/ARDS may be triggered from either a direct insult to the lungs as in pneumonia or aspiration (primary / pulmonary

Table I. A-ECC definition of ARDS

	Timing	Oxygenation	Chest radiography	Pulmonary capillary wedge pressure
Acute lung injury (ALI)	Acute onset	PaO_2/ FiO_2 <300mmHg (regardless of the PEEP level)	Bilateral infiltrates on frontal chest radiograph	<18mm Hg when measured or no clinical evidence of left atrial hypertension
ARDS	Acute Onset	PaO_2/ FiO_2 <200mmHg (regardless of the PEEP level)	Bilateral infiltrates on frontal chest radiograph	<18mm Hg when measured or no clinical evidence of left atrial hypertension

Table II. The Berlin definition of acute respiratory distress syndrome

Timing	Within 1 week of a known insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities—Not fully explained by effusions, lobar / lung collapse or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	PaO_2/FiO_2 200 - 300mmHg with PEEP or CPAP $\geq$5cm H_2O
Moderate	PaO_2/FiO_2 100 - 200mmHg with PEEP or CPAP $\geq$5cm H_2O
Severe	PaO_2/FiO_2 < 100mmHg with PEEP or CPAP $\geq$5cm H_2O

Table III. Etiology of ARDS

Direct lung injury	**Indirect lung injury**
Common causes:	**Common causes:**
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple transfusions.
Less common causes:	**Less common causes:**
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

ARDS) or from remote or systemic injuries such as sepsis (the most common cause), or trauma (secondary / extra pulmonary ARDS).

Pathophysiology

Acute lung injury results from direct or indirect injury of the alveolar capillary membrane. Injury to the alveolar capillary membrane leading to increased permeability is the hall mark in ARDS. Recovery of the alveolar capillary membrane is an important prognostic indicator.

Disruption of the alveolar capillary membrane with increased permeability, followed by accumulation of inflammatory cells, dysregulated inflammation and uncontrolled activation of coagulation pathway are the central pathophysiological events of ARDS.

Alveoli are lined by type 1 flat cells (90%) and type 2 cuboidal cells (10 %). Type 2 cells are important for surfactant production, ion transport and regeneration of type 1 cells. As a consequence of injury to the alveolar epithelium, there is an increase in the permeability of alveolar membrane which along with a failure of the fluid removal mechanism results in accumulation of protein-rich fluid in alveoli. Loss of surfactant causes collapse of the remaining alveoli.

Proinflammatory cytokines are produced by the inflammatory cells in alveolar fluid, injured epithelial cells and fibroblasts which initiate the injury and maintain the progression. The degree of inflammation depends on biological activity and the balance between pro- and anti-inflammatory cytokines like IL-8 and IL-1.

Activation of the procoagulation factors and inhibition of fibrinolytic pathways in the pulmonary capillary bed leads to intravascular as well as extravascular microthrombi formation in the alveolar compartment resulting in fibrin deposition and hyaline membrane formation.

Resolution of the disease depends on dynamic interaction between restoration of cellular function namely water transport, surfactant production and the coagulation cascade. The type 2 epithelial cells which are the progenitor cells for the alveolar capillary membrane proliferate to cover the denuded basement membrane and then differentiate into type 1 cells. Alveolar fluid is removed by passive diffusion along with ion transport. While the insoluble proteins in the alveolar fluid are removed by endocytosis and transcytosis by alveolar epithelial cells, soluble proteins are removed by passive diffusion along the cells. The mechanism by which inflammatory cells are removed is unclear. Apoptosis may play a major role as in other sites of inflammation.

Environmental and genetic factors that contribute to susceptibility and severity are the current areas of major research in ARDS. A genetic polymorphism of angiotensinogen converting enzyme (ACE) gene is linked to increased susceptibility and severity of acute lung injury.[8] Angiotensin 2 is a potent vasoconstrictor, stimulates the proinflammatory mediators like IL8 and a key factor in the Fas ligand (FasL) induced apoptosis of alveolar epithelial cells.[9,10] In experimental animal models, ACE deficient models have been shown to have less severe disease.

Respiratory physiology

As the disease progresses, alveoli are filled with fluid and cellular debris and there is surfactant loss-induced collapse of alveoli. Parts of lungs lose their compliance and become 'stiff'. The distribution of this process is typically uneven and so over expanded, normally expanded and atelectatic lung units co-exist. This leads to significant ventilation–perfusion (V/Q) mismatch which is one of the important hallmarks of ARDS. Regions with normal V/Q ratios coexist along with regions having high or low V/Q ratios. Moreover, some areas of the lung appear to collapse cyclically, expanding on inhalation and collapsing on exhalation, a process which is called 'cyclical or tidal atelectasis'. Much of the lung, especially in dependent regions, is so consolidated that it cannot be recruited for gas exchange. Only a fraction of the lung in ARDS participates in tidal ventilation, so that it is functionally like a 'baby lung'. The less affected lung regions must accommodate most of the tidal volume which places them at risk for alveolar over distension.

Some areas of the lung are well perfused but are not ventilated, leading to "shunting". The hypoxic pulmonary vasoconstriction, a physiologic reflex that tends to limit blood flow in poorly ventilated lung regions often fails in ARDS. Pulmonary hypertension develops due to small vessel thrombosis, hypoxia, hypercarbia and compression of pulmonary vessels due to over distension of normal alveoli. Severe pulmonary hypertension can cause dilatation of right heart and impairment of cardiac output due to interdependence of ventricles leading to decreased filling of left ventricle.

Iatrogenic insults in the form of ventilation induced lung injury such as oxygen toxicity, absorption atelectasis, barotrauma, volutrauma and atelectatic trauma may further complicate the picture. All of these result in the patient presenting with increased work of breathing and hypoxia.

Management

Management strategies for ALI/ARDS are targeted at decreasing mortality and morbidity, hastening recovery

with shorter duration of ventilation and optimizing long term pulmonary and neurologic function. Overall therapeutic approach is on lung protective ventilation with low tidal volume with the use of optimal PEEP, prevention of secondary complications such as ventilator induced lung injury (VILI) and noscomial infections. Identification of the ARDS trigger sources and achievement of source control are essential to optimize outcome. Because sepsis is a well known trigger for ALI, early antibiotic therapy is recommended. Adequate nutrition is also critical.

Many of the therapies and strategies proposed for ARDS are based on rational physiologic and pathologic principles, but they have not been shown to have unequivocal benefits. Improved understanding of the pathophysiology and advances in technologies have introduced new treatments and improved therapeutic strategies.

When conventional mechanical ventilation was introduced for the treatment of respiratory failure in the 1960s and 1970s, tidal volumes (Vt) of 10-15mL/kg actual body weight were commonly used to maintain arterial CO_2 values within the normal range. Life-threatening complications such as pneumothorax occurred and mortality was high. With the introduction of positive end-expiratory pressure (PEEP), improved oxygenation and fewer complications were achieved. Along with these, patho-anatomical and computerized tomographic studies informed physicians about the uneven distribution of aerated areas and dense consolidated regions of the lung in ARDS.[11] The 'Baby Lung' concept introduced by Gattiaoni in 1980 generated greater interest in low tidal volume strategy in ARDS.[12]

This was followed by better understanding of the VILI that evolved in the 1990s. The mechanisms of the evolution of VILI in ARDS are multiple and include volutrauma, barotrauma, biotrauma and atelectrauma. Additionally, effects of high concentrations of inspired oxygen induce absorption atelectasis, lung toxicity and possibly, systemic toxicity. The standard practice is to titrate the FiO_2 (with the objective of reducing $FiO_2$to less than 0.6) to a partial oxygen tension of 60–80 mmHg or, more importantly for oxygen delivery, an arterial oxygen saturation of 90%. Oxygen saturation values of around 90% are commonly accepted but oxygen delivery decreases quickly below 85%-88% considering the steep descent in the oxyhemoglobin dissociation curve.

The aim of lung protective ventilation strategies aim is to prevent atelectasis, reopen atelectatic regions and keep the lung open (open lung concept) avoiding over distension.

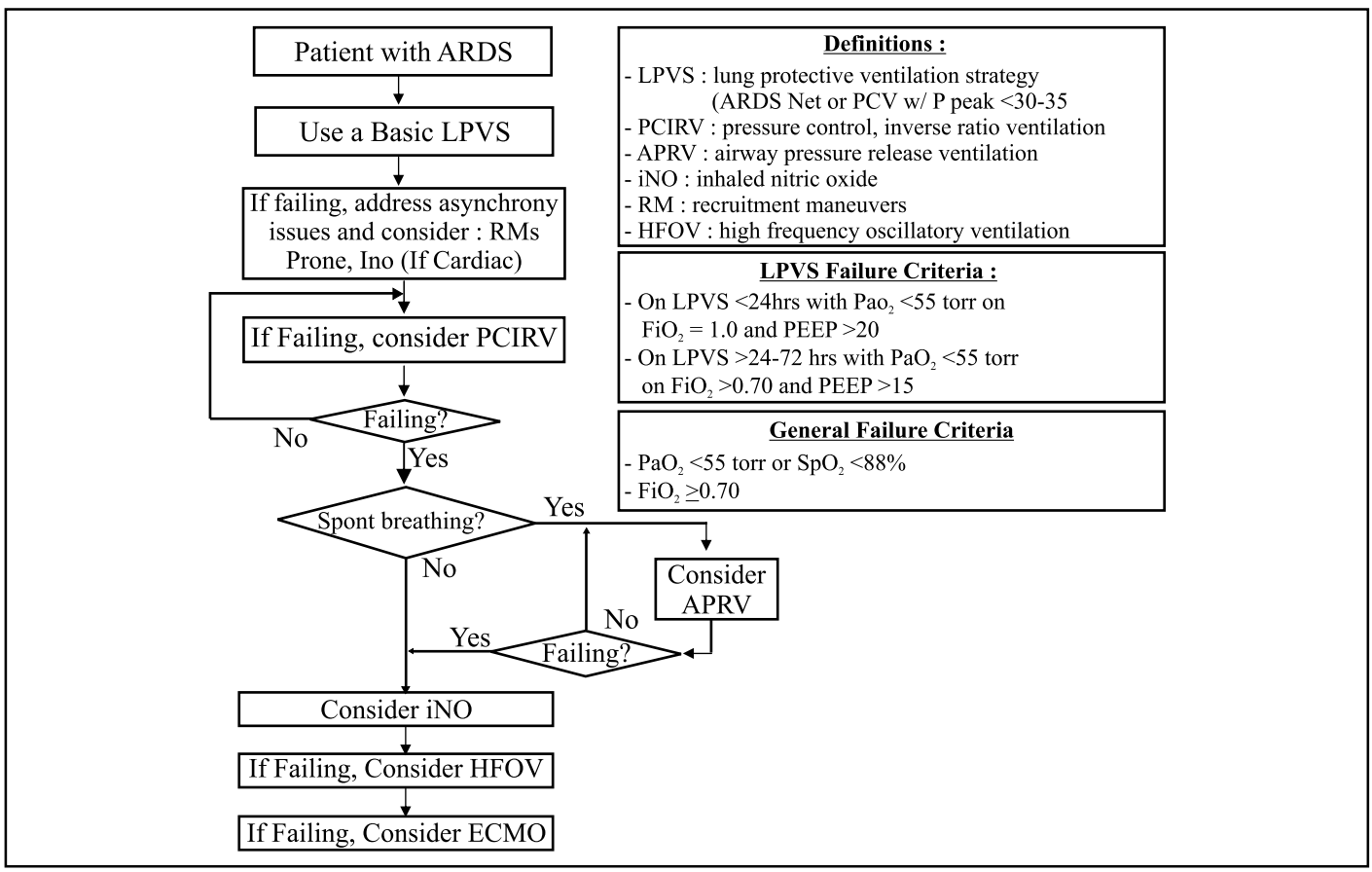

Fig.1. Abbreviated version of the ARDS ventilator management strategies[13]

High-pressure ventilation is avoided (keep the plateau pressure below 30 cm of H_2O). Permissive hypoxia and hypercapnia are accepted to prevent lung injury.

The ARDS network's new gold standard ventilation strategy is as follows: Sufficient PEEP (titrated on FiO_2 or respiratory function measurements), lung recruitment, avoiding plateau pressure above 30 cm H_2O, and tidal volume (Vt) not exceeding 6mL/kg of ideal body weight.

Prone position ventilation (PPV)

Prone position serves as a rescue therapy in children with refractory hypoxemia and has been used as a recruitment maneuver since 1974. When a child is in supine position the alveolar distending pressure measured as transpleural pressure is more in the ventral regions of the lung than in the dorsal region. This leads to over distension of the ventral alveoli and collapse of the dorsal alveoli. Increased lung weight in ARDS aggravates this situation. Prone position decreases this difference making ventilation more homogenous. Ventilation/ perfusion matching improves as new pulmonary units are recruited with more effective gas exchange.

The heart compresses the caudal lung region in supine position and diaphragm compresses the postero-caudal lung region. Sedation and paralysis aggravate these effects. In prone position, the heart becomes dependent, diaphragm's displacement decreases, both causing the recruitment of more alveoli. Differential production of nitric oxide in different lung regions, changes of hypoxic pulmonary vasoconstriction[14] and better draining of secretion are other proposed mechanisms for improvement in alveolar ventilation with prone position.

A recent review of all publications on meta-analysis of the efficacy of prone position in ALI and ARDS concluded that prone positioning was associated with reduced mortality in severe hypoxic respiratory failure.[15] Extended PPV is defined as PPV for 48 hours or until the oxygenation index was 10 or less. Extended PPV is emerging as an effective rescue therapy for patients with severe ARDS and severe hypoxemia. Complications of prone positioning are inadvertent extubation, airway complication, pressure sores, displacement of venous lines and indwelling catheters and brachial plexus injury.

High frequency oscillatory ventilation (HFOV)

HFOV, theoretically the ideal mode of avoiding VILI differs from conventional ventilation in several ways: conventional ventilation produces large tidal changes in inspiratory pressure whereas in HFOV the mean airway pressure (MAP) is held constant. The pressure waves in the HFOV circuit are generated by a diaphragm that oscillates at frequencies between 3 and 15 Hz (180–900 breaths/min). Both inspiratory and expiratory pressure waves are created as the diaphragm is actively driven in both directions. Therefore, expiration is also active, which may be beneficial in preventing hyperinflation and controlling CO_2 elimination.

The advantage of HFOV is decoupling of oxygenation and ventilation. Oxygenation is dependent upon MAP and FiO_2; ventilation is influenced by the power with which the diaphragm moves the frequency of oscillations and inspiratory / expiratory ratio. Numerous other mechanisms have been proposed for the ability of the HFOV to achieve adequate ventilation with a tidal volume less than dead space in HFOV. They are bulk convection, cardiac oscillation, Taylor dispersion, asymmetric velocity profiles, diffusion and pendelluft. The small tidal volumes delivered by HFOV produces minimal variation around the mean airway pressure and mean lung volume during tidal breathing; this clearly limits the volutrauma and atelectrauma.

HFOV has been mostly investigated as a rescue therapy for patients failing on conventional ventilation. Initial case series by Fort and colleagues,[16] Mehta and colleagues[17] suggested improved mortality in patients with fewer ventilator days before initiating HFOV as rescue therapy. Thus, HFOV is considered as a potential tool for rescue therapy for patients with severe hypoxia. The only pediatric prospective RCT on HFOV showed that physiological parameters, oxygenation and lung recruitment improved. However, the duration of mechanical ventilation and 30-day mortality did not differ between the HFOV and control group.[18] A recent Cochrane review[19] compared the effect of HFOV with conventional ventilation for ALI or ARDS and found a statistically significant reduction in the risk of requiring supplemental oxygen amongst survivors at 30 days in the pediatric study. There was not enough evidence to conclude whether HFOV reduced mortality or long-term morbidity in these patients.

Airway pressure release ventilation (APRV)

ARPV is a modified form of CPAP described by Stock and Downs in 1987 to enhance oxygenation by augmenting alveolar recruitment. APRV is being increasingly used as an alternative mode of ventilation for both salvage therapy in hypoxemic respiratory failure and lung protective ventilation. In APRV the patient is allowed to breathe at any point in the phase of respiratory cycle because of the unique valve construction of ventilators. Oxygenation in APRV occurs by a combination of several mechanisms:

alveolar recruitment, intrinsic PEEP and increased pulmonary and systemic flow. CO_2 clearance is achieved by intermittent release of the airway pressure and allowing ventilation. Further studies are required to compare APRV to ARDS net protocol ventilation to determine whether managing ARDS with APRV reduces mortality.

Surfactant therapy

The major rationale for surfactant therapy is the presence of surfactant dysfunction in the injured lung. A reduction in the content or composition of active large surfactant aggregates has been reported in bronchoalveolar lavage (BAL) fluid and tracheal aspirates from patients with ALI/ARDS or other diseases involving lung injury. Surfactant dysfunction is well documented in animal models of acute inflammatory lung injury. Surfactant dysfunction is more prominent in the early exudative phase and it is here that exogenous surfactant therapy has the greatest theoretical benefits.

Moller and colleagues[21] reported that children showed immediate improvement in oxygenation and less need for rescue therapy following treatment with surfactant. Among the 152 children with ALI/ARDS randomized by Wilson and colleagues[22] to receive surfactant or air placebo, surfactant treatment resulted in decreased OI, decreased mortality and higher percentage of response to conventional ventilation compared with placebo. A post hoc analysis indicated that the most of these beneficial effects are confined to patients with direct form of ALI /ARDS.

Inhaled nitric oxide (iNO)

Nitric oxide or endothelium derived relaxing factor is known to couple with cGMP system to mediate vasodilatation. It also modifies immune function and affects platelet aggregation. After the success of iNO in PPHN, inhaled NO is investigated as therapeutic potential in ARDS with the view of reversing the pulmonary vasoconstriction, relieving the micro vascular obstruction by reducing the platelet aggregation, improving the gas exchange by improving the ratio of ventilation to perfusion and reducing the neutrophil adhesion and local inflammation.

In 1998, the multi centered inhaled nitric oxide in ARDS study group[22] results showed early but non-sustained increase in oxygenation and transient decrease in oxygenation index. These short term physiologic improvements did not translate to a measurable decrease in mortality.

In a multicenter study of the use of iNO (10 ppm dose) in children with acute hypoxic respiratory failure,[23] although oxygenation acutely improved in the group treated with iNO, it did not translate into a survival benefit. Data from a post-hoc analysis suggested that patients with severe respiratory failure (oxygenation index >25) or immunocompromise may have benefited from the use of iNO. However, this analysis has been criticized. Inadequate lung inflation is the most frequent cause of poor response. Improper dosing, abnormal pulmonary vascular function or structure, unsuspected anatomical cardiac disease or myocardial dysfunction are other causes that can contribute to a lack of response to inhaled NO.

Reasons for this lack of clinical benefit are unclear. One possible explanation is that ARDS tends to be a heterogeneous lung disease, in contrast to persistent pulmonary hypertension of the newborn. Alternatively, the fact that most patients with ARDS die from sepsis, MODS or their primary illness may imply that no survival benefit is observed with improved oxygenation and decreased ventilator support.

Abrupt discontinuation of iNO may result in a rebound response characterized by decrease in oxygenation and increase in pulmonary vascular resistance. Slower weaning of the inhaled NO dose to discontinuation, addition of a phosphodiesterase inhibitor (e.g. milrinone) or sildenafil may prevent clinical compromising rebound effect. Methemoglobin levels and nitrogen dioxide should be monitored closely during NO therapy.

Steroids

It was speculated that the pro-inflammatory and anti-inflammatory processes during ALI/ARDS do not occur at similar time points and that fibrosis may represent an early response to lung injury, progressing "in parallel" with exudative and proliferative changes rather than in 'succession'.[24] Patients with unresolving ARDS have inadequate glucocorticoid receptor mediated down regulation of inflammatory transcription factor-Kb (NF- k B) despite elevated levels of circulatory cortisol, a condition recently defined as critical illness–related corticosteroid insufficiency (CIRCI).[25]

Recent consensus statement recommended early initiation of prolonged glucocorticoid treatment for patients with severe ARDS and before day 14 for patients with unresolving ARDS grading the evidence of survival benefit as weak (grade 2B).[26] Methylprednisolone should be given as a continuous infusion and tapered over 3-4 weeks. Neuromuscular blocking agents should be avoided along with steroids to minimize the risk of neuromuscular weakness. While patients are on steroids, infection

surveillance is essential to promptly identify and treat secondary complications.

Non-respiratory management of ARDS

The dilemma in fluid management of ARDS patient is how to support the hemodynamics without increasing alveolar fluid accumulation and worsening pulmonary dysfunction while the open lung strategy requires high PEEP and low tidal volume to optimize the cardiac output. Early case series in 1970s to 90s showed relationship between restrictive fluid management and improvement in pulmonary compliance and survival. Although no survival difference was found between conservative and liberal fluid-management strategies in adult ALI/ARDS, a conservative fluid approach resulted in improved oxygenation index, increased the number of ventilator-free days and ICU-free days, without more adverse effects.[27] Use of albumin with furosemide in hypoproteinemic adult patients with ALI may also be beneficial, although effects on mortality and duration of ventilation remain to be tested.[28,29] Diuretics are frequently administered to pediatric ALI/ARDS patients to manage fluid status. Although there is no definite data in pediatric ARDS, the general approach is conservative fluid management with diuretics after initial stabilization.

Anemia is very common in critically ill children. Higher hemoglobin aids in improving the oxygen carrying capacity of blood. Although oxygen delivery and consumption are greater in survivors than non-survivors in adults with ARDS[30] there is no evidence that transfusing to supra-normal hemoglobin levels will improve regional oxygen delivery or clinical outcome.[31] Fluid overload, 'transfusion associated acute lung injury (TRALI)' are potential risks of transfusion of blood products. Recent trial showed that a hemoglobin transfusion target of 7.0 g/dL is as safe as a target of 9.5 g/dL in stable critically ill children without profound hypoxia.[32] However, a conservative approach to transfusion thresholds for pediatric ARDS has not been studied in combination with permissive hypoxemia, which is gaining acceptance. In the absence of such data, it is reasonable to maintain hemoglobin concentration within the normal range for age (10 g/dL) in children with profound hypoxia or shock.

Both hyperglycemia and hypoglycemia are to be avoided, especially the latter in younger infants.

Ensuring adequate sedation and analgesia is the standard of care of mechanically ventilated children but there are no data supporting any specific regimens. Prolonged muscle relaxation has been associated with development of weakness and critical illness myopathy. Neuromuscular blockers should be used judiciously, especially in conjunction with steroids, to minimize the risk of myopathy and long-term weakness.

Mechanical ventilation and coagulopathy are the risk factors of gastrointestinal bleed. All children should receive prophylaxis for stress ulcer.

ARDS is associated with hypercatabolism which could lead to significant nutrition deficits. Nutrition support is necessary to prevent cumulative calorie deficits, malnutrition and deterioration of respiratory muscle strength. Early enteral nutrition has been associated with modulation of stress and systemic immune response as well as attenuation of disease severity. Early initiation of enteral nutrition is important to achieve the clinical benefits. In a randomized trial in critically ill children, small bowel feeding instead of the gastric feeding resulted in a greater amount of nutrition to be delivered successfully but did not decrease aspiration of gastric contents. Specialized nutrition support, with an enteral diet enriched with omega-3 fatty acid, gamma - linolenic acid (GLA) and antioxidant supplementation, should be considered in patients with ARDS.

Conclusion

ARDS is a common cause of PICU admission and causes profound changes in lung compliance and ventilation-perfusion mismatch leading to hypoxemia. Overall therapeutic approach is lung protective ventilation with low tidal volume and use of optimal PEEP, prevention of secondary complications such as ventilator induced lung injury (VILI), nosocomial infections and multiorgan dysfunction syndrome. Early HFOV, prone ventilation is used as rescue therapy along with inhaled nitric oxide and ECMO. Inspite of innumerable advances in the understanding of the disease and therapeutic options of ARDS patients, the mortality still remains as high as 36-50%. Though all pediatric intensive care units in developing nations may not be able to provide therapies such as iNO or ECMO, lung protective ventilation strategies combined with good supportive care will help to limit the mortality rate. Unfortunately, due to lack of definitive pediatric data to guide clinical ALI/ARDS management, pediatric critical care clinicians must extrapolate data from adult populations and rely on their own clinical judgement and their colleagues' experience for the management of ARDS.

Points to Remember

- ***Incidence of pediatric ARDS varies from 8.5 to 27 per 1000 pediatric intensive care unit admissions.***

- ***Can be due to varied causes leading to lung injury either directly or indirectly.***
- ***Low tidal volume with optimal PEEP strategy is employed for managing ARDS.***
- ***High frequency oscillatory ventilation (HFOV) is used as rescue therapy with inhaled nitric oxide and ECMO.***
- ***Fluid management, glycemic control, analgesia, management of anemia are equally important.***

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CLIPPINGS

Medical interventions for traumatic hyphema

Traumatic hyphema is the entry of blood into the space between the cornea (clear outer layer of the eye) and iris (colored disc behind the cornea) following a blow to the eye. Along with the appearance of blood, there may be one or more major injuries to the eye from the trauma, which could result in loss of vision. In most cases, the blood is absorbed, but in some cases, there is a secondary hemorrhage (the appearance of fresh blood in the eye after the initial trauma). Complications resulting from secondary hemorrhage include glaucoma, corneal bloodstaining, or damage to the optic nerve (the nerve that carries visual information from the eye to the brain). These complications also can result in permanent loss of vision.

Objective was to assess the effectiveness of various medical interventions in the management of traumatic hyphema.

Selection criteria: Two authors independently assessed the titles and abstracts of all reports identified by the electronic and manual searches. In this review, we included randomized and quasi-randomized trials that compared various medical interventions versus other medical interventions or control groups for the treatment of traumatic hyphema following closed globe trauma. We applied no restrictions regarding age, gender, severity of the closed globe trauma, or level of visual acuity at the time of enrolment.

Authors' conclusions: Traumatic hyphema in the absence of other intraocular injuries uncommonly leads to permanent loss of vision. Complications resulting from secondary hemorrhage could lead to permanent impairment of vision, especially in patients with sickle cell trait/disease. We found no evidence to show an effect on visual acuity by any of the interventions evaluated in this review. Although evidence was limited, it appears that patients with traumatic hyphema who receive aminocaproic acid or tranexamic acid are less likely to experience secondary hemorrhaging. However, hyphema in patients treated with aminocaproic acid takes longer to clear.

Other than the possible benefits of antifibrinolytic usage to reduce the rate of secondary hemorrhage, the decision to use corticosteroids, cycloplegics, or nondrug interventions (such as binocular patching, bed rest, or head elevation) should remain individualized because no solid scientific evidence supports a benefit. As these multiple interventions are rarely used in isolation, further research to assess the additive effect of these interventions might be of value.

Gharaibeh A, Savage HI, Scherer RW, Goldberg MF, Lindsley K. Medical interventions for traumatic hyphema. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD005431. DOI: 10.1002/ 14651858.CD005431.pub3. Assessed as up to date: August 30, 2013.

CRITICAL CARE - II

WEANING FROM VENTILATOR

***Shanthi S**

Abstract: *Mechanical ventilation in critically ill children, though life saving, may result in a number of complications especially if the duration is prolonged. Hence every child should be weaned off the ventilator at the earliest opportunity. However a premature attempt at weaning can also increase the morbidity and mortality. Traditionally patients were weaned slowly with gradual reduction of ventilatory support. A lot of research has been carried out on this issue of weaning in adults and children. Many studies recommend a daily spontaneous breathing trial to assess for the readiness to extubate. This article will focus on the various weaning methods in children and the common causes of weaning failure.*

Keywords: *Weaning from ventilator, Children, Spontaneous breathing trial, Readiness to extubate.*

Mechanical ventilation (MV) is a life saving intervention in critically ill children. The indications for ventilation include a) primary lung failure which results in decreased oxygenation, e.g., pneumonia, cardiogenic and non-cardiogenic pulmonary edema and b) pump failure which leads to both decreased oxygenation and ventilation eg., traumatic brain injury, neuromuscular disease and poisoning due to narcotics.

MV in general delivers positive pressure breaths in contrast to the negative pressure ventilation in spontaneously breathing individuals. Hence, MV is associated with a number of complications such as ventilator associated lung injury, air leak syndromes and ventilator associated pneumonia. In order to prevent or reduce these complications the children getting MV should be weaned from the mechanical support at the earliest opportunity. On the other hand, premature attempts at weaning may lead to reintubation and further worsening of the patient's condition.

* Professor of Pediatrics,
Stanley Medical College,
Chennai.

Weaning is defined as liberation from MV while spontaneous breathing is allowed to assume the responsibility for effective gas exchange.[1] Extubation is defined as the removal of the endotracheal tube.

Weaning patients from ventilators continues to be an important issue in the management of critically ill children. A lot of research has taken place, yet the weaning process, remains more physician oriented and subjective most of the time. Thus, weaning has been considered as a mix of art and science.

One should look at the following factors in deciding whether patient is ready for weaning: a) the underlying disease process which had necessitated MV should have improved. This is the most important criterion b) the patient should be capable of breathing spontaneously without excessive respiratory effort and c) gas exchange should be adequate.

It is important to understand that it is the patient who determines the time for initiation of weaning. However the physician should consider the possibility that a patient 'just' may be able to tolerate weaning.[2]

The standard indices for assessing patient weaning ability are given in Table I.[1,3,4]

Weaning can be easily achieved in post-operative patients, patients with drug overdose and patients whose conditions cause pure lung failure that reverse rapidly. In the above group MV can be discontinued in 77% of patients within 72 hours of initiation of MV.[5,6] Over 50% of ventilated PICU patients can be extubated by 48 hours after admission, but the rest often require prolonged ventilatory support.[7] On the other hand 50% of unplanned extubations end in success indicating early extubation could have been possible.[8]

Predictive indices for weaning

Several indices have been developed to predict success in weaning and extubation. These include rapid shallow breathing index (RSBI), maximum inspiratory pressure, minute ventilation, vital capacity, airway occlusion pressure, compliance, resistance, oxygenation and pressure index (CROP index). They have been used in research but in

Table I. Assessment of weaning ability

1.Resolution of the etiology of respiratory failure and attainment of stable respiratory status
- Spontaneous respiratory effort
- Absence of tachypnea : <60 for infants,<40 for preschool and school children, <30 for adolescents
- pH 7.32-7.47
- PaO_2 > 60 mm Hg
- $PaCO_2$ < 60 mm Hg
- PIP < 20 cm H_2O and PEEP <5 cm H_2O
- SpO_2 > 94% on a Fio_2 of <0.5

2.Hemodynamic stability including no evidence of shock
- Good perfusion
- Age appropriate BP
- No requirement for vasoactive medications except dopamine <5µg/kg/min

3.Neurologic function
- Easily arousable to verbal or physical stimulation - GCS>11
- Capable of moving an uninjured upper and lower extremity against gravity.

4.Metabolic factors
- Acceptable serum potassium, magnesium and phosphorus concentrations

5.No clinical need for increased ventilator support in the last 24 hours.

6.Core temperature below 38.5°C

7.No planned operative procedures requiring heavy sedation in the next 12 hours.

clinical practice they lack proven benefit over clinical judgement. Of all the above indices RSBI [frequency/tidal volume in litres (f/Vt)] was found to be a good determinant of weaning success and failure. This test has been used as a screening test in clinical practice with high sensitivity. An f/Vt ratio of 100 discriminates between successful and unsuccessful attempts at weaning.[9] (Less than 100: more likely to be successful). Most of the above indices are tested in the adults. However adult weaning criteria are poor predictors of weaning outcome in children.[10]

Techniques of weaning

There are two approaches to weaning: a) the traditional method and b) the modern method which assesses the patient's readiness to extubate as soon as the patient meets criteria to initiate weaning (Table I).

Traditional method: In this method infants and children are weaned slowly with a gradual reduction of ventilatory support. This is done by reducing the ventilator rate, FiO_2, PIP and CPAP/PEEP. At each step of weaning, the child is reassessed clinically and he/she must demonstrate the ability to breathe effectively without increase in effort of breathing. For many years intermittent mandatory ventilation (IMV) and synchronized IMV (SIMV) were used for weaning. Esteban et al in their study on comparison of 4 methods of weaning found IMV inferior to pressure-support (PS) and T-piece.[11] Pressure-support ventilation (PSV) alone or SIMV with PS have also been used for weaning.With pressure-support ventilation, the inspiratory pressure is initially set to provide the required support and then reduced gradually. The amount of pressure support to be provided depends on the clinical circumstance. A relative contraindication to PSV is a high baseline spontaneous respiratory rate.[1]

Multiple T-piece trials several times a day is one of the oldest methods of weaning. The patient receives oxygen through a T-tube circuit initially 5-10 minutes in duration, slowly increasing the time on T-tube several times a day till the patient can sustain spontaneous breathing for several hours. This method has become unpopular because it requires a lot of time on the part of the intensive care staff.[2]

Modern method: In this method once the patient meets

Table II. Criteria for terminating SBT.[1]

1. RR outside the acceptable range for age
   - For age< 6 months 20–60/min
   - 6months–2 years 15–45/min
   - 2–5 years 15–40/min
   - > 5 years 10–35/min
2. Use of accessory respiratory muscles:
   - Intercostal/subcostal/suprasternal/supraclavicular retractions
   - Flaring of ala nasi
   - Paradoxical breathing pattern
3. Diaphoresis
4. Agitation, anxiety
5. Altered level of consciousness
6. Tachycardia (HR higher than the 90th percentile for a given age)
7. Hypotension for age
8. SpO_2 < 95% with a FiO_2 of 0.4

the criteria for initiation of weaning as given in Table I, the patient is subjected to spontaneous breathing trial(SBT) or readiness to extubate trial(RET). If SBT is successful the patient is extubated. The duration of the trial ranges from 30 min to 2 hours.[1] If the patient fails SBT, MV is reinstituted at the previous level and the SBT is tried 24 hr later. When patients pass a SBT 50%-75% of patients are deemed ready to extubate.[12, 13]

There are 3 methods of SBT.[11-16]

1. T-piece trials
2. CPAP trials
3. PS trials

The general guidelines for SBT are: a) inform the parent and the child (if age appropriate) that an attempt to remove MV will be made and what to expect, b) a cardio pulmonary cerebral assessment is made and pre-SBT baseline values are documented in a flow sheet and maintained at the bed side, c) the child's ECG, HR, RR, SpO_2, NIBP and $ETCO_2$ (preferable) are continuously monitored, d) a nurse or physician should be at the bedside to closely monitor and check for signs of failure of SBT, e) stop any sedative infusion the child is getting and f) whenever possible make the child sit upright in the bed.

T-piece trial

- Disconnect the patient from the ventilator.
- Connect the T-piece to the endotracheal tube.
- One end of the T-piece is attached to a humidified oxygen source and the other end is connected to a corrugated tube to ensure a higher FiO_2.
- The oxygen flow rate is kept at least three times the minute ventilation of the patient
- Continue to monitor the child for the trial duration of 2 hour.
- If at any point of time during the trial the child shows any one sign of deterioration (Table II) the trial should be stopped, and MV reinstituted at the previous settings.

CPAP trial

The patient is not removed from the ventilator but the CPAP mode is selected. CPAP of 5 cm is set. The general guidelines and the criteria for terminating a trial are the same as for T-piece.

Table III. Causes of weaning failure.[5]

1. Inadequate respiratory drive
   - Nutritional deficiencies
   - Sedation
   - CNS abnormality
   - Sleep deprivation
2. Inability of the lung to carry out gas exchange effectively if the underlying cause of the respiratory failure has not improved sufficiently
3. Respiratory muscle weakness and fatigue
   - Hypokalemia, hypomagnesemia, hypophosphatemia, hypocalcemia
   - Corticosteroids
   - Inadequate cardiovascular performance
   - Persistently increased work of breathing - improper ventilator settings, underlying disease
   - Hyper catabolic state such as sepsis
   - Critical illness polyneuropathy/myopathy
4. Psychological dependency
5. Combination of the above

Minimal pressure support (PS)

Select the PS mode on the ventilator. The amount of PS set is to overcome the resistance to breathe through the endotracheal tube (ETT). The PS selected varies in different studies.

Farias, et al[15] used a PS of 10 cm of water for all patients. Randolph, et al[12] described a minimal PS trial in which the level of PS was adjusted for the endotracheal tube size. 3-3.5mm ETT = PS of 10 cm H_2O; 4-4.5 cm ETT = PS of 8cm H_2O; >5mm ETT = PS of 6cm of H_2O.

The general guidelines and the criteria for terminating a trial are the same as for T-piece.

Weaning failure

After patients have been disconnected from ventilator up to 25% may require reinstitution of ventilation due to increased respiratory distress. (Table III) lists the various causes for weaning failure.[11, 16]

Extubation

If the RET/SBT is successful then patient can be extubated. The patient must be awake, alert with intact airway reflexes, hemodynamically stable and should be able to manage his secretions.

Extubation failure has been variably defined as reintubation within 24–72 hours. It ranges from 2-20% in pediatric patients.[7]

Upper airway obstruction (UAO) is the most common cause of extubation failure in children contributing to 37% in a study by Kurachek et al.[17] The leak test where in air is heard to leak around the ETT at low pressure usually <20-25 cm H_2O is used to predict UAO after extubation.[18–20] However the test may not be always reproducible. A negative test is not a contraindication for extubation if all other conditions for extubation are favorable.

Patients may also fail extubation because they are unable to protect their airways or clear their secretions. A prospective observational study showed that the strongest predictors of extubation failure in patients who passed a SBT trial were a) poor cough, b) secretion volume of 2.5 mL/hr or more and c) poor mentation as determined by the inability to complete any of the four following tasks on command: open eyes, follow observer with eyes, grasp hand and stick out tongue.[21] In this series reintubation was needed in 12% of patients when one of these predictors was present and 80% when all three were present.

Other reasons for extubation failure are increased work of breathing leading on to respiratory failure, age <24 months, dysgenetic or syndromic condition, chronic

respiratory disorder, chronic neurologic condition and the need to replace the ETT at admission for any reason.[17]

Role of steroids in extubation

The routine administration of corticosteroids is a frequent adjunct to extubation. Though it reduces stridor it has no effect on reintubation. Two well designed trials demonstrated opposite effects on reducing extubation failure.[22, 23]

Use of weaning protocols in children

Protocol based weaning results in faster, earlier weaning with better outcomes in adults.[24,25] Data are limited in children and the results are contradictory in different studies. No advantage over clinical weaning was shown in one prospective study.[12] In a study by Dennis et al a protocol directed weaning by respiratory therapist was found to reduce weaning time and total ventilator cost in pediatric patients.[26] More research is needed to address this issue. However a consistent approach to ventilator weaning is likely to shorten ventilator time and improve outcome. It may be worthwhile to do a once daily SBT if the weaning criteria (Table I) are met.

Relevant pediatric and adult studies of weaning and extubation

Esteban et al[11] conducted a prospective, randomized, multicenter study involving 546 patients who had received mechanical ventilation and who were considered by their physicians to be ready for weaning. One hundred thirty patients had respiratory distress during a two-hour trial of spontaneous breathing. These patients were randomly assigned to undergo one of four weaning techniques: IMV, PSV, intermittent trials of spontaneous breathing conducted two or more times a day if possible or a once-daily trial of spontaneous breathing. They concluded that a once-daily trial of spontaneous breathing led to extubation about three times more quickly than intermittent mandatory ventilation and about twice as quickly as pressure-support ventilation. Multiple daily trials of spontaneous breathing were equally successful.

Farias, et al[15] studied 257 consecutive infants and children who received MV for at least 48 hours and were deemed ready to undergo a breathing trial by their primary physician. They were randomized to undergo a trial of SBT with either PS of 10 cm of water or a T piece. There was no difference between the groups in the percentage of patients who remained extubated for 48 hours (67.2% PS vs. 67.4% T piece).[4, 15]

Chavez, et al[7,27] used a 15-min SBT to determine extubation readiness in pediatric patients. The SBT was performed when the attending intensivist deemed the patient ready for extubation and consisted of providing a continuous flow rate (3 L/min for infants and 10 L/min for older children) via an anesthesia bag adjusted to provide a CPAP of 5 cm H_2O. Of the 70 patients, 64 passed (91%) and, of those, 5 subsequently failed extubation (7.8%) (One reintubation, four required non-invasive ventilation).

Forando, et al[28] randomized 294 eligible children between 28 days and 15 years of age who were receiving mechanical ventilation for at least 24 hours. In the test group (155) the children underwent a daily evaluation to check readiness for weaning with SBT with 10 cm H_2O pressure support and a positive end-expiratory pressure of 5 cm H_2O for 2 hours. In the control group (139), weaning was performed according to standard care procedures. The time to extubation was shorter in the test group, where the median mechanical ventilation duration was 3.5 days as compared to 4.7 days in the control group.

Non-invasive ventilation (NIV) and weaning

Weaning with NIV is being increasingly employed now. In some patients who take a long time to wean but require fairly low ventilator assistance, it is possible to extubate them to NIV. A Cochrane review on non-invasive ventilation (NIV) as a weaning strategy for MV in adults with respiratory failure concluded that NIV reduces rates of death and pneumonia without the risk of weaning failure or reintubation.[29] NIV has been used in children who have failed readiness to extubate trial.[1] They are extubated and put on NIV using a nasal or face mask.

Tracheostomy and weaning

In children who need prolonged ventilatory support tracheostomy is often done to aid weaning. This helps by reducing the upper airway resistance thereby reducing the work of breathing, reducing dead space and improving patient comfort. Interaction with parents improves nutritional status of the child as this facilitates oral feeding.

Points to Remember

- ***The most important criterion for weaning is that the underlying disease process which necessitated MV should have improved.***
- ***Once-a-day SBTs are found to reduce the duration of ventilation.***
- ***Intermittent mandatory ventilation is not recommended for weaning.***

- ***T-piece and pressure support are found to be effective in weaning.***
- ***Upper airway obstruction is the most common cause of extubation failure in children.***
- ***NIV may become the weaning method of choice in future.***

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BOOK REVIEW

Case Scenarios in Pediatric and Adolescent Practice

Editors: Dr.A.Parthsarathy, Dr.Alok Gupta, Dr.Anupama Borker, Dr.Dhanya Dharmapalan

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Pages: 947

This book is yet another contribution of the ever enthusiastic Prof. A.Parthasarthy, to the field of pediatrics. Each chapter is covered by eminent personalities in their respective fields as section editors / contributors / reviewers. This book is prepared in such a way that it covers varied case scenarios ranging from the most common to the rarer disease.

It covers all specialties including surgery as well as common investigations and day to day procedures so that a general pediatrician feels complete going through the book. It is also well supported by clear pictures / photographs to enhance the under standing of the readers. This book will definitely serve as ready resource in day to day practice to any general pediatrician both young and experienced.

Reviewed by: Dr.G.Durai Arasan,
Associate Editor, IJPP, ICH and HC, Senior Assistant Professor of Pediatrics,
Madras Medical College, Chennai

NEWS AND NOTES

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CRITICAL CARE - II

MYOCARDITIS – STRATEGIES TO IMPROVE SURVIVAL

***Meera Ramakrishnan**

Abstract: *The spectrum of presentation of pediatric myocarditis ranges from minor flu-like illness with chest pain to acute cardiogenic shock in a previously healthy child. The management of patients with myocarditis depends on the severity of illness. For patients with milder symptoms who can fall into the category of sub-acute heart failure, the mainstay of therapy is still supportive management with oral anti-failure medications such as angiotensin-converting enzyme inhibitors, beta-blockers and diuretics. In fulminant myocarditis, despite the severe symptoms, chances of spontaneous recovery are very high. This makes aggressive supportive care, including mechanical circulatory support, very rewarding. The role of immunosuppressive/immunomodulation therapy with intravenous gamma-globulin, continues to be controversial. In patients with severe heart failure unresponsive to conservative management with mechanical ventilation, inotropes and rhythm control, extracorporeal support is being used in various parts of the world as treatment prior to spontaneous recovery or as bridge to heart transplantation.*

Keywords: *Myocarditis, Extracorporeal support, Angiotensin-converting enzyme inhibitors (ACE inhibitors), Mechanical ventilation, Heart failure.*

Myocarditis is an inflammatory disease that may be due to infections, toxins or autoimmune causes. It is defined as 'a process characterized by an inflammatory infiltrate of the myocardium, with necrosis or degeneration of adjacent myocytes not due to ischemic damage associated with coronary artery disease'.[1] Infections by bacteria, protozoa and viruses can lead to myocarditis. Due to the variable presentation of the illness the exact contribution by various organisms is unknown. However, data from various autopsies and myocardial biopsies indicate that viruses are the most common cause, at least in the developed nations. With greater usage of non-invasive techniques such as polymerase chain reaction (PCR) and in situ hybridization, there is greater awareness of the causative role of new viruses such as parvo B19 and human herpes 6 apart from the classic enterovirus, adenovirus and influenza virus.[2,3,4,5]

* Head,
Pediatric ICU and ER,
Manipal Hospital,
Bangalore.

Clinical features

The spectrum of illness caused by myocarditis varies widely. In the mildest form, patients may have mild symptoms typical of a viral illness and often recover without specific therapy. Other common presentations include moderate to severe chest pain or new onset of heart failure. Severity of heart failure symptoms may also range from mild, to severe hemodynamic collapse. Most children present with fulminant myocarditis, characterised by severe heart failure symptoms and / or cardiogenic shock requiring treatment with inotropes, vasopressors or mechanical circulatory support. Despite the severity of presentation, with aggressive management there is up to 80% survival rate.[6,7] This article will focus mainly on the methods to improve the survival of the critically ill myocarditis patient.

Management

Management of all critically ill patients starts with the assessment and stabilization of airway, breathing and circulation. Patients with fulminant myocarditis often have features of decreased perfusion to various organs of the body due to cardiogenic shock. These have to be addressed in a systematic manner with focus on correcting the underlying deranged physiology. The failing heart should be appropriately supported until such time that it spontaneously recovers.

Intubation and ventilation

Cardiac output is responsible for delivering oxygen to the tissues. In the process, the heart utilizes oxygen. Even though myocarditis is not an ischemic illness, the heart consumes oxygen that the body can ill afford. Hence the motive of the treating physician should be to reduce the oxygen consumption of all parts of the body as much as possible and divert the spare oxygen to the ailing heart. For example, the respiratory muscles have to work harder

due to pulmonary edema increasing the oxygen consumption. It is best to secure an airway when there is increased work of breathing. It is also wise to intubate a patient with altered sensorium due to poor oxygen delivery to the brain, in situations of impending cardiac arrest and prior to transport to a medical facility with more facilities for aggressive management.

Rapid or modified rapid sequence intubation is used depending on the oxygen saturation of the patient. For example, when the functional residual capacity (FRC) is decreased significantly due to pulmonary edema bag mask ventilation prior to intubation will improve the oxygen reserve of the patient.

Drugs for intubation

All sedatives are myocardial depressants and usage of any of the drug can cause significant hypotension and even cardiac arrest. This is especially true in a person who has no catecholamine stores left. The following protocol is preferred by the author. Fentanyl is the sedative used in doses of 1-2 μg/kg. Fentanyl can decrease cardiac output by causing bradycardia, by reducing the sympathetic drive. Premedication with atropine is done and low dose epinephrine infusion is started. The latter is to avoid sudden cardiac arrest in a patient who is in extremis. Vecuronium is also used in doses of 0.3 mg/kg for neuromuscular blockade. It is a neuromuscular blocker of intermediate duration which in the doses mentioned becomes long acting. It does not cause release of histamine and has very minimal cardiovascular side effects.

Ketamine in low doses can be used along with rocuronium. Etomidate has no cardiovascular side effect and can be safely used if it is clear that the patient does not have septic shock. There are numerous choices of drugs available to the physician for intubation; one has to use the drug with least amount of side effect and what the team is most comfortable with.

Cardiopulmonary interaction

Once the patient is intubated, cardiopulmonary interaction should be optimized to create a balance between the oxygen delivery and oxygen consumption.

As earlier discussed intubation with sedation and paralysis eliminates the work of breathing (WOB). The patient can be cooled down without any risk of shivering in situations of fever. Sedation also abolishes the tachycardia caused by anxiety. All of these will decrease oxygen consumption (VO2) and improve myocardial oxygen delivery.

Intubation and positive pressure ventilation with PEEP reduces venous return (VR) to the heart and decreases pulmonary edema as determined by the Starlings equation. This in turn facilitates gas exchange and improves oxygen delivery (DO_2). Pulmonary vascular pressures are the least at FRC. Adjusting the PEEP to FRC decreases the right ventricular afterload. PVR is further reduced by avoiding hypercarbia and hypoxia. Predominant right heart involvement is not common generally in myocarditis. However when it is present, the prognosis is poor.[8,9,10] The after load of the left ventricle (wall stress) is the product of transmural pressure and the radius of the ventricle (Laplace law).Since the VR is decreased the radius of the LV is smaller. By changing the pericardial pressure from the usual negative value to the positive value offered by PEEP, the after load of the LV is also reduced.Cardiac output is maintained by optimizing the preload, afterload and the contractility of the heart.

Diuretics

The Frank Starlings law states that as the stretch to the myocardium increases the cardiac output increases. However after a certain point the cardiac output plateaus and further increase in preload causes the stroke volume to reduce. The heart is excessively stretched in situations of shock due to myocarditis. Hence after stabilizing the airway one can attempt to reduce the preload of the heart with diuretics. Furosemide, either as a bolus dose or more appropriately as an infusion is used to obtain a gentle diuresis and hence an optimal preload.

Inotropes

In order to increase cardiac contractility inotropes and in situation of hypotension, vasopressors are used. Most inotropes act through β receptor stimulation. β receptor activation has been shown to increase risk of arrhythmias, apoptosis of the myocardial cell and mortality while β blockers reduce mortality in patients with chronic heart failure.[11-16] However in an acute situation inotropes are needed to restore cardiac output and maintain the perfusion to various organs of the body. There are many types of agents available which increase the cellular calcium level and hence increase the contractility. The choice of the agent used depends on its mechanism of action and its side effect. In brief, the agents and their properties are as follows.

Dobutamine is a synthetic catecholamine with potent β2-agonist with less β1agonist properties. It increases myocardial contractility, reduces systemic vascular resistance and reduces pulmonary capillary wedge pressure. However, dobutamine can be much more arrhythmogenic than other catecholamines. Due to its β2 stimulation, care should be taken when used in hypotensive patients.

Milrinone works by increasing cyclic GMP levels by inhibiting phosphodiesterase 3. It increases cardiac index by increasing stroke volume and it decreases systemic vascular resistance and hence the afterload of the failing heart. It can decrease systemic blood pressure and pulmonary capillary wedge pressure. All these properties are very similar to dobutamine. However it has a long half-life of 4-6 hours which prevents close titration that is essential in a critically ill child. Its main advantage is in the fact that it is less proarrhythmic than dobutamine. Both dobutamine and milrinone may be diligently combined with vasopressors such as norepinephrine and dopamine in hypotensive patients.

Levosimendan is a calcium sensitizer that increases the sensitivity of troponin C for Ca^{++} and hence the force and duration of the cardiomyocytes' contraction. Levosimendan, also acts as a vasodilator by opening ATP-sensitive potassium channels in vascular smooth muscle. Thus by lowering the afterload of the left ventricle it may increase the cardiac output and lower myocardial oxygen consumption. The advantage of levosimendan over classical inotropes would be to increase the force of contraction without enhancing the influx of calcium into the cytoplasm thereby controlling the risk of arrhythmias. It has a long half-life of several days and hence is very appropriate in improving hemodynamic in children in end-stage heart failure. It has been shown to be useful in improving hemodynamics for several months of life without mechanical support.[17]

Mechanical circulatory support

In patients with fulminant myocarditis and cardiogenic shock not responding to pharmacologic therapy, intra-aortic balloon counterpulsation (IABP) can be used.

Intra-aortic balloon counterpulsation (IABP)

IABP is the most widely used left ventricular assist device in adults. Getting the appropriate size catheter in children is difficult. The process consists of using a flexible catheter with a balloon of up to 50 cc volume. This is inserted via the femoral artery and the tip is placed 1-2 cm beneath the subclavian artery and above the renal arteries under fluoroscopic guidance. The balloon inflates in diastole and rapidly deflates in systole. Increasing the volume in the aorta during the diastole leads to augmentation of the diastolic blood pressure. This in turn improves the coronary blood flow. The rapid deflation leads to a decrease of 40-50 cc aortic volume leading to the reduction of LV afterload. These mechanisms theoretically improve myocardial oxygen supply while reducing the oxygen requirement by reducing the LV work. Data however does not support its routine use in patients with myocarditis and shock.

Mechanical circulatory assistance

If IABP is not effective in maintaining adequate cardiac output, then extra-corporeal membrane oxygenation (ECMO) or ventricular assist devices (VAD) may be employed.

These may be used in patients with persistence of poor cardiac output as evidenced by low urine output, poor perfusion, hypotension, high CVP and low mixed venous oxygen saturation despite maximal respiratory and pharmacologic support. Patient would need VA ECMO since ventricular function needs to be assisted. For this, most places use carotid and internal jugular cannulation. VA ECMO allows the heart to get appropriate time to recover. It also allows significant reduction in inotrope requirements thereby reducing the risk of arrhythmias. The majority of survivors recover myocardial function within 72 hours of ECMO support, although patients with myocarditis or cardiomyopathy can have good survival rates even after prolonged ECMO support.

Sub-acute management

Once the patient has recovered from the shock, drugs such as angiotensin converting enzyme (ACE) inhibitors, β blockers and aldosterone antagonists are started to reduce inflammation and lessen necrosis and fibrosis. These medications have been shown to improve symptoms, prolong life and regress the adverse left ventricular remodelling in patients with myocarditis who progress to dilated cardiomyopathy.

ACE inhibitors should be initiated at low doses, with upward titration to maximally tolerated doses. Patients should be closely monitored for potential side effects, including renal insufficiency, hyperkalaemia and angioedema. Relative contraindications to the use of ACE inhibitors include renal failure, hyperkalemia, bilateral renal artery stenosis and hepatic failure.

Betablockers - Carvedilol has also been shown to reduce mortality in patients with dilated cardiomyopathy. They are started after the patient is stable on ACE inhibitor. Bronchospastic disease, heart block or significant underlying bradycardias are contraindications to the use of beta blockers.

Digoxin can be considered in patients with significant left ventricular systolic dysfunction who remain ill despite therapy with ACE inhibitors and β blockers. However,

no survival benefit for digoxin has ever been shown in patients with heart failure caused by dilated cardiomyopathy.[18] Contraindications to the use of digoxin include renal failure and heart block.

Aldosterone antagonist spironolactone is also used in the recovery phase of myocarditis. Its use has been shown to reduce progressive fibrosis that often occurs in the remodelling phase. Serum potassium should be monitored at least weekly because of the risk of hyperkalemia with combinations of ACE inhibitors and spironolactone.[19]

Immune modulators

Prednisolone has for most parts not been found to be useful except in occasional patients with rare causes of myocarditis in subsets such as eosinophilicand autoimmune myocarditis and potentially for giant cell myocarditis. Use of intravenous gamma globulin (IVIG) is controversial. Its use has been more on the basis of personal /institutional preference .Several small studies in children have shown its use to be associated with improvement in ventricular function.[20-24] This improvement has however not been consistently found.

The use of other immunosuppressive therapies such as corticosteroids, azathioprine, cyclosporine, anti-lymphocyte antibody (muromonab [OKT3]) and anti-TNF-β antibody is controversial and currently data in children are limited. Patients with myocarditis caused by autoimmune disease will most likely benefit from immunosuppressive therapy.[25]

Conclusion

In conclusion, myocarditis is an inflammatory disease of the heart. In children it is most often due to viral infection. Knowing the exact agent of the illness is unnecessary as the treatment of the virus does not change the outcome. The management of the illness is entirely symptomatic. Survival is very good in children and hence aggressive management including mechanical assistance is appropriate. The use of immune modulators including immunoglobulin is very controversial.

Points to Remember

- ***Fulminant myocarditis has very high mortality.***
- ***Aggressive management has upto 80% chances of survival.***
- ***Inotropes to be used only initially to improve the cardiac output.***
- ***Prolonged β receptor stimulation increases cardiomyocyte apoptosis.***
- ***Mechanical circulatory assistance is useful when the support needed is high.***
- ***In the recovery phase of myocarditis β blockers, spironolactone and ACE inhibitors should be used.***
- ***Use of immunomodulators are controversial.***

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CLIPPINGS

Dosage intervals of amoxicillin for the treatment of acute middle ear infection Updated

Acute otitis media (AOM) is a common problem in children, for which amoxicillin, with or without clavulanate, is frequently prescribed as a treatment of choice. The conventional recommendation is either three or four daily doses. However, nowadays it is frequently prescribed as once or twice daily doses. If once or twice daily amoxicillin, with or without clavulanate, is as effective for acute otitis media as three or four times a day, it may be more convenient to give the medication once or twice a day to children and hence improve compliance.

Objectives: To compare the effectiveness of one or two daily doses with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of AOM in children; and to compare complication rates and adverse reactions.

Selection criteria: We included randomised controlled trials (RCTs) of children aged 12 years or younger with AOM, diagnosed by acute ear pain (otalgia) and inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C).

Authors' conclusions: This review showed that the results of using once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three doses for the treatment of AOM.

Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD004975. DOI: 10.1002/14651858.CD004975.pub3.Assessed as up to date: March 15, 2013.

CRITICAL CARE - II

NOSOCOMIAL INFECTIONS

***Shuba S**
****Rajakumar PS**

Abstract: *An infection acquired in hospital by a patient who was admitted for a reason unrelated to it, is known as nosocomial infection. It is an infection occurring in a patient admitted in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, as well as occupational infections among staff of the facility. It is one of the important causes of mortality and morbidity, increase in duration of stay and cost in the intensive care units. The most common ones are blood stream infections, pneumonia including ventilator-associated pneumonia, urinary tract infections, surgical site infection and gastroenteritis due to Clostridium difficile. The incidence of hospital acquired infections (HAI) can be reduced by following the guidelines for their prevention.*

Keywords: *Nosocomial infection, Hospital-acquired infection, Ventilator-associated pneumonia, Catheter-related blood stream infection.*

A nosocomial infection, also called 'Hospital Acquired Infection' (HAI) can be defined as:

An infection acquired in hospital by a patient who was admitted for a reason other than that infection. It is an infection occurring in a patient admitted in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, as well as also occupational infections among staff of the facility.[1]

It is one of the important causes of mortality and morbidity, increase in duration of stay and cost in the intensive care units. There is a vast difference in incidence of HAI between developing countries and developed countries. The incidence varies between 15.1% and 18.3%.[2,3] A prevalence survey conducted under the auspices of WHO in 55 hospitals of 14 countries representing 4 WHO Regions (Europe, Eastern Mediterranean, Southeast Asia and Western Pacific) showed an average of 8.7% of hospital patients had nosocomial infections.[4] A prospective study from India, showed a crude infection rate of HAI to be 19.3/100 patients among them 187 patients were treated in the PICU for ≥48h.[5]

* Professor of Pediatrics and Pediatric Intensivist

** Associate Professor of Pediatrics and Pediatric Intensivist, Sri Ramachandra Medical College and Research Institute, Porur, Chennai.

Factors influencing the risk of infection

1. Microbiological agent factors: The amount of innoculum, virulence of the organism, antimicrobial resistance. The organism may be bacterial, fungal or viral. It may be a cross infection or endogenous flora.

2. Host factors: Loss of skin integrity (intravascular devices), loss of respiratory defenses as cough, cilia propulsion, intubation, sedation, loss of GI defenses as low pH, dysmotility, use of H_2 blockers, nasogastric tubes, anatomical defects as surgical sites, age, gender and genetic makeup, nutritional status, immunosupression, immunization status, preexisting diseases such as diabetes, malignancy and renal failure.

3. Enviromental factors: Over crowding, high healthcare worker patient ratio, use of prophylactic antibiotics, visitor policy, infection control practices and reservoir of infectious organisms.

Modes of transmission in HAI: Direct physical contact, indirect contact (e.g.,) through contaminated hands, droplets ≥5μm size through sneezing or coughing (e.g., influenza infection) and airborne dissemination of organism by aerosolization (e.g., measles).[6]

The common HAIs are blood stream infections, pneumonia including ventilator associated pneumonia, urinary tract infections, surgical site infection and gastroenteritis due to Clostridium difficile. Various studies from different countries show varying rates of nosocomial infections with blood stream infection (BSI) being the commonest in most, while in others, it is pneumonia.

During 2002-2005, among various ICUs in 8 developing countries the most common nosocomial infection was ventilator-associated pneumonia (41%), followed by central venous catheter (CVC) - related bloodstream infections (30%) and catheter-associated urinary tract infections (29%).[7,8,9] During the same period, though the device utilization was remarkably similar, ICUs in US showed a lower incidence of nosocomial infections than the ICUs of developing countries.[10] In a study in AIIMS of the 44 episodes of HAI, 27 (61%) were healthcare-associated pneumonia (HAP), 12 (27%) were bloodstream infections (HA-BSI) and four (9%) were urinary tract infections.[5]

Most of the organisms which cause HAI are multidrug resistant. The Infectious Diseases Society of America (IDSA) has used the acronym ESKAPE to refer to Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa and Enterobacter species, which are the usual multidrug resistant organisms causing majority of hospital-acquired infections.[11]

Definition of device-associated nosocomial infection

$$\frac{\text{Number of new device associated nosocomial infections in a period x 1000}}{\text{Total device days for the same period}}$$

Hospital-acquired pneumonia

HAP (Hospital-acquired pneumonia) is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. Very little data is available about non-ventilated HAP.

VAP (Ventilator-associated pneumonia) refers to pneumonia that arises more than 48–72 hours after endotracheal intubation. Some patients may require intubation after developing severe HAP and should be managed similar to patients with VAP.

Ventilator-associated pneumonia (VAP)

According to the National nosocomial infections surveillance system (NNIS) of CDC, USA, the incidence of VAP in US PICUs declined from 6 to 2.1 per 1000 ventilator days from 1999 to 2008, although international nosocomial infection control consortium (INICC) international report from 36 countries, showed VAP rates per 1000 ventilator days to be between 8.1 and 46.3, including 30 in India.[12,13]

Definition of pneumonia (CDC definition 2008)

Until recently, VAP was defined by the CDC as 'pneumonia that develops in patients on mechanical ventilation for more than 48 hrs'. CDC revised the guidelines in 2007 to indicate that 'there is no minimum period of time that the ventilator must be in place' to diagnose VAP. Clinical and Lab Criteria have been defined for various age groups (Fig.1). Based on the time of onset of pneumonia, VAP can be further categorized into 'early' (within1-4 days of ventilation) and 'late' (4 days of ventilation).

Symptoms of lower respiratory tract infection other than pneumonia (e.g., bronchitis, tracheobronchitis)

Child with >1 year with no clinical or radiological signs of pneumonia and two or more symptoms or signs (fever> 38°F, cough, new or increased sputum production, rhonchi, wheezing) and one or more positive cultures from deep tracheal aspirate or bronchoscopy or positive antigen test.

Child < 1year with no clinical or radiological evidence of pneumonia and two or more symptoms or signs (fever > 38°F, cough, new or increased sputum production, rhonchi, wheezing, apnoea, bradycardia) and one or more of the following positive cultures from deep tracheal aspirate or bronchoscopy or positive antigen test or serologic diagnosis.

Clinical pulmonary index score (CPIS)

This score was developed by Pugin et al as a means of overcoming the limited sensitivity and specificity of isolation techniques through a combination of six clinical, radiological and microbiological criteria: temperature, white cell count, sputum, oxygenation, culture of tracheal aspirates and radiology. Each criterion is graded from 0 to 2 and a total score of 6 points suggests a diagnosis of VAP.[14] There are no large data regarding CPIS in children, though studies have shown varying sensitivity and specificity; a score of 8 had more sensitivity and specificity.[15,16]

Organisms

In contrast to pneumonia in non-ventilated patients, Gram-negative bacteria predominate in VAP. In the PICU, Pseudomonas aeruginosa is the most common followed closely by the Gram-positive organism, S.aureus. Viral infections can also occur. In 13 children autopsied with clinical diagnosis of VAP, nine had shown the histomorphologic features, suggesting viral inflammation.

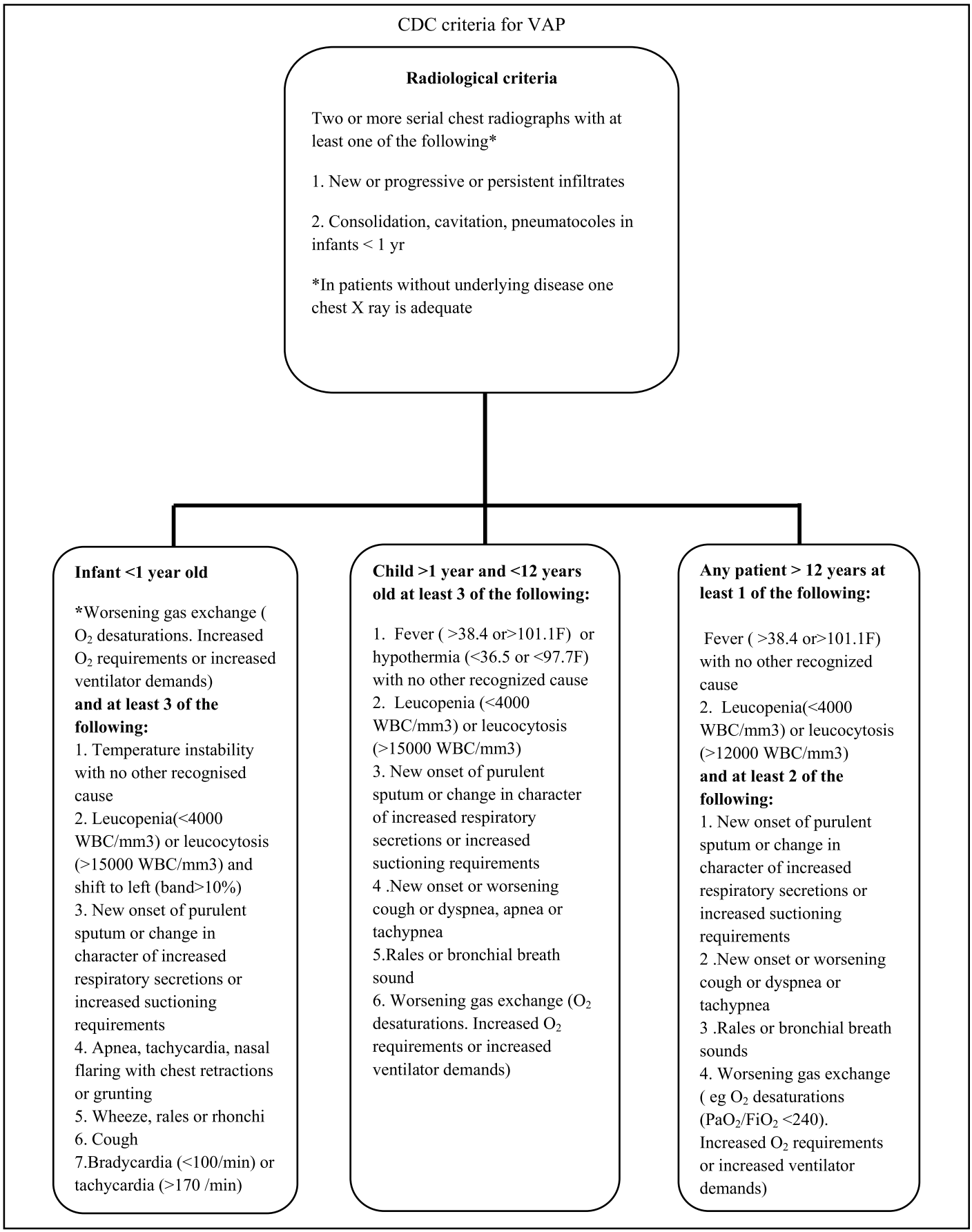

Fig.1. CDC criteria for VAP

The viruses identified in five patients were adenovirus, respiratory syncytial virus and cytomegalovirus.[15,17,18,19,20]

Diagnosis

The different techniques used for obtaining cultures are the following: **Bronchoscopic bronchoalveolar lavage** is the most widely used method because of its ability to obtain specimens closest to the affected tissue while minimizing contamination. **Mini-BAL** is a modification whereby a smaller volume of saline is injected and then aspirated. **Protected specimen brush** is used to obtain secretions instead of saline instillation and aspiration.

Non-bronchoscopic bronchoalveolar lavage (NBBAL) has diagnostic accuracy comparable to BAL and may be more suitable for children. In this method, a double lumen plugged catheter is inserted into the endotracheal tube and advanced blindly until slight resistance is felt. The inner catheter is then extended and the plug expelled. Aliquots of warm sterile saline are injected, and the aspirate is collected through the catheter.

Tracheal aspirate (TA): This involves culturing of secretions obtained through suctioning the endotracheal tube. Though easy to obtain, TA suffers from low specificity as a result of contamination from upper respiratory tract organisms.

Gram Stain: Commonly used Gram stain parameters include: (i) 25 polymorphonuclear leukocytes per high power field, (ii) more than 2% inflammatory cells; (iii) presence of polymorphonuclear leukocyte cells with intracellular organisms (ICO) with criteria for positivity ranging from 2%-10%.[12]

Prevention of VAP

1. General Strategies to prevent VAP

i. Ensure surveillance of VAP Rates.

ii. Educate healthcare personnel.

iii. Perform hand hygiene.

iv. Limit the use of mechanical ventilation.

- Use noninvasive ventilation whenever possible.
- Minimize the duration of ventilation.
- Perform daily assessments of readiness to wean-give sedation holiday and assess

v. Implement a multidimensional approach.

2. Core strategies to prevent VAP

i. Prevent aspiration of secretions

- Maintain patients in a semi-recumbent position. 30-45°
- Avoid gastric overdistention.
- Avoid unplanned extubation and reintubation.
- Use a cuffed endotracheal tube with in-line or subglottic suctioning, to be used when there is prolonged ventilation.
- Maintain an endotracheal cuff pressure of at least 20 cm H_2O.

ii. Prevent colonization of the aerodigestive tract

- Use orotracheal intubation.
- Perform comprehensive oral care. Clean mouth frequently with 0.12% chlorhexidine

iii. Prevent use of contaminated equipment.

- Remove condensate from ventilatory circuits.
- Keep the ventilatory circuit closed during condensate removal.
- Change the ventilatory circuit only when visibly soiled or malfunctioning.
- Store and disinfect respiratory therapy equipment properly.
- Use sterile water to rinse reusable respirator equipment.[13]

Pediatric specific VAP bundle includes hand hygiene, elevation of head, proper position of orogastric and nasogastric tube, elimination of routine instillation of saline before ET suction, changing inline suction only when visibly soiled or malfunctioning, regular oral care, ventilator tubing in dependent position, drainage of ventilator circuit before repositioning patient and drainage of the ventilator circuit condensate every 2–4 hrs.[21]

Approach to treatment of VAP is outlined in Fig.2. Aerosal therapy: Role of aerosolized antibiotics in VAP has not been studied in children though its use in the setting of cystic fibrosis in children is well established.

Blood stream infection

Catheter-associated bloodstream infections (CA-BSIs) are a significant cause of morbidity, mortality, and added medical costs to hospitalized adult and pediatric patients. The incidence varies from 9.2 per 1000 catheter days to 2.4 to 5.3 in USA using CDC NNIS definition.[10]

Nosocomial blood steam infections defined as isolation of the microorganism from the blood stream of the patients

Table I. CDC Definition of CRBSI

Laboratory confirmed
• Recognised pathogen from ≥ 1 blood culture OR
• Common skin contaminant in ≥ 2 blood cultures associated with symptoms (fever, chills, hypotension) ≤ 1 year of age
• Common skin contaminant in ≥ 2 blood cultures AND
• Associated with symptoms (fever,>38°C or <37°C, apnoea, bradycardia), clinical sepsis ≤ 1 year of age
• Fever, >38°C or <37°C, apnea, bradycardia AND
• Negative or no blood culture done
• Physician initiates sepsis treatment
• No primary infection elsewhere

who develop signs of sepsis beyond 48 hours of hospital admission with or without local or systemic symptoms.

Catheter-related bloodstream infection (CRBSI, also called catheter-related sepsis) is defined as the presence of bacteraemia originating from an IV catheter.

Pathogenesis

Immediately after insertion, the surfaces of the CVC become coated with plasma proteins, particularly fibrin. Bacteria migrate from skin along the catheter track and/or from the catheter hubs down the lumen(s) and become embedded in this protein sheath. This process is termed colonization; studies using electron microscopy have shown that this happens within hours of insertion. Endoluminal colonization is also important (Fig.3).

Certain organisms such as staphylococci and Candida secrete a biofilm layer or 'slime' that gives them protection against antimicrobial agents. The presence of adherent thrombus , increases the risk of CRBSI.

CRBSI triggers a systemic inflammatory response, ranging from fever and leucocytosis through to septic shock and multiple organ failure.[22]

Organisms

The predominant organisms responsible for nosocomial infection in the PICU were Klebsiella pneumonia, Staphylococcus aureus and Enterobacter species and yeast species and most are multidrug resistant.[9,23] Some studies have indentified candida[24] or Staphylococcus as the most common organism.[2,7,10]

Diagnosis

Diagnosis of CRBSI is based on the following:

The presence of a CVC, signs of catheter insertion site infection, clinical symptoms and signs of bacteremia, resolution of the symptoms and signs of bacteremia after removal of the suspect CVC, positive blood culture and growth of the same organism from the catheter (Table I).

The 'gold standard' is the combination of a positive blood culture with the same organism isolated from the catheter.

Quantitative blood culture CRBSI is suggested when the number of microbes from a CVC sample of blood is five times that from a simultaneously collected peripheral sample. This is not widely available.

Acridine orange staining of blood taken from the CVC and endoluminal brush sampling shows high sensitivity and specificity but is not widely available.

Differential time to positivity CRBSI is suggested when blood from the CVC demonstrates microbial growth at least 2 hours earlier than growth detected in blood collected simultaneously from a peripheral vein. Most currently used automated blood culture systems can readily provide this information.[22]

CDC Guidelines for prevention of intravascular catheter device infection 2011

Central venous catheters

- Weigh the risks and benefits of placing a central venous device.

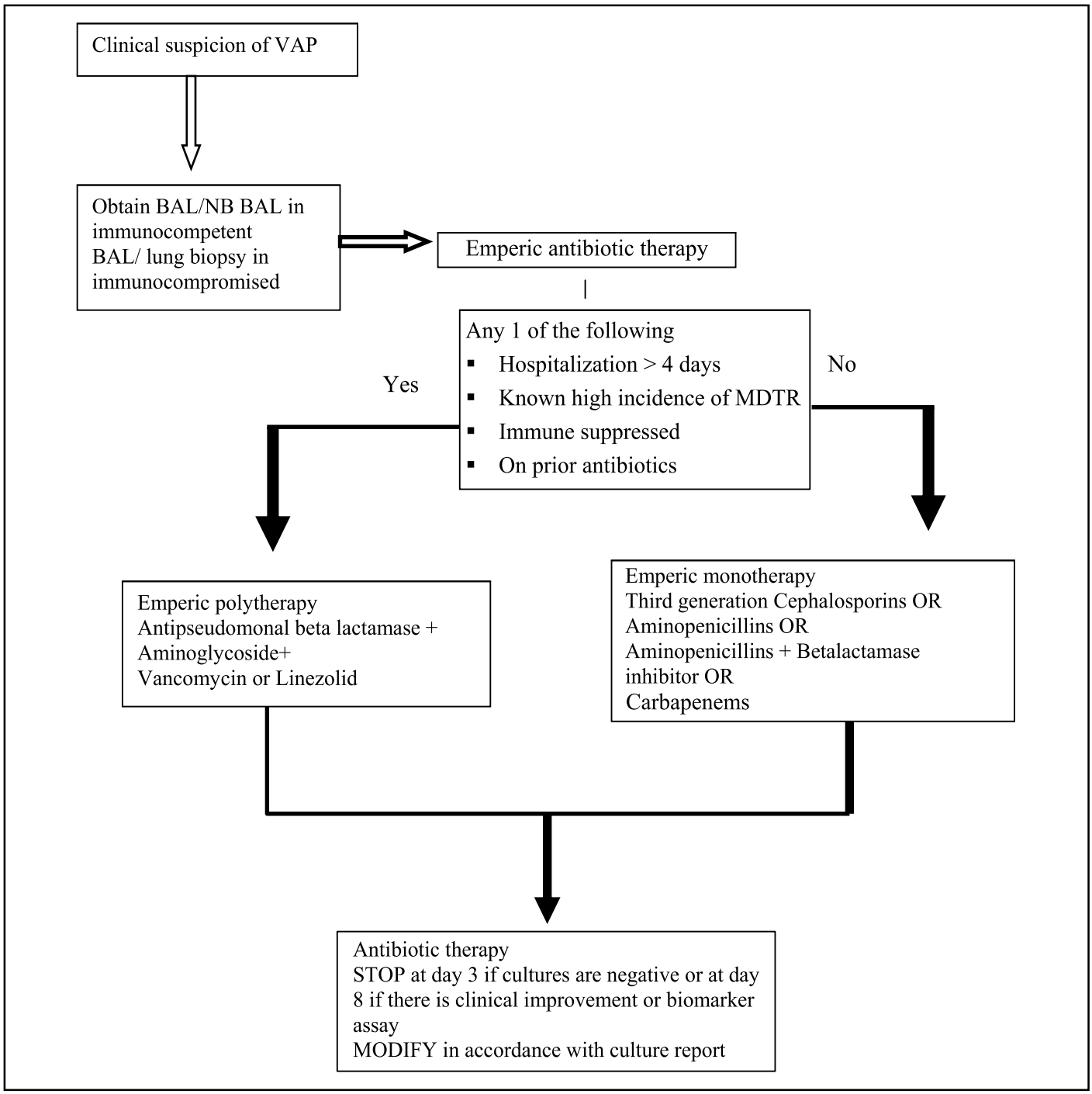

Fig.2. Treatment algorithm for VAP - CDC guidelines

- A subclavian site would be preferred in adult patients to minimize infection risk while pediatric studies including a meta analysis have shown that femoral CVCs are not associated with higher rates of infection as compared with other sites (RR 1.35 CI 0.84–2.19, p = 0.2).[25,26]
- Use ultrasound guidance to place central venous catheters.
- Use a CVC with the minimum number of ports or lumens essential for the management of the patient.
- Promptly remove any intravascular catheter that is no longer essential.
- When adherence to aseptic technique cannot be ensured, as emergency scenario, replace the catheter as soon as possible.

Hand hygiene and aseptic technique

- Perform hand hygiene procedures, and maintain aseptic technique for the insertion and care of intravascular catheters.

Skin preparation

- Clean skin with a >0.5% chlorhexidine preparation with alcohol and allowed to dry before insertion and during dressing changes.

Catheter site dressing regimens

- Use either sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site.
- If the patient is diaphoretic or if the site is bleeding or oozing, use a gauze dressing. Replace catheter site dressing if the dressing becomes damp, loosened, or visibly soiled
- Do not use topical antibiotic ointment or creams on insertion sites.
- Use povidone iodine antiseptic ointment or bacitracin/ gramicidin/polymyxin B ointment only for the hemodialysis catheter.
- Replace dressings used on short-term CVC sites every 2 days for gauze dressings and 7 days in transparent dressings but consider the risk of dislodgment in pediatrics.

Patient cleansing

- Use a 2% chlorhexidine wash for daily skin cleansing to reduce CRBSI.

Catheter securement devices

- Use a sutureless securement device.

Systemic antibiotic prophylaxis

- Do not administer systemic antimicrobial prophylaxis routinely for prevention CRBSI.

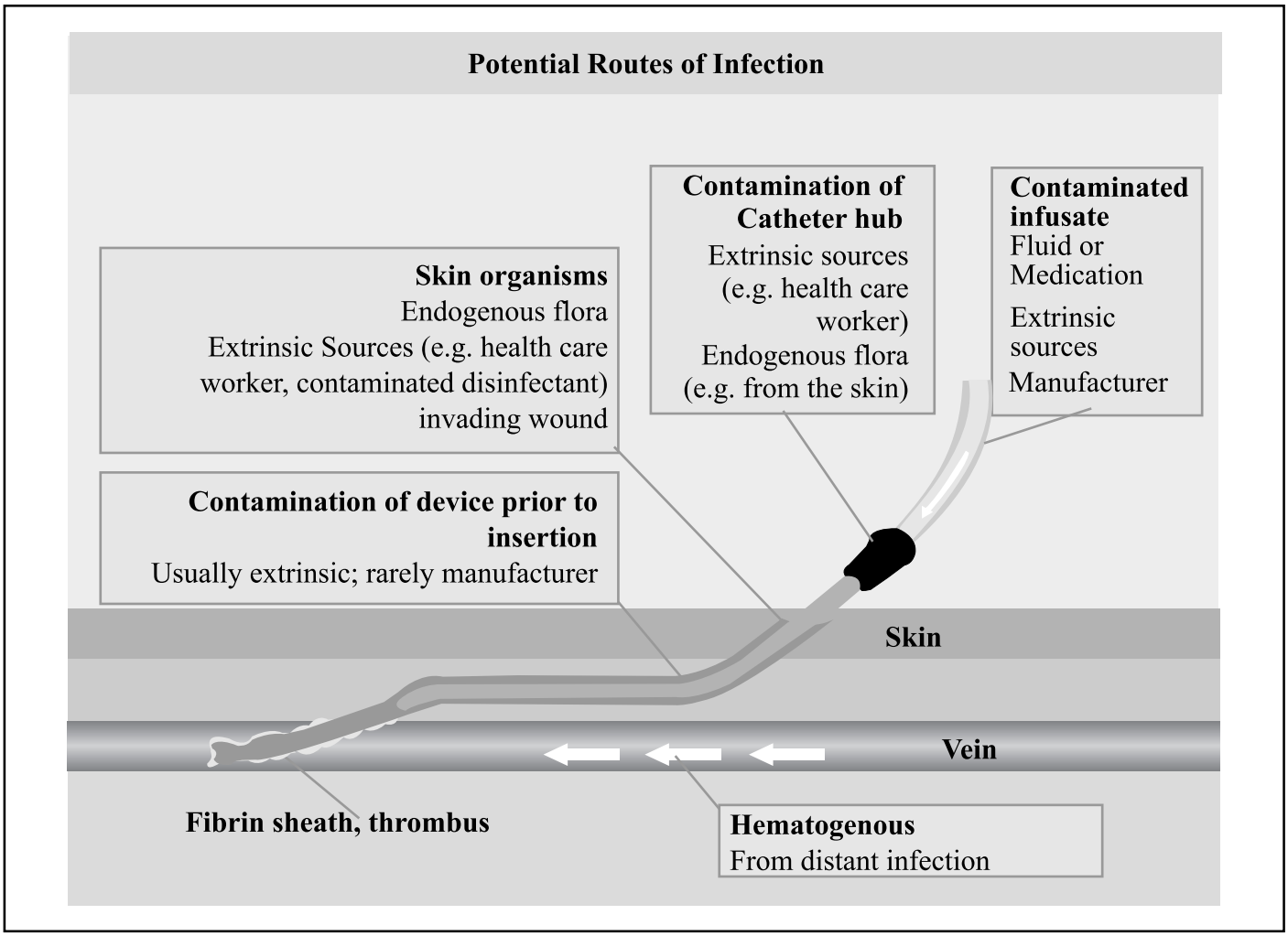

Fig.3. Potential routes of infection

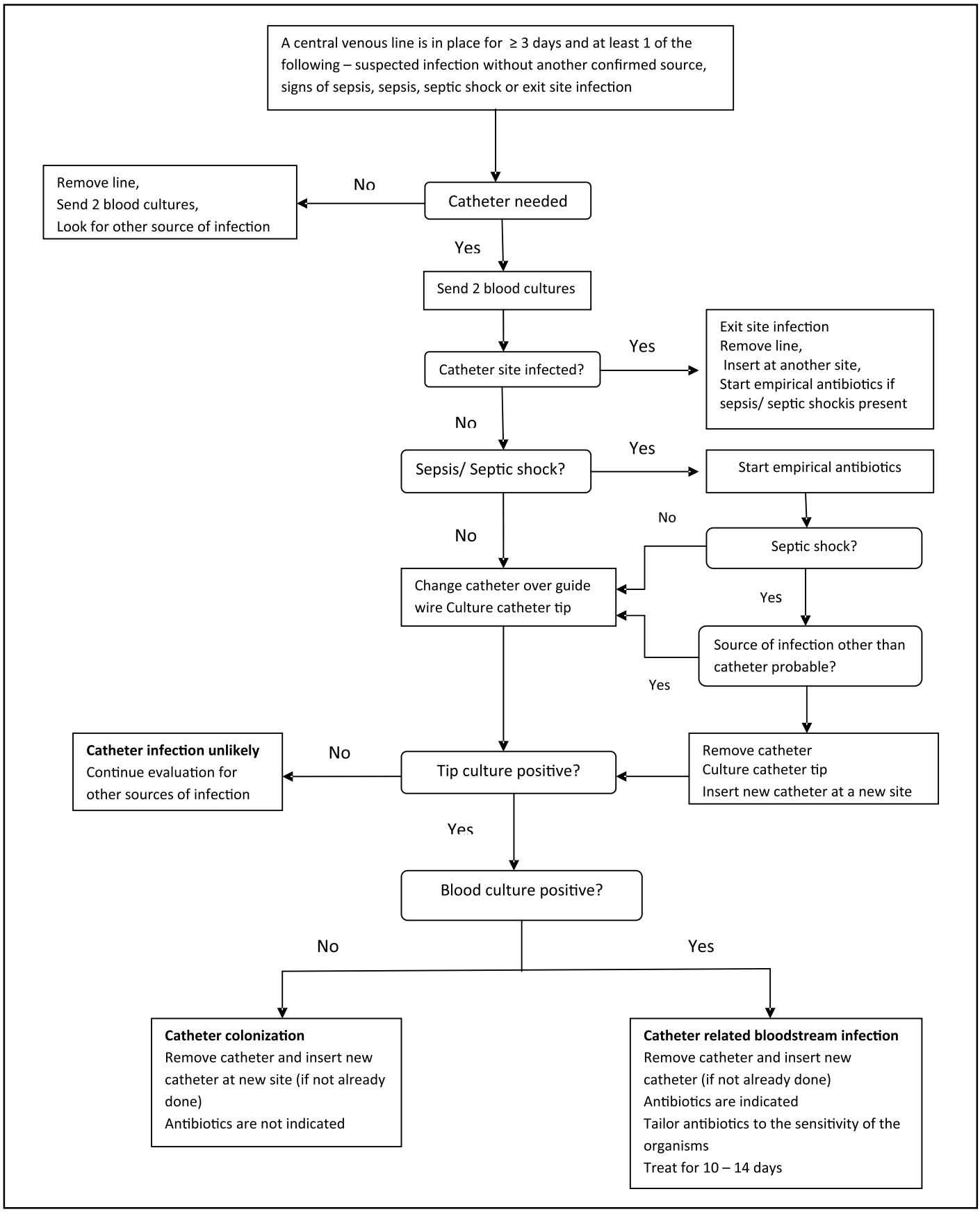

Fig.4. An approach to CRBSI

N Engl J Med 348;12 www.nejm.org march 20, 2003

Table II. CDC Guidlines

Symptomatic	• $\geq 10^5$ microorganisms/mL urine, not >2 species, and symptoms (at least one of the following: fever >38° C, urgency, frequency, dysuria, suprapublic tenderness) • Symptoms (at least two of the following: fever >38° C, urgency, frequency, dysuria, suprapublic tenderness) and at least 1 of 5 urinary laboratory criteria *or* physician diagnosis or treatment for UTI • Patient ≤1 year of age with or without an indwelling urinary catheter has at least 1 of the following signs or symptoms with no other recognized cause: fever (>38°C core), hypothermia (<36°C core), apnea, bradycardia, dysuria, lethargy, or vomiting and at least one of the following findings: • Positive dipstick for leukocyte esterase and/or nitrite, pyuria (urine specimen with ≥10 WBC/mm3 • Microorganisms seen on Gram's stain of unspun urine and • A positive urine culture of between $\geq 10^3$ and $<10^5$ CFU/ml
Asymptomatic	• Indwelling urinary catheter within 7 days before urine culture and • $\geq 10^5$ Microorganisms/mL urine, not >2 species, and • Asymptomatic, or • No indwelling urinary catheter within 7 days of urine culture and • $\geq 10^5$ Microorganisms/mL urine, not >2 species in two urine cultures with same organism(s)

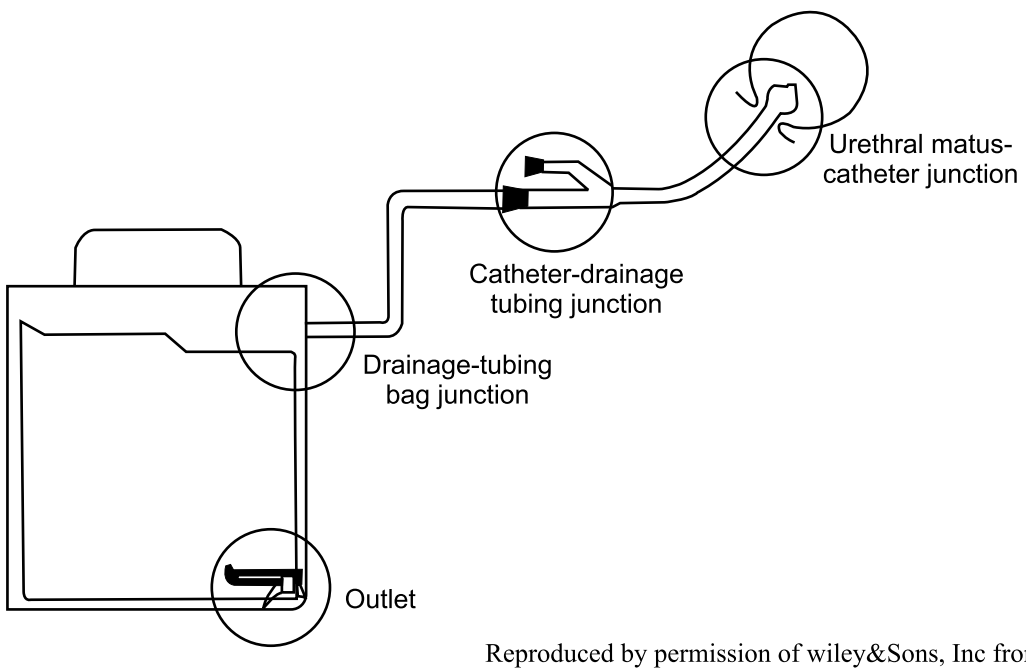

Fig.5. Source of infection for CAUTI

Table III. Surgical site infection (SSI) CDC Guidelines

Superficial incisional, primary or secondary	• Occurs within 30 days of operative procedure and • Involves only skin and subcutaneous tissue of the incision and • At least one of the following: purulent drainage from incision, organisms isolated from aseptically obtained incisional fluid or tissue, one sign or symptom (pain, tenderness, redness, swelling, heat) and • Surgeon opens incision and incision is not cultured or is culture positive
Deep incisional, or secondary	• Occurs within 30 days of operative procedure or within 1 year if an implant is left in place and • Involves deep soft tissues of the incision, and • At least one of the following: purulent drainage from the deep incision but not from the organ/space of the surgical site, spontaneous dehiscence of surgical site or symptomatic patient has site opened by surgeon and incision is not cultured or is culture positive, abscess found on direct examination (radiologic, histopathologic, or during operation), or surgeon diagnosis
Organ space, primary or secondary, indicated specific type (e.g., cardiac)	• Occurs within 30 days of operative procedure or within 1 year if an implant is left in place, and • Infection involves any part of the body, excluding superficial or deep incisional areas, opened or manipulated during the operative procedure, and • Patient has one of the following: purulent drainage via a drain placed into organ/space; organisms cultured from aseptically obtained specimen from organ/space; abscess found on direct examination, during reoperation, or by radiologic or histologic examination or surgeon diagnosis.

Antibiotic lock prophylaxis, antimicrobial catheter flush and catheter lock prophylaxis

- No role

Anticoagulants

- Do not routinely use anticoagulant therapy.

Antimicrobial / antiseptic impregnated catheters and cuffs

- Use a chlorhexidine/silver sulfadiazine or minocycline/rifampin-impregnated CVC in patients whose catheter is expected to remain in place >5 days, however it is expensive.

Education of health personnel

Replacement of CVCs, including PICCs and hemodialysis catheters

- Do not routinely replace CVCs, PICCs, hemodialysis catheters, or remove for fever routinely or exchange over guidewire.

Replacement of administration sets and needleless intravascular catheter systems

- In patients receiving routine fluids there is no need to replace sets before 96-hour intervals, but at least every 7 days and those used to administer blood, blood products, or fat emulsions within 24 hours. Transducers also should be replaced very 96 hours.

In pediatric patients both central line insertion and central line maintenance bundles are important.[27] An approach to CRBSI is given in (Fig.4).

Catheter-associated urinary tract infection (CAUTI) - CAUTI is a common problem in PICU. The common sources of infection are shown in (Fig.5). CDC guidelines for CAUTI are depicted in (Table II).

Organism

Candida (52.1%) and Enterococcus (13%) were most common followed by Escherichia coli (11.6%) and Klebsiella pneumoniae (10.1%). Catheterization and duration of catheterization were the risk factors for nosocomial UTI ($p<0.001$).[9,23,28]

Prevention

1. Insert catheters only for appropriate indications and remove early.
2. Use proper technique for catheter insertion includes hand hygiene before and after any manipulation of the device.
3. Use of the smallest bore catheter is needed with proper securement of the catheter after insertion to prevent movement.
4. The catheter should be maintained as a closed drainage system with unobstructed urine flow.
5. Neither systemic antimicrobials, bladder irrigation with antimicrobials is needed.

Proper catheter care has brought down CAUTI rates from 5.9 to 2.6.[29]

Surgical site infection (SSI)

CDC guidelines of definition of SSI are given in Table III.

Prevention strategies of SSI

Preoperative Measures

- Administer antimicrobial prophylaxis-administer within 1 hour prior to incision.
- Remote infections:
  - Identify and treat before elective operation or postpone operation
- Do not remove hair at the operative site unless necessary-do not use razors. If necessary, remove by clipping or by use of a depilatory agent.

Intraoperative measures

- Operating Room Traffic to be regulated and doors to be kept closed

Postoperative measures

- Surgical Wound Dressing-Protect primary closure incisions with sterile dressing for 24-48 hrs post-op.
- Control blood glucose level during the immediate post-operative period.
- Discontinue antibiotics within 24hrs after surgery end time (48hrs for cardiac surgery).[30]

Points to Remember

- ***The most common nosocomial infections are blood stream infections, pneumonia including VAP, urinary tract infections and surgical site infections.***
- ***In VAP Gram negative organisms and Staph aureus are the main causative organisms.***
- ***VAP is diagnosed based on clinical, radiological and lab findings.***
- ***For prevention of VAP the main strategies are hand hygiene, prevention of aspiration of secretions, prevention of colonization of aerodigestie tract and prevention of use of contaminated equipments.***
- ***Prevention of catheter related blood stream infections involves aseptic insertion, proper catheter safe dressing and periodic education of health care personnel in handling catheters.***

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NEWS AND NOTES

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CRITICAL CARE - II

SNAKEBITE ENVENOMATION IN CHILDREN: CRITICAL CARE ISSUES

***Mahadevan S**
****Ramesh Kumar R**

Abstract: *The highest burden of snake envenomation existed in South Asia, Southeast Asia and Sub-Saharan Africa where >100,000 instances of envenoming occur annually. Among the Southeast Asian countries, India has emerged as the country with the highest mortality with snake envenomation. Snake venom is the most complex of all natural venom and poisons of which, 90% are pharmacologically active peptides and proteins. The composition of the venom is species-specific, i.e., neurotoxins predominate in the venom of elapids, while cytotoxic and anticoagulant D procoagulant substances are most often found in the venom of vipers and colubrids. The amount of venom injected is not related to the size of the snake or the fangs, or the number of strikes.*

Neurotoxic features vary from early morning neuroparalytic syndrome to locked-in syndrome in snake bite. Physicians should recognize the locked-in syndrome (LIS) to prevent the dangerous error of diagnosing brain death. The most common coagulopathy associated with snake envenoming is a procoagulant or consumption coagulopathy. Renal involvement following snake bite envenomation is seen predominantly with the bite of the vipers. Compartment syndrome is rare in children and usually affects upper limb. Aims of first aid treatment include (i) attempt to retard systemic absorption of venom (ii) preserve life and prevent complications (iii) arrange the transport of the patient to a place where he or she can receive medical care and (iv) to do NO HARM. Twenty-minute whole blood clotting time (20WBCT) is a very useful and informative bedside standard test in the management of snake envenomation. Antivenom treatment should be given as soon as it is indicated.

Keywords: *Snake bite, Children, Locked-in syndrome, Snakebite induced coagulopathy, Anti-snake venom.*

Globally, 4,21, 000 envenoming and 20,000 deaths occur each year due to snake bite.[1,2] The highest burden exists in South Asia, Southeast Asia and Sub-Saharan Africa where >1,00,000 envenoming occured annually.[1,2] Among the southeast Asian countries, India has emerged as the country with the highest mortality.[2] More than 330 species of snakes are found in India, of which more than 60 species are venomous snakes – some of which are found in abundance and can cause severe envenoming.[3] Approximately 70% of snake bites are 'dry' bites and do not result in envenomation. A recent snakebite mortality survey in India[3] found that snakebite related deaths occurred more in the rural areas (97%), more common in males (59%) peaked at ages 15–29 years (25%) and during the monsoon months of June to September. This proportion represents about 45,900 annual snakebite deaths nationally or an annual age-standardized rate of 4.1/100,000, with higher rates in rural areas (5.4/100,000).[3] Annual snakebite deaths were greatest in the states of Uttar Pradesh (8,700), Andhra Pradesh (5,200), and Bihar (4,500).[3]

The most important species causing envenomation in India are the spectacled cobra (Naja Naja) and common krait (Bungarus Caeruleus) which are neurotoxic, and the saw scaled viper (Echis carinatus) and Russell's viper (Daboia Russelii), which are hemotoxic,[3] but other species, may cause fatal envenomation in particular areas, such as the Central Asian cobra (Naja Oxiana) in the far north-west, monocellate cobra (N. Kaouthia) in the north-east, greater black krait (B. Niger) in the far northeast, Wall's and Sind krait (B. Walli and B. Sindanus) in the east and west and hump nosed pit-viper (Hypnale Hypnale) on the southwest coast.[3]

In this article evidence based facts of pathophysiology of snake venom and critical care issues of neurological complications (locked-in syndrome), venom-induced consumption coagulopathy (VICC), acute kidney injury (AKI), compartmental syndrome and method of administration of snake anti venom (SAV) are discussed.

* Senior Professor of Pediatrics,
Division Head - Pediatric Critical Care Units,
Dean, JIPMER, Puducherry.

** Assistant Professor,
Pediatric Critical Care Units,
JIPMER - Women and Children Hospital, Puducherry.

Pathophysiology of snake venom

Snake venom is the most complex of all natural venom and poisons.[1,2,4] The venom of any species might contain more than 100 different toxic and non-toxic proteins and peptides, as well as non-protein toxins, carbohydrates, lipids, amines and other small molecules.[4] Of these, 90% are pharmacologically active peptides and proteins, which are responsible for almost all of its biological effects.[1,2] Clinically relevant components of the venom have cytotoxic, hypotensive, neurotoxic, or anticoagulant effects. The composition of the venom is species-specific, i.e., neurotoxins most often predominate in the venom of elapids, while cytotoxic and anticoagulant D procoagulant substances are most often found in the venom of vipers and colubrids.[5] The amount of venom injected to the prey is not related to the size of the snake or the fangs, or the number of strikes. Some venomous snakes fail to inoculate their victims with venom ('dry bites').

Cytotoxic enzymes (phospholipases A2, metalloproteinases) activate pro-inflammatory mechanisms that cause edema, blister formation and local tissue necrosis at the site of a venomous snake bite. These enzymes also favor the release of bradykinin, prostaglandin, cytokines and sympathomimetic amines, which are responsible for the pain experienced by the victims.[6,7] Aminopeptidases modify the physiological function of the victims and peptides of the venom act as angiotensin-converting enzyme inhibitors, causing a drop in arterial blood pressure.[7,8] Safarotoxins and endothelins are potent vasoconstrictors of coronary arteries and may cause myocardial ischemia or cardiac arrhythmias.[7,8]

Neurotoxins are major components of elapids. These toxins do not cross the blood–brain barrier, but cause paralysis by affecting the neuromuscular transmission at either presynaptic or post-synaptic levels. Presynaptic neurotoxins are phospholipase $\alpha 2$ complexes (β-neurotoxins such as taipoxin, paradoxyn, trimucrotoxin, viperotoxin, pseudocerastes, textilotoxin and crotoxin) that inhibit the release of acetylcholine from the presynaptic terminal. Such inhibition may be irreversible as these toxins interfere with the formation of new acetylcholine vesicles.[9] On the other hand, post-synaptic neurotoxins are three-finger protein complexes (α-neurotoxins) that have a curare-like mechanism of action, causing a reversible blockage of acetylcholine receptors.[10,11] The best characterized α-neurotoxins are irditoxin.[5] Some venom contains both α and β-neurotoxins, producing complex blockages of neuromuscular transmission.

Metalloproteinases activate factor X and serine proteases are potent prothrombin activators. In addition, a number of non-enzymatic proteins (snake venom C-type lectins) and some of the three-finger toxins have anticoagulant or procoagulant activity and may be either agonists or antagonists of platelet aggregation.[5] Paradoxically, components of the snake venom may also have immunomodulatory, anti-inflammatory and antitumor effects and are currently under investigation as potential therapeutic agents for human diseases.[12,13] Toxin ('ancrod') a serine protease derived from the venom of the Malayan pit viper has been used for years for therapy of patients with acute ischemic stroke because of its defibrinogenating properties.[14]

Therefore, every patient envenomed by snake bite becomes a natural experiment, providing new insights into the pathophysiological actions of venom toxins, while presenting a therapeutic challenge to treating physician.[1] This experiment is, however, biologically inappropriate since a venom has been evolutionarily selected to subdue prey animals that are much smaller than human beings.[1]

Systemic manifestations

Venom components cause vasodilatation and capillary leakage, which, alone or together with the hypovolemia resulting from acute bleeding, may cause hypotension and shock.[6,15] Acute renal failure may occur in severe envenomation and may be related to hypovolemic shock, consumption coagulopathy, rhabdomyolysis and direct nephrotoxicity causing tubular necrosis.[6,16] Pituitary hemorrhages, causing acute hypopituitarism, may occur after the bite of Russell's vipers, because of the presence of hemorrhagins in their venom.[6] Clinical manifestations due to thrombotic and hemorrhagic complications are common in those bitten by vipers and colubrids. The toxins alter the coagulation system and the function of platelets in different ways, representing the basis for the occurrence of thrombosis and hemorrhages in every site of the body.[6,17]

Neurological complications

Neurotoxic features of snake bite vary from early morning neuroparalytic syndrome to several cranial nerve palsies.[18] Different names described in literature are brain stem suppression reflex, LIS in snake bite, early morning snake bite syndrome and peripheral LIS.[19] And are most often related to the toxic effects of the venom, i.e., anticoagulant D procoagulant activity or neurotoxicity. Either anticoagulant/procoagulant or neurotoxic effects may be seen in the same venom which can lead to more complex and severe neurological damage.[5] Most venom neurotoxins bind to receptors with high affinity, making reversal of

paralysis by anti-venom implausible.[1] However, rapid improvement in neurotoxicity has been noted when postsynaptic toxins were implicated-e.g. after envenoming by Asian cobras.[16] Binding of toxin ±, a three-finger-fold polypeptide (venom of black-necked spitting cobra), to the acetylcholine receptor was reversible by antibodies in vitro and rodents, although this venom is not neurotoxic in man.[16]

The time lag between the bite and onset of paralysis is usually 4-12 hours.[20] The earliest manifestation is ptosis followed by external ophthalmoplegia. Paralysis then progresses to involve muscles of palate, jaw, tongue, larynx, neck, and muscles of deglutition-usually but not strictly in that order.[1, 20] The proximal muscles of the limbs are involved earlier than distal and there can be complete quadriplegia and 'locked-in' state.[1, 20] Recovery starts in the reverse order and the median time of onset for recovery of respiratory failure is 2 days.[20] The initial involvement of levator palpebrae superioris, as in botulism, myasthenia gravis and Graves' disease, might be attributable to the small size, unusual anatomy and physiology and the low safety part of the neuromuscular junctions of this muscle, features shared by all the extraocular muscles.[1] The subsequent pattern of descending paralysis is difficult to explain neurophysiologically.[1, 6]

In LIS, patient is conscious yet unable to communicate and has absent pupillary reflex (internal ophthalmoplegia due to autonomic dysfunction).[18, 20] LIS can be of three types[18, 19]: **a) classic:** in this case patient has quadriplegia and anarthria with preservation of consciousness and vertical eye movements. **b) incomplete LIS:** is similar to classic except remnants of voluntary movement other than vertical eye movement are present. **c) in total LIS:** there is total immobility and inability to communicate, with preserved consciousness. Usual causes of LIS are stroke, trauma or encephalitis of ventral pontine area, but can also be caused by extensive bilateral destruction of corticobulbar and corticospinal tracts in the cerebral peduncles.[19] LIS can also be caused by peripheral causes such as severe Gullain-Barre' syndrome, neuromuscular junction blockade (myasthenia gravis, toxins, snake bite), etc.[19] Duration of LIS varies from 30 hours to six days.[18] The common krait is a nocturnally active snake with painless bite and hence many patients with neurological manifestations present to the emergency room without history of snake bite.[18]

LIS in snake bite occurs due to neuromuscular paralysis of voluntary muscles which in turn is caused by neuromuscular transmission blockade (krait venom acts pre-synaptically while cobra venom acts post-synaptically).[1, 18] Irreversible binding of the toxin to presynaptic portion makes clinical recovery slow in krait envenomation as recovery occurs only with the formation of new neuromuscular junctions.[1, 18] Physicians should recognize the LIS, so as to prevent the dangerous error of diagnosing brain-death. The occurrence of both internal and external ophthalmoplegia, which would mimic brain death in many ways, thus prompting an intensivist to consider withdrawing ventilator support, would be disastrous.[21] Supportive care needs to be continued until the effects of the venom wear off with excellent outcomes. The diagnosis of brain-death includes documentation of coma, lack of brain-stem reflexes and apnea in the absence of conditions that mimic brain death like severe electrolyte and acid-base disturbances, drug intoxication and neuromuscular blocking agents.[22] In fact, confirmatory tests like cerebral angiography, electroencephalography, etc. are considered in situations like LIS, where a misdiagnosis of brain death is possible.[20]

Snakebite induced coagulopathy: disseminated intravascular coagulation (DIC) or venom-induced consumption coagulopathy (VICC)

The most common coagulopathy associated with snake envenoming is a procoagulant or consumption coagulopathy.[23] The diagnostic features of DIC are problematic for snakebite because an elevated D-dimer, prolonged prothrombin time, and low fibrinogen are features of VICC that are always present, and thrombocytopenia is often associated with VICC, as well. Patients with VICC may have no other systemic manifestations of illness and appear asymptomatic.[23, 24] The course of VICC differs from DIC with the rapid onset of the coagulopathy within hours of the snakebite and resolution over 24 to 48 hours. VICC can either resolve spontaneously or after antivenom therapy over 24 to 48 hours.[23, 24]

The pathogenesis of initiation of coagulation activation in VICC differs from DIC.[23] In DIC, the activation of the coagulation system leading to thrombin generation is mediated by the tissue factor/factor VIIa pathway, which is not balanced by anticoagulant system due to impairment in the major anticoagulant pathways. In addition, there may be impairment of the fibrin removal due to depression of the fibrinolytic system. This series of events does not occur in VICC. In contrast, the initiation of coagulation activation in VICC is usually due to the action of a snake procoagulant toxin at one point in the coagulation pathway and not via the tissue factor/factor VIIa pathway.[24] Depending on which part of the pathway the toxin acts, the resultant coagulopathy can range from mild, with thrombin-like-enzymes (vipers) that cause a partial or complete consumption of fibrinogen alone, to more severe coagulopathy, seen with prothrombin activators (elapids), factor X activators (Russell's viper)

that cause severe deficiencies of fibrinogen, factor V, factor VIII and activation of factor X respectively.[25]

A significant difference between VICC and DIC is that, in VICC, there is no obvious fibrin deposition, microvascular thrombotic obstruction and resultant end-organ damage or organ failure. VICC is usually only complicated by bleeding, whereas DIC is characterized by both end-organ failures resulting from microvascular thrombi as well as bleeding complications. Metalloproteinase prothrombin activators activate the coagulopathy pathway and simultaneously cause injury to the blood vessel integrity, increasing the risk of bleeding. This differs from DIC where there is no such injury to vessel walls.[23]

Current consensus diagnostic criteria for DIC when applied to VICC often produce a score of 5 and therefore suggest overt DIC.[26, 27] VICC presents possibly a unique clinical syndrome that will often meet the currently accepted diagnostic criteria for DIC, but is clearly different based on the current understanding of the pathophysiology of conditions, the time course and the prognosis. This is the reason that it has been believed for so long that snakebite can cause DIC. However, it is also why it is important that the term VICC is used to clarify the clinical syndrome.[23]

Coagulopathy is usually a direct effect of toxins in the venom. It follows that the removal of those toxins, using antivenom, should allow the return to normal homeostasis. Of course, antivenom cannot repair injuries caused by the coagulopathy, such as critical organ damage, nor can it 'switch off' secondary phenomena activated during the coagulopathy, such as hyperfibrinolysis.[17] It is, therefore, necessary to give the correct antivenom as early as possible, once coagulopathy is detected, in sufficient amounts, and be prepared to give supplementary doses if required. Equally, it is important to avoid giving other therapies that may exacerbate the coagulopathic process like heparin, warfarin, FFP and cryoprecipitate.[17] In snakebite coagulopathy, such treatments are generally ineffective and may be potentially dangerous. Heparin will not 'switch off' the pathologic VICC, and hence will not help, but yet may induce its own degree of pathologic changes to clotting, thus making worsening the situation. The addition of FFP or cryoprecipitate may only add fuel to the venom-stoked fire, especially with procoagulant unless all venom has been removed.[17, 23]

Snake bite induced thrombotic microangiopathy (TMA)

In a proportion of patients with VICC, a clinical syndrome consistent with thrombotic microangiopathy has been reported and is characterized by acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia.[23, 24, 28] The etiology of TMA associated with snake envenoming remains unclear and even a good definition is currently unavailable. This thrombotic microangiopathy appears to occur only in conjunction with VICC in several different snakes including vipers and elapids. Consistent with thrombotic microangiopathy, it progresses despite the resolution of the coagulopathy, suggesting a different but related process.[23, 24] The existence of the overlapping clinical syndromes of VICC and thrombotic microangiopathy in snake envenoming is the likely cause for the mistaken idea that snakebite causes DIC.[23]

The treatment of TMA associated with snake envenoming is controversial. In most patients, TMA associated with snake envenoming resolved with supportive care, and in many cases it is not recognized as such.[23]

Acute kidney injury

Renal involvement following snake bite envenomation has been reported with many snake species, but the most severe of these, i.e. acute renal failure, is seen predominantly with the bite of the vipers. In India, this is usually seen with the bite of Russell's viper and the saw-scaled viper bites that are the most widespread viper species in India.[29] The frequency of snake bite as a cause of acute renal failure has been variably reported as 1.2% in Thailand, 3% - 32% in India and as high as 40% in Myanmar.[29-31] Snake venom can cause cellular injury through enzymes, polypeptide toxins, cytokines and mediators. Snakes that cause renal failure are either myotoxic or hemotoxic snakes causing rhabdomyolysis, intravascular hemolysis, disseminated intravascular coagulation (DIC) or hemorrhage.[31]

Renal failure occurs a few hours to several hours after the bite, with a rapid rise of blood urea nitrogen and serum creatinine. Non-oliguric renal failure is not uncommon and averages two to three weeks in duration. The renal histology mainly consists of acute tubular necrosis (ATN) (73%) and acute interstitial nephritis (AIN) (5-15%), while glomerular changes are rare.[29, 31] Degeneration, necrosis and regeneration of tubular epithelial cells have been seen in bite by either hematotoxic or myotoxic snakes (metalloproteases and phospholipase A2), in addition to interstitial edema and cellular infiltration, which consist of lymphocytes, plasma cells and mononuclear phagocytic cells.[29, 31, 32] Immunologic mechanism plays a minor role in the pathogenesis of AKI.[32] However, diffuse AIN out of proportion to tubular degeneration has been rarely seen in Russell's viper bite.[30, 31] Although many factors can contribute to the development of AIN, snake venom has

been postulated to directly result in the development of the interstitial inflammation via various cytokines, mediators and adhesion molecules.[29, 31]

Nevertheless, the role of direct nephrotoxicity of snake venom is still not clear, but hypersensitivity to venomous or antivenom protein has been occasionally found to cause acute renal failure.[31] The contribution of the anti-venom to the development of the AIN needs to be determined as there is no significant data to implicate this relationship. The histological finding of AIN correlated with poor prognosis for chronic kidney disease (CKD).[29]

Delay to administer an adequate dose of anti-venom increases the risk for developing acute renal failure more than 2 times and presence of cellulitis, and bite during the winter, low platelet count, bleeding, intravascular hemolysis and hypotension at presentation are independently associated with risk of AKI and dialysis requirement.[29,30] Management of snake bite induced AKI primarily involves supportive care along with timely administration of antivenom. Hence, anti-venom should be available in health centers and emergency services of small communities, rather than being concentrated in tertiary care hospitals.

Compartment syndrome

Envenomation of a limb can lead to cutaneous necrosis, compartment syndrome and even necrotizing fasciitis.[33] Compartment syndrome in snake bite is a rare phenomenon particularly in children and it usually affects upper limbs.[33,34] In fact, the same amount of venom affects children more severely than adults because of the reduced total dilution volume in children.[34] The principal local effect of venom is edema which occurs within 2 hours after a bite and intensifies during the following 3 days.[33] Swelling and vasoconstriction lead to ischemia and compromise the vitality of the limb. Consider compartment syndrome if any of the following are noted (6 Ps): **P**ain on passive stretching, **P**ain out of proportion, **P**ulselessness, **P**allor, **P**aresthesia and **P**aralysis. However, detection of arterial pulses by palpation or Doppler ultrasound probes, does not exclude intracompartmental ischemia. The most reliable test is to measure intracompartmental pressure directly through a cannula introduced into the compartment and connected to a pressure transducer or manometer. McQueen and Court-Brow consider that a difference of 30 mm Hg between diastolic and compartment pressure is the threshold of fasciotomy.[35] Early treatment with antivenom remains the best way of preventing irreversible muscle damage.

Management of snake envenomation

The following steps or stages are often involved in the management of snake envenomation: (i) First aid treatment (ii) Transport to hospital (iii) Rapid clinical assessment and resuscitation (iv) Detailed clinical assessment and species diagnosis (v) Diagnosis and investigations/laboratory tests (vi) Antivenom treatment (vii) Observing the response to antivenom (viii) Decision about further dose(s) of antivenom (ix) Supportive care (x) Treatment of the bitten part (xi) Rehabilitation (xii) Treatment of chronic complications.[36] Treatment in the field consists of safe identification of the species of snake whenever possible and rapid transport of the patient to the nearest health care facility.[37]

First aid treatment

Aims of first aid treatment include attempt to retard the systemic absorption of the venom and preserve life and prevent the complications before the patient can receive medical care, safe transport and to do **NO HARM**. The priorities for treatment of people bitten by snakes are transport to medical care as quickly as possible irrespective of nature of bite and symptoms.[1,37] First-aid treatment is carried out immediately and can be performed by the snake-bite victim or by anyone else who is present and able.

In most tropical developing countries, traditional methods are employed. These methods include: tying tourniquets making local incisions or punctures ('tattooing') at the site of the bite attempts to suck the venom out of the wound, use of (black) snake stones, electric shock, topical instillation or application of chemicals, herbs or ice packs. Traditional treatment delays presentation, distorts the clinical picture, and can cause bleeding, infection, gangrene and other complications.[1]

Tying tight bands (tourniquets) around the limb remains the main first aid method adopted by victims.[37] Tourniquets expose the victim to the risk of ischemic damage, potentially increase the necrotic action of the venom, present dangers of neurotoxic blockage and clotting when the tourniquet is released and are ineffective in retarding venom flow.[37] In light of these problems the pressure immobilization method (PIM) was developed in Australia in the late 1970's.[37]

Pressure Immobilization Method (PIM): Bitten limb should be bandaged and immobilized with a splint in the same way as for a sprain.[38] Obstruction of lymphatic and venous drainage delays systemic absorption of large molecular weight neurotoxins without the use of tight tourniquets, which are dangerous.[38] However, the clinical efficacy of these methods has not been adequately investigated.[38] Walking for more than 10 minutes, even if the bandage was applied, invalidated the effect of the bandage.[39]

In view of limitations both tourniquets and PIM are rejected for use in India by 'Pediatric Management of snakebite: The National Protocol'.[37] The first aid treatment is based around the mnemonic: **'Do it R.I.G.H.T.'** as recommended by National Protocol.[37] It consists of: **R.** = **R**eassure the patient. Seventy per cent of all snakebites are from non-venomous species. Only 50% of bites by venomous species actually envenomate the patient. **I.** = **I**mmobilize in the same way as a fractured limb. Children can be carried. Use bandages or cloth to hold the splints, but not to block the blood supply or apply pressure. Do not apply any compression in the form of tight ligatures, they do not work and can be dangerous!. **G.H**. = **G**et to **H**ospital immediately. Traditional remedies have NO PROVEN benefit in treating snakebite. **T.** = Tell the doctor of any systemic symptoms such as ptosis that manifest on the way to hospital. Ideally, tight bands, bandages and ligatures if applied, should not be released until the patient is under medical care in hospital, resuscitation facilities are available and antivenom treatment has been started.

Analysing the efficacy of the other methods : The early use of antivenom, rapid transport of patients to hospitals in rural areas by volunteer motorcyclists and education of paramedics and ambulance crews about how to resuscitate patients during transport to hospital - are in progress.[38]

Identification of envenoming snake species

Identification of the species on the basis of descriptions provided or recognition from pictures or inspection of skilled snakes is often unreliable. A useful method is to distinguish clinical syndromes of envenoming by analysis of a series of reliably identified bites (Fig.1.).[40,41] Indirect confirmation is possible by immunological detection of toxin antigens in the victim's blood or tissue fluids.[1] A limitation of the use of immunoassays is that venom antigens differ in their immunogenicity.

Diagnosis and testing

Bite marks to determine whether the biting species was venomous or non-venomous are of no use. Many venomous species are in possession of more than one set of fangs and non-venomous species can leave just two punctures from enlarged teeth, which can appear to be fang-like.[37] The diagnosis of snake envenomation should be based on one or more of the following features: history of snake bite, presence of fang marks, presence of local manifestations, such as pain and swelling at the site of the bite, or systemic manifestations, such as spontaneous bleeding or features of neurotoxicity and/or whether the dead snake was brought in for identification.[36]

20-minute whole blood clotting test (20WBCT)

It is very useful and informative bedside standard test for coagulopathy in the management of snake envenomation.[37] It is simple to carry out but crucially requires a clean, new and dry test tube. A 2 mL of fresh venous blood is left undisturbed for 20 minutes, and then gently tilted once. If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenemia ("incoagulable blood") as a result of venom-induced consumption coagulopathy. In India, incoagulable blood is diagnostic of a viper bite and rules out an elapid bite. If the vessel used for the test is not made of ordinary glass, or if it has been cleaned with detergent, its wall may not stimulate clotting of the blood sample (surface activation of factor XI - Hageman factor) and test will be invalid. If there is any doubt, repeat the test in duplicate, including a "control" (blood from a healthy person such as a relative).

Other tests

Hematological abnormalities: A transient increase of hemoglobin (Hb) indicates hemoconcentration resulting from a generalized increase in capillary permeability (e.g. in Russell's viper bite). More often, there is a decrease in Hb reflecting blood loss or, in the case of Indian and Sri Lankan Russell's viper bite, intravascular hemolysis. Decreased platelet count may be seen in the victims of envenoming by vipers and Australasian elapids. An early neutrophil leukocytosis is evidence of systemic envenoming from any species. On blood film, fragmented red cells ('helmet cell', schistocytes) are seen when there is microangiopathic hemolysis. Plasma/serum may be pinkish or brownish if there is gross haemoglobinemia or myoglobinemia.

Biochemical abnormalities: Aminotransferases and muscle enzymes (creatine kinase, aldolase etc.) will be elevated if there is severe local muscle damage or, particularly, if there is generalized muscle damage (sea snake, Sri Lankan and South Indian Russell's viper bites). Mild hepatic dysfunction is reflected in slight increases in other serum enzymes. Bilirubin is elevated following massive extravasation of blood. Potassium, creatinine, urea or blood urea nitrogen levels are raised in the renal failure of Russell's viper, hump-nosed viper bites and sea snake bite. Early hyperkalemia may be seen following extensive rhabdomyolysis in sea snake-bites. Bicarbonate will be low in metabolic acidosis (e.g. renal failure).

Snake antivenom (SAV)

Antivenom is the only specific antidote to snake venom. A most important decision in the management of a snake-

bite victim is whether or not to administer antivenom. First introduced by Albert Calmette at the Institute Pasteur in Saigon in the 1890s for the treatment of envenoming, SAV was quickly accepted without formal clinical trials.[1] Antivenom is immunoglobulin [usually pepsin-refined F(ab')2 fragment of whole IgG] purified from the plasma of a horse, mule or donkey (equine) or sheep (ovine) that has been immunized with the venoms of one or more species of snake. 'Specific' antivenom, implies that the antivenom has been raised against the venom of the snake of the same species that has bitten the patient and that it can therefore be expected to contain specific antibody that will neutralize that particular venom and perhaps the venoms of closely related species (paraspecific neutralization). Monovalent antivenom neutralizes the venom of only one species of snake. Polyvalent (polyspecific) antivenom neutralizes the venoms of several different species of snakes, usually the most important species, from a medical point of view, in a particular geographical area. In India, SAV (Serum Institute of India, Pune) is a polyvalent venom which contains antisera against Naja naja, Bungarus caerulus, Vipera russeli and Echis carinatus. It is available in both liquid and lyophilized form.

SAV administration criteria

Antivenom treatment should be given as soon as it is indicated. SAV should be given only to patients in whom its benefits are considered likely to exceed its risks. Since antivenom is relatively costly and often in limited supply, it should not be used indiscriminately.[42] The prophylactic use

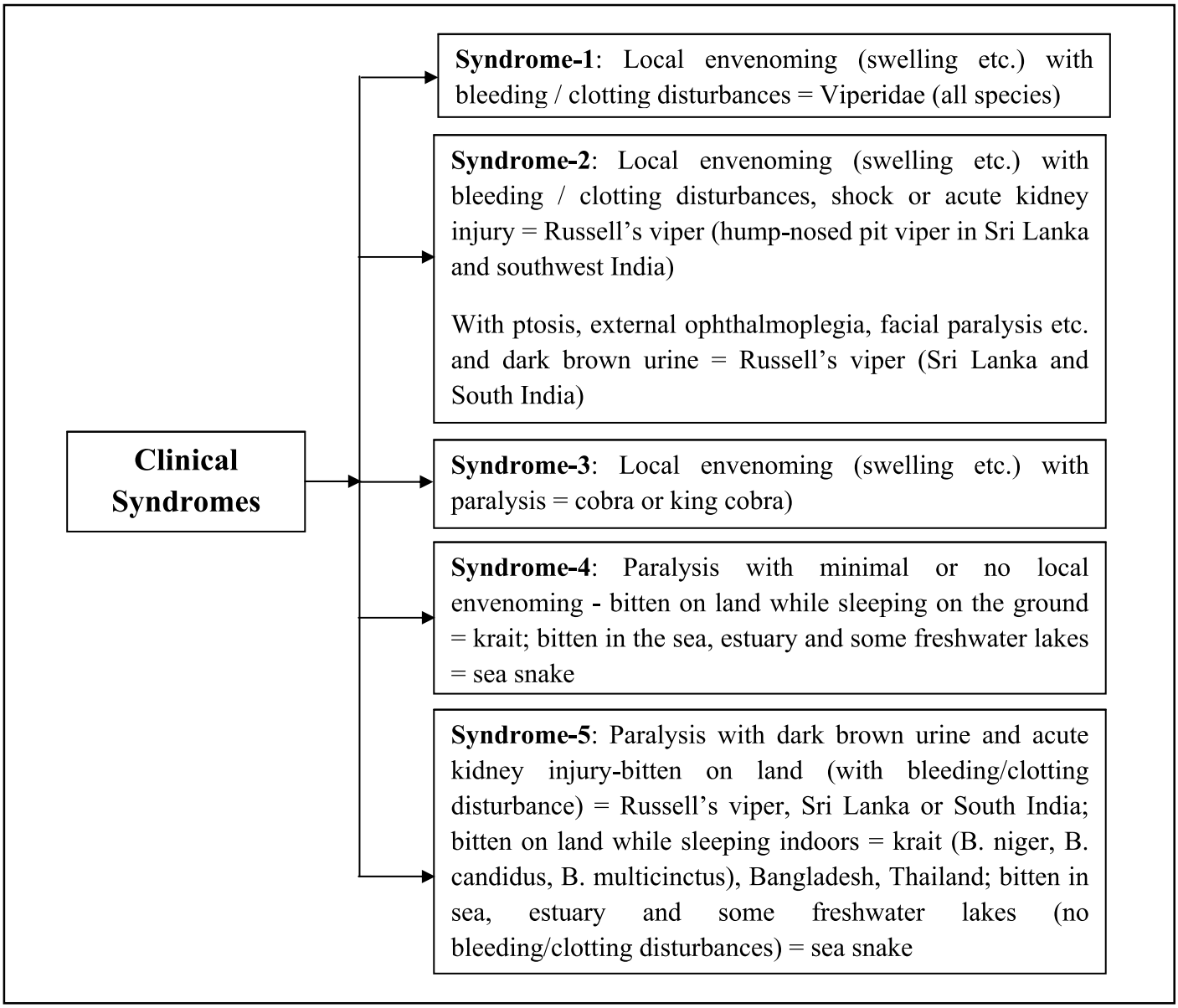

Fig.1. Clinical syndrome approach

of SAV should be avoided due to inherent risk of hypersensitivity reaction. Symptomology is no help as a means of determining severity of envenomation as it is too dynamic and constantly evolving.[37] Essentially systemic envenomation will be evident from the 20WBCT, signs of spontaneous bleeding or by visual recognition of neurological impairment such as ptosis.[37] Severe local symptoms are defined as swelling rapidly crossing a joint or involving half the bitten limb, in the absence of a tourniquet. Once the tourniquet has been removed for more than one hour, if the swelling rapidly continues, this should be viewed as venom generated and not due to the continuing effect of the tourniquet. Isolated local swelling is not grounds for administering SAV. [37] Antivenom may reverse systemic envenoming even when this has persisted for several days or, in the case of hemostatic abnormalities, for two or more weeks. Therefore, it is appropriate to give antivenom for as long as evidence of the coagulopathy persists. Whether antivenom can prevent local necrosis remains controversial, but there is some clinical evidence that, to be effective in this situation, it must be administered within the first few hours after the bite.[43]

SAV doses and administration

The initial dose of ASV to be given to a patient has been the subject of much debate. Published data has indicated that Russell's Viper injects on average 63 ± 7 mg of venom in the first bite.[44] Hence, the initial dose should be calculated to neutralize the average dose of venom injected. This ensures that the majority of victims should be covered by the initial dose and keeps the cost of SAV to acceptable levels.[37, 42] As each vial of polyvalent SAV neutralizes 6 mg of Russell's viper venom, the initial dose is 8-10 vials for both adults and children.[37] A maximum ASV dose is around 25 vials because range of venom injected was shown to be between 5 mg- and 147 mg.[37] There is no good evidence to suggest children should receive either more SAV because of body mass or less in order to avoid adverse reactions.

Reconstituted SAV is diluted in 5 to 10 mL/kg bodyweight of NS or 5% dextrose or RL and should be administered over one hour at constant rate with hemodynamic monitoring because slow (over 120 minutes) or rapid (over 20 minutes) infusion would not reduce the rate of severe systemic hypersensitivity reactions.[45] There is no benefit in administering each dose over longer periods and indeed lengthening the period before the SAV is able to neutralize the venom is counter intuitive.[37]

Adverse reactions to SAV

Adverse reactions, either anaphylactic or pyrogenic, have often been identified as reasons not to administer SAV in smaller local hospitals/dispensary. The fear of these potentially life threatening reactions has caused reluctance amongst some doctors to treat snakebite. However, if handled early and with the primary drug of choice, these reactions are easily surmountable and should not restrict doctors from treating snakebite. Early intervention against this kind of reactions has been shown to have more positive outcomes.[46] Patients should be monitored closely as there is evidence that many anaphylactic reactions go unnoticed.[47]

SAV should be discontinued and adrenaline 0.01 mg/kg body weight IM should be given if any of following signs appeared: urticaria, itching, fever, shaking chills, nausea, vomiting, diarrhea, abdominal cramps, tachycardia, hypotension, bronchospasm and angio-edema.[37] In addition, 0.2 mg/kg of antihistamine IV and 2mg/kg of hydrocortisone IV are given to provide longer term protection against anaphylactic reactions. A proportion of patients, usually more than 10%, develop a reaction either early (within a few hours) or late (five days or more) after being given antivenom.[45] Recent systematic review and meta-analysis found substantial beneficial effect of adrenaline premedication, but a marginal benefit with the combination of antihistamines and corticosteroids premedication used against early adverse reaction.[48] Once the patient has recovered, the SAV can be restarted slowly for 10-15 minutes, keeping the patient under close observation. Then the normal drip rate should be resumed. SAV test doses have been abandoned. They have no predictive value in anaphylactic or late serum reactions and may pre-sensitize the patient to the protein.[37] Inappropriate use of antivenom should be strongly discouraged as they expose patients who may not need treatment to the risks of antivenom reactions and they also waste valuable and scarce stocks of antivenom.[42] To retain their full potency within the limits of stated expiry dates, lyophilized antivenom (shelf life about 5 years) should be stored at below 25ºC and liquid antivenom (shelf life 2-3 years) should be stored at 2-8 ºC and not frozen.

Trial of anticholinesterase

Anticholinesterase drugs have a variable, but potentially very useful effect in patients with neurotoxic envenoming, especially those bitten by cobras.[49] A trial of anticholinesterase (eg 'Tensilon test') should be performed in every patient with neurotoxic envenoming, as it would be in any patient with suspected myasthenia gravis. However, this should not delay antivenom treatment or endotracheal intubation. Patients must be observed closely as they may deteriorate while the trial of anticholinesterase is being carried out.

Atropine sulphate or glycopyrronium is given by intravenous injection followed by neostigmine bromide by intramuscular injection 0.04 mg/kg. Short acting edrophonium chloride (Tensilon) is ideal for this test but is rarely available in this region. It is given by slow intravenous injection in dose of 0.25mg/kg. The patient is observed over the next 30-60 minutes (neostigmine) or 10-20 minutes (edrophonium) for signs of improved neuromuscular transmission. Ptosis may disappear and ventilator capacity (peak flow, FEV-1 or maximum expiratory pressure) may improve. Patients who respond convincingly can be maintained on neostigmine methylsulphate, 0.01-0.04 mg/kg every 2-4 hours for 24 hours by intramuscular, intravenous or subcutaneous injection together with atropine to block muscarinic side effects.

Repeat doses of SAV

In anti-hemostatic bites, once the initial dose has been administered over one hour, no further SAV is given for 6 hours.[37] This reflects the period the liver requires to restore clotting factors.[41] Repeat dose SAV is considered if persistence or recurrence of blood incoagulability after 6 hours or of bleeding after 1-2 hours and deteriorating neurotoxic or cardiovascular signs after 1-2 hours. In the case of neurotoxic bites, once the first dose has been administered and a Neostigmine test given, the victim is closely monitored. If after 1-2 hours the victim has not improved or has worsened then a second and final dose should be given. At this point the victim would have received sufficient neutralizing capacity from the SAV and will either recover or require mechanical ventilation; in either event further SAV will achieve nothing.[37]

Supportive care

Antivenom treatment can be expected to neutralize free circulating venom, prevent progression of envenoming and allow recovery. However, these processes take time and the severely envenomed patient may require life support systems such as treatment of shock, assisted ventilation and dialysis until the severely damaged organs and tissues have had time to recover.

Conclusion

First aid treatment must avoid compression and emphasize immobilization and rapid transport to hospital. Physicians should recognize the 'locked-in' syndrome to prevent the dangerous error of diagnosing brain-death. The most common coagulopathy associated with snake envenoming is a procoagulant or consumption coagulopathy. Good evidence based research will further refine and develop protocols in the future.

Points to Remember

- ***Among the Southeast Asian countries, India has the highest mortality due to snake envenomation and approximately 70% of snake bites are 'dry' bites and do not result in envenomation.***
- ***Clinically relevant components of the snake venom have cytotoxic, hypotensive, neurotoxic, or anticoagulant effects.***
- ***The amount of venom injected is not related to the size of the snake or the fangs, or the number of strikes.***
- ***Physicians should be aware and recognize the 'locked-in' syndrome, so as to prevent the dangerous error of diagnosing brain-death.***
- ***A significant difference between VICC and DIC is that, in VICC, there is no obvious fibrin deposition, microvascular thrombotic obstruction, and resultant end-organ damage or organ failure.***
- ***It is important to avoid giving therapies that may exacerbate the coagulopathic process like heparin, warfarin, FFP and cryoprecipitate.***
- ***Thrombotic microangiopathy associated with snake envenoming can be resolved with supportive care, and in many cases it is not recognized as such.***
- ***The priorities for treatment of people bitten by snakes are transport to medical care as quickly as possible irrespective of nature of bite and symptoms.***
- ***Unless a bite by a neurotoxic elapid can be excluded, the bitten limb should be bandaged and immobilized with a splint (pressure immobilization) or a pressure pad.***
- ***20-minute whole blood clotting test (20WBCT) is very useful and informative bedside standard test for coagulopathy in the management of snake envenomation.***
- ***Antivenom treatment should be given as soon as it is indicated and should be administered over one hour at constant rate with hemodynamic monitoring.***
- ***Antivenom is relatively costly and often in limited supply, it should not be used indiscriminately.***

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CLIPPINGS

Patient-reported quality of life outcomes for children with serious congenital heart defects

To compare patient-reported, health-related quality of life (QoL) for children with serious congenital heart defects (CHDs) and unaffected classmates and to investigate the demographic and clinical factors influencing QoL, a retrospective cohort study by UK National Health Service. UK-wide cohort of children with serious CHDs aged 10–14 years requiring cardiac intervention in the first year of life in one of 17 UK pediatric cardiac surgical centers operating during 1992–1995. A comparison group of classmates of similar age and sex was recruited. Authors concluded that Children with serious CHDs experience lower QoL than unaffected classmates. This appears related to the burden of clinical intervention rather than underlying cardiac diagnosis. Participation in sports activities is positively associated with increased emotional well-being. Child self-report measures of QoL would be a valuable addition to clinical outcome audit in this age group

Knowles RL, Day T, Wade A, Bul l C, Wren C, Dezateux C (UKCSCHD). Patient-reported quality of life outcomes for children with serious congenital heart defects. Arch Dis Child 2014;99:413-419 doi:10.1136/archdischild-2013-305130.

CRITICAL CARE - II

DERMATOLOGICAL EMERGENCIES IN CHILDREN

Anjul Dayal

Abstract: *Emergencies in dermatology are well recognized and are associated with significant morbidity and mortality. Early recognition of these conditions with institution of prompt medical care can help in reducing the associated morbidity and mortality. This article reviews relevant dermatologic emergencies with emphasis on current trends in management.*

Keywords: *Stevens-Johnson syndrome, Pemphigus, Staphylococcal scalded skin syndrome, Toxic epidermal necrolysis.*

Dermatological emergencies

Although skin is the largest organ of the body, somehow skin diseases are often neglected. Dermatological emergencies in children are not uncommon and sometimes require treatment at tertiary level intensive care unit which may lead to mortality or debilitating morbidity. It is imperative that these disorders are recognized at the earliest and managed adequately to avoid negative consequences.[1] As skin is the first protective barrier for entry of pathogenic micro-organisms, loss of skin makes children prone to secondary infections and also substantial fluid loss which may go unnoticed. In this article we review in brief, some of the common and potentially fatal dermatological emergencies. The disorders described here are not in the order of fatality or occurrence and detailed pathogenesis and treatment is outside the preview of this article.

Staphylococcal scalded skin syndrome[2]

Staphylococcal scalded skin syndrome (SSSS) is a spectrum of superficial blistering skin disorders caused by exfoliative toxin produced by the infecting Staphylococcus species. It differs from the more severe toxic epidermal necrolysis (TEN) as the cleavage site in SSSS is intraepidermal, as opposed to TEN, which involves necrosis of the full epidermal layer. Also in SSSS, the mucous membranes are spared whereas in TEN, the mucous membranes (mouth, conjunctiva, trachea, esophagus, anus, vagina) are almost always affected.

Children are more at risk because of lack of immunity and immature renal clearance capability (exfoliative toxins are excreted by kidneys). A biopsy of the affected area will demonstrate separation of the epidermis at the granular layer. An inflammatory cell infiltrate is typically not present. In TEN, an inflammatory (lymphocytic) infiltrate is present and the plane of separation is deeper, at the level of the basement membrane. With prompt diagnosis and therapy, death rarely occurs; the stratum corneum is quickly replaced, and healing usually occurs within 5 to 7 days after start of treatment. Penicillinase-resistant antistaphylococcal antibiotics by IV must be started immediately. Nafcillin 12.5 to 25 mg/kg IV q 6 h for neonates > 2 kg and 25 to 50 mg/kg for older children is given until improvement is noted, followed by oral cloxacillin 12.5 mg/kg q 6 h (for infants and children weighing <20 kg) and 250 to 500mg q 6 h (for older children). Vancomycin should be considered in areas with a high prevalence of methicillin-resistant S. aureus or in patients failing to respond to initial therapy. Clindamycin may also be used to inhibit bacterial ribosomal production of exotoxin.

Fluid rehydration and hemodynamic stability is the mainstay of the treatment. If disease is widespread and lesions are weeping, the skin should be treated as for burns. A strict watch should be kept for input and output of the child to manage adequacy of fluids and to avoid both under perfusion and over hydration.

Another key PICU management is to monitor and treat electrolyte imbalance. A close watch for the onset of severe sepsis or multiorgan involvement should be done and the child should be preferably treated at the centre with the facility of hemodynamic monitoring and respiratory care.

Steroids are not indicated and may worsen the immune function. Non-steroidal anti-inflammatory agents and other agents that potentially reduce renal function should be avoided.

* Consultant Pediatric Intensivist,
Continental Children's Center,
Continental Hospitals,
Hyderabad.

Complications of staphylococcal scalded skin syndrome may include the following: dehydration, shock, hypothermia, generalized bacteremia and/or sepsis and local or remote spread of infection.[3] This entity can lead to scarring, disability and death.

Clostridial myonecrosis[4]

Clostridial myonecrosis (i.e., gas gangrene) is a destructive infectious process of muscle associated with infection of the skin and soft tissues. It is caused by the anaerobic, gas-forming bacilli of the Clostridium species. This organism produces collagenases and proteases that cause widespread tissue destruction and produces a toxin, which is associated with the high mortality.

The skin initially exhibits tense edema, but its pale appearance progresses to a magenta hue. Hemorrhagic bullae and a thin, watery, foul smelling discharge are common. A gram stain examination of wound discharge reveals abundant Gram-positive rods with a paucity of leukocytes.

Gas in the wound is a relatively late finding and by the time crepitation is observed, the patient may be near death. Approximately 15% of blood cultures are positive, but this is also a late finding.

The mortality rate for gas gangrene is as high as 60%. It is highest in cases involving the abdominal wall and lowest in those affecting the extremities. Among the signs that prognosticate a poor outcome are leukopenia, thrombocytopenia, hemolysis and severe renal failure. Myoglobinuria is common and can contribute significantly to worsening renal function. Frank hemorrhage may also be present and indicates disseminated intravascular coagulation.

The child with clostridium myonecrosis needs an urgent surgical evaluation. Surgery can range from a small area of debridement and fasciotomy to limb amputation or bowel resection .Hyperbaric oxygen and systemic antibiotics are important adjuncts.

The treatment of choice is high-dose penicillin G. Clindamycin (dose: 10mg/kg, 6–8 hourly duration) is usually added because of its ability to suppress toxin production. Cephalosporins should not be used alone for prophylaxis or treatment of known clostridial infections. Cardiovascular collapse mandates careful monitoring of intravenous fluid resuscitation, which may require large volumes. Adjunctive therapies for treating clostridial infections include G-CSF, granulocyte transfusions and IVIg. IVIg has been used successfully in settings of pediatric septic shock and multiple organ failure.

Necrotizing fasciitis[5]

This is an aggressive soft tissue infection involving the fascia with extensive undermining and tracking along anatomic planes. Cellulitis is a frequent occurrence and progressive necrosis to subcutaneous tissue results from thrombosis of the perforating vessels.

Necrotizing fasciitis can be caused by organisms such as beta hemolytic streptococci, staphylococci (MRSA), Vibrio vulnificus or Aeromonas hydrophila, or a combination of a variety of organisms, including aerobic streptococci, staphylococci and coliforms, as well as anaerobic Peptostreptococcus and Bacteroides. 90% of these infections have a polymicrobial cause.

If an open wound exists, probing the edges with a blunt instrument permits ready dissection of the superficial fascia well beyond the wound margins and this is the most important diagnostic feature of necrotizing fasciitis.

As with other gangrenous soft tissue infections, the most important component of the treatment plan is aggressive, total debridement and parenteral antibiotics. Limited or staged debridement has no place in the treatment of this very aggressive, life-threatening infection.

Antibiotic therapy is a key consideration. Possible regimens include a combination of penicillin G and an aminoglycoside, as well as clindamycin (to cover streptococci, staphylococci, gram-negative bacilli and anaerobes). Every effort should be made to quickly identify the offending organisms and antibiotic therapy should be changed accordingly. Misdiagnosis and delay in diagnosis are common and associated with significant morbidity and mortality.

These children are at a very high risk of developing septic shock and multiorgan dysfunction syndrome. They usually require cardiac support (vasoactive agents), respiratory support (ventilation), renal support (renal replacement therapy) and invasive hemodynamic monitoring and should be treated preferably at ICU setting.

Purpura fulminans[6]

Purpura fulminans is a aggressive disorder characterized by intravascular thrombosis and hemorrhagic infarction of the skin that is rapidly progressive and is usually associated with vascular collapse and disseminated intravascular coagulation.

There are 3 forms of this disease classified by the triggering mechanisms:

- Neonatal purpura fulminas
- Idiopathic purpura fulminans
- Acute infectious purpura fulminans

Neonatal purpura fulminans

This form of disease is associated with a hereditary deficiency of the natural anticoagulants protein C and S as well as antithrombin III (ATIII).

Idiopathic purpura fulminans

This type follows a bacterial or viral illness after a variable latent period. Deficiency of protein S is considered to be central to the pathogenesis of this disorder.

Acute infectious purpura fulminans

This is the most common form which occurs with a bacterial infection. Here there is an imbalance between anticoagulant and procoagulant endothelial cell activity which is usually caused by bacterial endotoxin.

The bacterial infections usually implicated in this disorder are meningococcus, varicella, Gram-negative bacilli, staphylococci, Rickettsia species, streptococci and measles.

Clinical presentation and treatment

Neonatal purpura fulminans

Within the first three days of birth, a neonate develops purpuric lesions over many different skin sites, including the perineal region, the flexor surface of the thighs and abdominal skin.

Severe forms (associated with complete deficiency of protein C) are characterized by a sudden onset of widespread purpuric lesions that progress to gangrenous necrosis and are associated with disseminated intravascular coagulation.

Apart from the initial supportive measures, platelet concentrate and fresh frozen plasma transfusion must be started. The debridement of the dead tissue is mandatory. These should be subsequently replaced by low molecular weight heparin and later on oral anticoagulation with warfarin must be started.

The protein C, protein S and ATIII genes must be analyzed in the patient and parents.

Idiopathic purpura fulminans

Idiopathic purpura fulminans usually follows viral or bacterial infection with rapidly progressing purpura that may lead to skin necrosis, gangrene of the limbs or digits and major organ dysfunction.

Lesions begin as erythematous macules that progress within hours to sharply defined areas of purpura. Critically impaired circulation to skin and lower limbs may develop within a few hours. The disease usually begins 7-10 days after the onset of the precipitating infection.

Acute management consists of antibiotic treatment, volume resuscitation and ventilatory and inotropic support. Protein C replacement is given rarely.

It is important to recognize compartment syndrome early in patients with tense limbs and distal ischemia, where an early fasciotomy may save the limb.

Acute infectious purpura fulminans

This is usually associated with and complicates sepsis or septic shock (i.e., sepsis-associated fulminans).

The four primary features of this syndrome are large purpuric skin lesions, fever, hypotension, and disseminated intravascular coagulation. This disease is usually associated with either meningococcemia or staphylococcal toxic shock syndrome.

The treatment has to be aggressive with fluids, ventilation and inotropic support, blood products and broad spectrum antibiotics, including anti MRSA antibiotic. IVIG has been used as the disorder is mediated by strong antigens.

There are few reported cases of early administration of activated protein C concentrates which has shown to minimize purpura skin injury and to reduce the inflammatory cascade before irreparable tissue injury occurs.[7,8]

Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN)[9]

SJS and TEN are the two very severe and potentially fatal drug hypersensitivity reactions characterized by extensive denudation of skin or mucosal epithelium.

Although both are the part of same spectrum of disease, there are some differentiating points: SJS has less than 10% body surface area (BSA) with epidermal detachment and two or more mucosal surfaces involved; SJS/TEN overlap has 10% to 30% BSA with detachment and mucosal surfaces typically involved; and TEN has more than 30% detachment and mucosal surfaces are usually involved.

SJS is characterized by an erythema multiforme-like eruption of the skin of variable severity and extensive

mucosal erosions of at least two sites (lips or oral tissue, ocular tissue and genital mucosa). TEN has a skin eruption characterized by dusky red plaques which results in denudation of large area of skin. Epidermal detachment can be elicited by placing lateral pressure on a dusky plaque (Nikolsky's sign).

Both start with initial flu-like prodrome followed by various degrees of fever, lymphadenopathy, systemic toxicity with dehydration, leukocytosis, proteinuria and microscopic hematuria.

A causal drug can usually be identified. The eruption follows drug exposure by 1 week to 2 months (Table I).

Although the drugs are the main offenders there are other factors that can induce these reactions (Table II).

Biopsy may reveal necrolysis and interface dermatitis and can help to rule out SSSS. Biopsy of perilesional, non-involved skin for direct immune fluorescence can help to rule out autoimmune bullous disease.

Supportive care is the mainstay of treatment of SJS or TEN. If systemic illness is significant or if the BSA involved exceeds 10% to 20%, the patient should be cared for in an intensive care unit or burn unit setting as far as possible.

In the absence of a proven effective specific agent, the success in treating SJS and TEN is highly dependent on supportive care. Since SJS and TEN can deteriorate rapidly, intensive care unit or burn centre care is recommended. Fluid loss and electrolyte imbalance should be closely monitored and corrected. Fluid with 0.45% NaCl supplemented with 20 mEq of KCl per litre should be given to maintain a normal urine output. Appropriate early and aggressive replacement therapy is required in case of hyponatraemia, hypokalaemia or hypophosphataemia which occur quite frequently. Essential supportive care includes thermoregulatory equipment, monitoring and replacement of fluid and electrolytes as indicated.

A controlled-pressure thermoregulated bed is very helpful. Appropriate antibiotic treatment is suggested only for secondary bacterial infection.

Pain control and nutritional support are imperative. Lines should be placed through non-involved skin and changed every 3 days if possible.

Multiple studies have shown good results with IVIG which if used should be started early to halt progression.

Randomized controlled studies have not been performed in the treatment of TEN because it is rare and associated with a high rate of mortality. There are multiple, open-label, prospective studies, retrospective case series, and case reports in evidence of support of IVIG in the treatment of SJS/TEN.

When compared to reports that have demonstrated efficacy of IVIG in treatment of SJS/TEN, reports showing minimal or no benefit of IVIG treatment may have had poorer outcomes due to the low dose of IVIG used and longer time gap from onset of disease to the use of IVIG.

Table I. Drugs commonly associated with SJS and TEN

- Sulfonamide antibiotics (trimethoprim sulfamethoxazole)
- Aminopenicillins
- NSAIDs
- Cephalosporins
- Corticosteroids
- Acetaminophen
- Carbamazepine
- Phenobarbital
- Valproic acid
- Quinolones
- Allopurinol

Table II. Etiology of Stevens-Johnson syndrome

- Drugs
- Bacterial infections
- Mycobacterial and mycoplasma infections
- Fungal infections (e.g., histoplasmosis, coccidioidomycosis)
- Viral infections
- Radiation therapy
- Inflammatory bowel disease
- Vaccines

Pemphigus vulgaris[10]

It is a group of autoimmune blistering diseases of the skin and is characterized by intraepidermal blisters and presence of circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes.

This can be induced by drugs such as penicillamine, captopril, cephalosporin, pyrazolones and NSAIDs.

The primary lesion of pemphigus vulgaris is a flaccid blister filled with clear fluid that arises on healthy skin. The blisters are fragile; therefore, intact blisters may be sparse. The contents soon become turbid, or the blisters rupture, producing painful erosions, which is the most common skin presentation.

The mucous membrane most often affected is the oral cavity. Erosions may be seen on any part of the oral cavity and can also spread to involve the larynx, where the patient is often unable to eat or drink adequately because the erosions cause much discomfort.

Other mucosal surfaces may be involved, including the conjunctiva, esophagus, labia, vagina, cervix, vulva, penis, urethra, nasal mucosa and anus.

Nikolsky sign:a firm sliding pressure with a finger separates normal-appearing epidermis, producing an erosion. This sign is not specific for pemphigus vulgaris and is found in other active blistering diseases.

To establish a diagnosis of pemphigus vulgaris, the following tests can be done:

1) Histopathology from the edge of a blister which demonstrates an intradermal blister. The earliest changes consist of intercellular edema with loss of intercellular attachments in the basal layer.

2) Direct immunofluorescence (DIF) on normal-appearing perilesional skin: demonstrates deposits of antibodies (IgG1 & IgG4) on the surface of the keratinocytes. The best location for DIF testing is on normal perilesional skin.

3) Indirect immunofluorescence (IDIF) using serum which demonstrates the presence of circulating IgG autoantibodies that binds to epidermis. The titer of circulating antibody correlates with disease course.

The aim of treatment is to decrease blister formation, promote healing of blisters and erosions and determine the minimal dose of medication necessary to control the disease process. Corticosteroids have been the main stay of treatment. The initial dose of prednisolone is 1 mg/kg/day. Most patients obtain remission within 4 to 12 weeks. The dosage is maintained for 6 to 10 weeks and then decreased by 10 to 20 mg every 2 to 4 weeks.

If prednisolone fails to induce a remission, or if the patient develops serious adverse effects, adjuvant immunosuppressive drugs should be considered early in the course of the disease.

The most commonly used steroid-sparing immunosuppressive drugs are azathioprine, mycophenolate mofetil, cyclophosphamide and rituximab.[11]

Intravenous immunoglobulin therapy has been suggested as efficacious in pemphigus vulgaris treatment. Plasmapheresis is used in refractory cases.

Photodynamic therapy has been suggested as a possible adjunctive treatment for recalcitrant ulceration. Epidermal growth factor may speed healing of localized lesions.

Conclusions

Skin disorder resulting in emergencies might often be missed especially if not associated with other signs of systemic illness. Hence, it is important to closely examine the child brought with the skin manifestation and early recognition of the conditions which may lead to significant morbidity and mortality. Treating these disorders requires a good team approach at a medical facility with easy access to intensive care and isolation if required.

Points to Remember

- ***In dermatological emergencies, there are very few diagnostic laboratory tests.***
- ***Diagnosis, treatment, and management are based heavily on clinical assessment and clinical judgment.***
- ***A case-based approach will decrease the morbidity and mortality in children.***
- ***Most often these emergencies require a multi-disciplinary approach.***
- ***As the child may very rapidly deteriorate, it is essential that a child with severe skin problem should be treated at pediatric tertiary care facility.***

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CLIPPINGS

Lipid-lowering agents for nephrotic syndrome

Nephrotic syndrome is the collective name given to a group of symptoms that include proteinuria, lipiduria, hypoalbuminaemia, oedema, hypercholesterolaemia, elevated triglycerides and hyperlipidaemia. Hyperlipidaemia is thought to aggravate glomerulosclerosis (hardening of blood vessels in the kidneys) and enhance progression of glomerular disease. Studies have established that reduction in total cholesterol and low density lipoprotein (LDL) cholesterol is associated with reduction in risk of cardiovascular diseases. In 2011, the European Society of Cardiology and European Atherosclerosis Society guidelines for the management of dyslipidaemia recommended use of statins as first-line agents in the management of nephrotic dyslipidaemia. However, the effectiveness and safety of statins for people with nephrotic syndrome remains uncertain. Furthermore, the efficacy of second-line lipid-lowering drugs, such as ezetimibe and nicotinic acid, has not been proven in patients with nephrotic syndrome who are unable to tolerate statin therapy.

Objectives: This review aimed to evaluate the benefits and harms of lipid-lowering agents in adults and children with nephrotic syndrome.

Selection criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at participants with nephrotic syndrome that compared any lipid-lowering agent to placebo, no treatment or other lipid-lowering agents, given for not less than four weeks, were included.

Authors' conclusions: None of the included studies reported patient-centred outcomes including all-cause mortality, cardiovascular mortality, or non-fatal myocardial infarction; only single studies reported cholesterol (HDL, LDL and total cholesterol), triglycerides, serum creatinine, blood urea nitrogen, liver enzymes, and protein (serum, urine). High quality RCTs need to be conducted to assess the safety and efficacy of lipid-lowering drugs for people with nephrotic syndrome.

Kong X, Yuan H, Fan J, Li Z, Wu T, Jiang L. Lipid-lowering agents for nephrotic syndrome. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD005425. DOI: 10.1002 14651858.CD005425.pub2. Assessed as up to date: March 18, 2013.

GENERAL ARTICLES

APPROACH TO CHILD WITH DISORDER OF SEXUAL DIFFERENTIATION

***SomaV**
****Ajooba R**

Abstract: *Children with disorder of sexual differentiation (DSD) are a special group requiring assistance in planning and executing their treatment by a multidisciplinary team which includes the pediatrician, endocrinologist, pediatric surgeon, urologist, psychologist and social worker. A thorough knowledge of the pathophysiology of sex steroid metabolism, gonadal development and various factors including genetic conditions that predispose to the aberration in development of gonads might be useful in management of these children. This article presents discussion of the above facts with appropriate review of literature.*

Keywords: *Disorder of sexual differentiation, Child, Approach.*

A newborn with indeterminate sex or a child presenting later with disorders of sex differentiation (DSD) is an unique challenge to the pediatrician and it needs a team effort to deal with these problems. The overall incidence of genital ambiguity is 1 in 4500 (0.02%) live births[1] and some degree of male undervirilization or female virilization can be expected in 2% of live births.[2] At present the main controversies in management are centered around three major issues namely etiological diagnosis, gender assignment and timing of surgery. In order to establish an etiological diagnosis and decide an appropriate management plan, the understanding of the physiology of sex determination and differentiation is essential

Physiology of sex differentiation

Genetic sex (XX or XY) is determined at the time of conception. The differentiation of gonads, i.e., gonadal sex is determined in turn by the genetic sex, eg., male differentiation happens due to the presence of 'SRY gene' on the short arm of the 'Y' chromosome. The differentiated gonads then secrete hormones which determine the development of internal and external genital organs i.e., the phenotypic sex. The differentiation of the bipotential gonad (developing from the urogenital ridge) into testes or ovary is influenced by a series of genes and transcription factors, eg., SFI, SOX9, SRY, WNT4, WT1, DAX1, TDF, ATRX and MAMLD1 (Fig.1).

The development of fetal adrenals and biosynthesis of the steroid hormones (Fig.2) occurs simultaneously. Some genes are expressed in both adrenal and gonadal tissue eg., SF1 and DAX1. Hence, mutation of these genes can affect both adrenal and gondal development. Gonadal dysgenesis is also associated with Wilms tumor, which can be explained by the fact that WT1 gene is expressed in both kidneys and gonads.

Disorders of sex differentiation is defined as congenital conditions in which chromosomal, gonadal or anatomical sex is atypical.[3] Defects in 4 different levels can lead to these disorders:

1. Sex chromosome aneuploidy
2. Disorders of gonadal differentiation due to mutation in the genes influencing the process
3. Defects in steroid biosynthesis leading to decreased testosterone resulting in male undervirilization or androgen excess resulting in female virilization
4. Target organ insensitivity due to mutation of androgen receptor gene

The previous terminologies such as intersex, true hermaphrodites, sex reversal or gender based classification like male or female pseudohermaphroditism have been abandoned and a new classification system (Table I) of DSD has been proposed by the international consensus group in the year 2006 which has been well accepted worldwide. The new classification also includes Turner, Klinefelter and XXX syndrome as sex chromosome aneuploidy.

* Assistant Professor,
Department of Pediatrics,
Mahatma Gandhi Medical College & Research Institute,
Pondicherry.

** Postgraduate, Department of Pediatrics,
Arupadai Veedu Medical College & Hospital, Pondicherry.

The initial evaluation of these patients needs a detailed study of clinical examination and rational investigation plan which should preferably be done by a multidisciplinary team in a centre of excellence, where the genital surgery is done by a pediatric urologist. The multidisciplinary team should consist of pediatric endocrinologist, geneticist, urologist, surgeon, neonatologist, radiologist and psychologist. A whole life approach is needed so that services are provided to meet the changing needs of the patient as they pass through adolescence to adult life.[3]

Diagnosis of specific disorder

History: During the newborn period, history of persistent vomiting, progressive weight loss, anorexia, lethargy and dehydration suggest congenital adrenal hyperplasia. During childhood, inguinal hernia in a girl child, bilateral undescended testes, abnormal position of urethral meatus, small penis can be a clue for 46XY DSD. At adolescence, failure to develop puberty or attain menarche, virilization at puberty or infertility is suggestive of 46XY DSD. Antenatal history of exposure of the mother to androgens or signs of virilization in mother during pregnancy implies that the cause of virilization is either a maternal androgen secreting tumor or placental aromatase deficiency. Family history of unexplained neonatal death, baby born with ambiguous genitalia, virilization of female at puberty and infertility points towards a hereditary cause.

Physical examination: The first step in physical

Table I. New classification of disorder of sex differentiation (DSD)[3]

Sex Chromosome DSD	46 XY DSD	46 XX DSD
45 XO (Turner syndrome)	**Disorders of gonadal development**	**Disorders of gonadal development**
47XXY (Klinefelter syndrome)	1. Complete gonadal dysgenesis	1. Ovotesticular DSD
	2. Partial gonadal dysgenesis	2. Testicular DSD
	3. Gonadal regression	3. Gonadal dysgenesis
	4. Ovotesticular DSD	
46XO/46XY(mixed gonadal dysgenesis/ovotesticular DSD)	**Disorder of androgen synthesis/function**	**Androgen excess**
	1. Androgen biosynthetic defect (eg. deficiency of 17 hydroxylase, 3betahydroxysteroid dehydrogense, 17–20 lyase, 17betahydroxysteroid dehydrogenase, 5alphareductase and lipoid adrenal hyperplasia (StAR mutation)	1. CAH - deficiency of 21 hydroxylase, 3â (OH) steroid dehydrogenase, 11 hydroxylase
	2. Androgen receptor defect: complete and partial androgen insensitivity syndrome	2. Placental aromatase deficiency
46XX/46XY (ovotesticular DSD)	3. LH receptor defect: Leydig cell hypoplasia	3. Matermal androgen secreting tumour
	4. Disorder of anti-mullerian hormone: persistent mullerian duct syndrome	Others eg., cloacal extrophy, vaginal atresia.

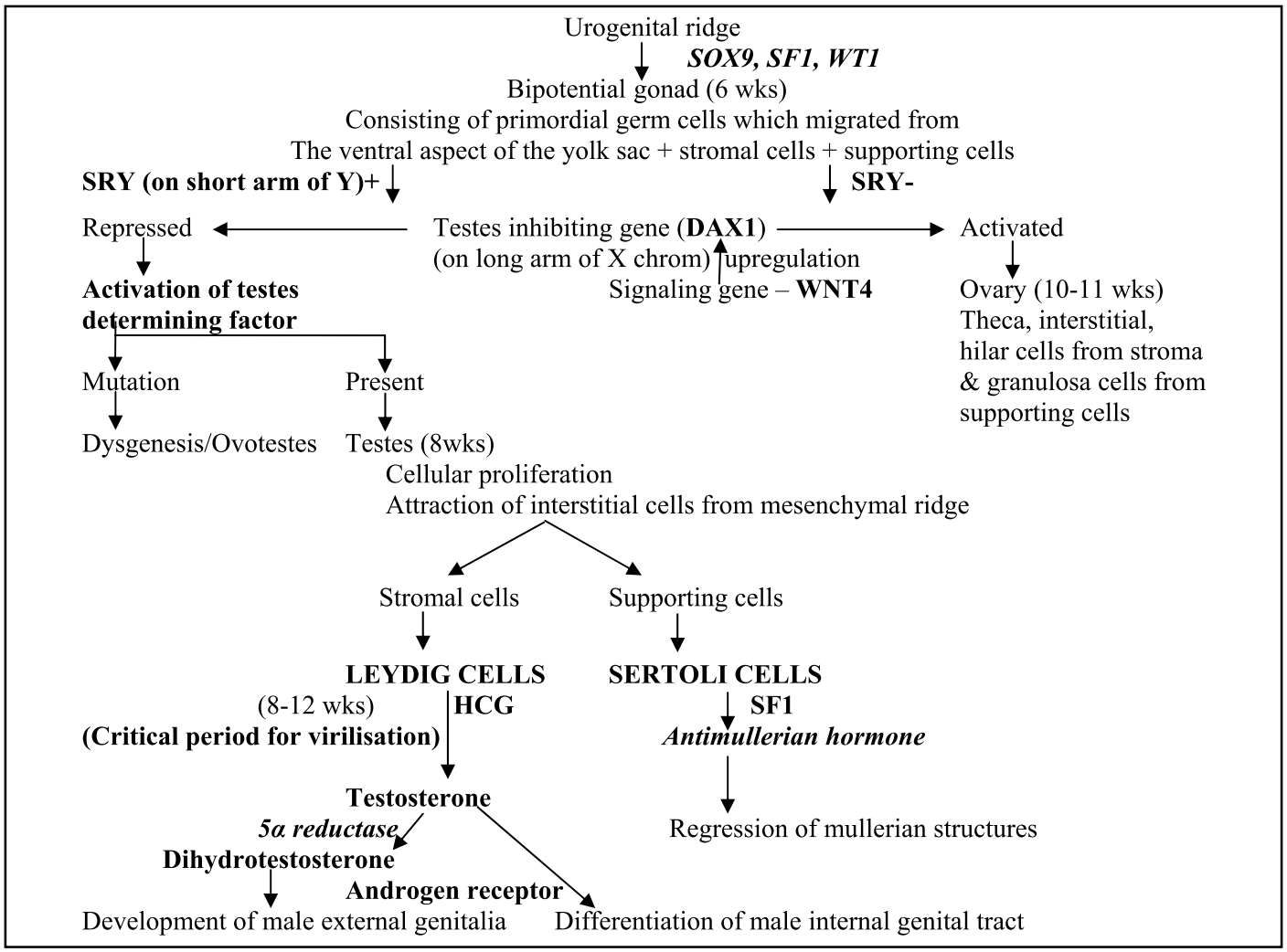

Fig.1. Physiology of sex differentiation

examination is to look for features of malformation/ syndrome associated with DSD, eg., microcephaly, ptosis, anteverted nares, broad alveolar ridge, syndactyly 2nd–3rd toe, mental retardation in 'Smith-Lemli-Opitz syndrome'; short limb dysplasia, anterior bowing of tibia and femur in 'Campomelic dysplasia', abdominal mass in Wilms Tumor (WT), congenital nephrotic syndrome in 'Denys-Drash syndrome', mental retardation, aniridia, abdominal mass (WT) in 'WAGR syndrome'.

Dehydration, lethargy, acidotic breathing (salt wasting symptoms) is suggestive of CAH due to '21 hydroxylase deficiency', '3βHSD deficiency' or lipoid adrenal hyperplasia (StAR gene mutation). Blood pressure is raised in CAH due to '11β hydroxylase and 17α hydroxylase deficiency'.

Presence of 1 or 2 palpable gonads in the inguinal region effectively rules out 46XX DSD. Only one palpable gonad is suggestive of mixed gonadal dysgenesis. A normal term phallus length is 3.5±0.7 cm.[4] A length <2 cm is considered abnormal. A normal term female clitoris is <1cm.[5] A length >1 cm is abnormal. Hyperpigmentation of labioscrotal folds is seen in DSD due to CAH. Hypospadias with separation of scrotal sacs or undescended testes is suggestive of DSD. If urethral opening is at the base of the phallus, it could be urogenital sinus (urethra and vagina connected internally as well as exit in the perineum through a common opening) in a virilized female. Anogenital ratio,[6] i.e., the ratio of distance between anus and posterior fourchette to distance between anus and base of phallus/ clitoris, if more than 0.5, suggest virilization. The following are the different stages of virilization described by Prader.[7]

Stage I: Clitoromegaly without labial fusion

Stage II: Clitoromegaly and posterior labial fusion

Stage III: Greater degree of clitoromegaly, single perineal orifice and almost complete labial fusion

Stage IV: Increasingly phallic clitoris urethra-like urogenital sinus at the base of the clitoris and complete labial fusion

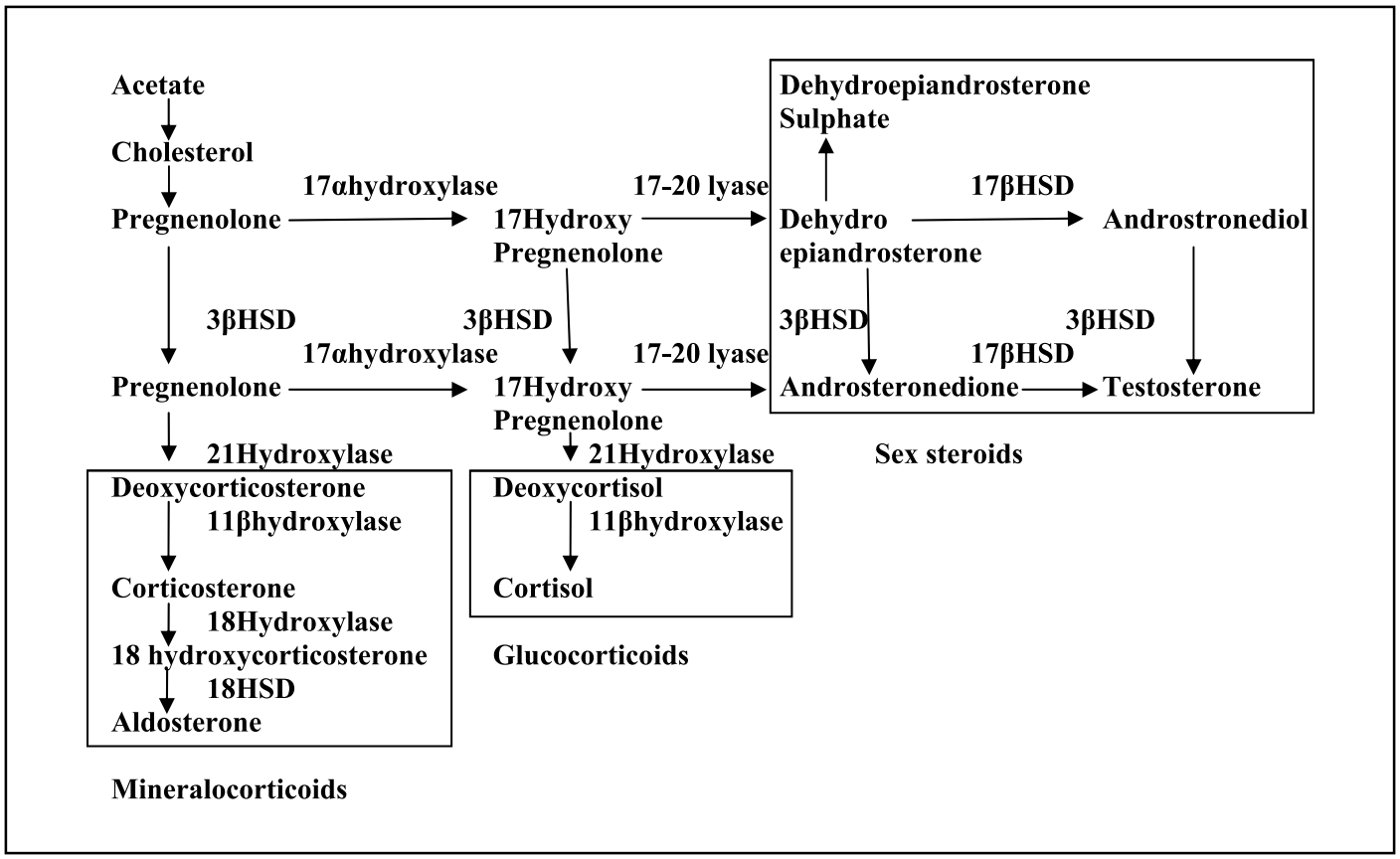

Fig.2. Biosynthesis of steroid hormones

Stage V: Penile clitoris, urethral meatus at the tip of the phallus and scrotum like labia (appear like males without palpable gonads)

Investigations

The first investigation to be done is a karyotyping with at least 20 metaphases to assess for mosaicism. A rapid florescent in situ hybridization using probes specific for 'SRY gene' can detect 'Y' chromosome material within hours.[8] An alternative is a rapid karyotype analysis by quantitative fluorescence polymerase chain reaction.

Radiological studies[9]: A pelvic ultrasound should be done to determine whether mullerian structures (uterus) are present or to help detect and locate undescended testes. A micturatring cystourethrogram can determine whether a urogenital sinus is present in a suspected virilized female.

Biochemical studies: In the absence of palpable gonads, 17 hydroxyprogesterone, deoxycorticosterone (DOC), dihydroapiandosterone (DHEA), plasma rennin, serum electrolytes is done initially. An increased 17 hydroxy-progesterone and plasma renin activity with decreased serum sodium, increased serum potassium with hypoglycemia and hypotension is suggestive of 21 hydroxylase deficiency. An increase in dihydroepiandosterone and 17 hydroxypregnelonone along with the above criteria is suggestive of 3 β hydroxysteroid dehydrogenase deficiency. Normal 17 hydroxyprogesterone with increased DOC, low serum potassium, decreased plasma rennin activity and hypertension is suggestive of 11β hydroxylase deficiency.

In the presence of palpable gonads, 17 hydroxyprogesterone, testosterone, DHEA, DOC, LH, plasma rennin, serum electrolytes and antimullerian hormone should be assayed initially followed by ACTH and HCG stimulation test. An increased DOC, decreased testosterone associated with hypertension and hypokalemia is suggestive of '17β hydroxylase deficiency'. High testosterone to dihydrotestosterone ratio is suggestive of '5α reductase deficiency'. Normal testosterone/DHT ratio with increased LH points towards 'androgen insensitivity'. ACTH stimulation test can identify the block in testosterone biosynthetic pathway. Absent response to ACTH stimulation with salt wasting features, increased plasma renin activity and massive adrenals on radio imaging is diagnostic of lipoid adrenal hyperplasia. HCG stimulation test can assess the presence of functional androgen producing testicular tissue. Ratio of testosterone to DHT after HCG stimulation is a sensitive indicator to diagnose 5α reductase deficiency.

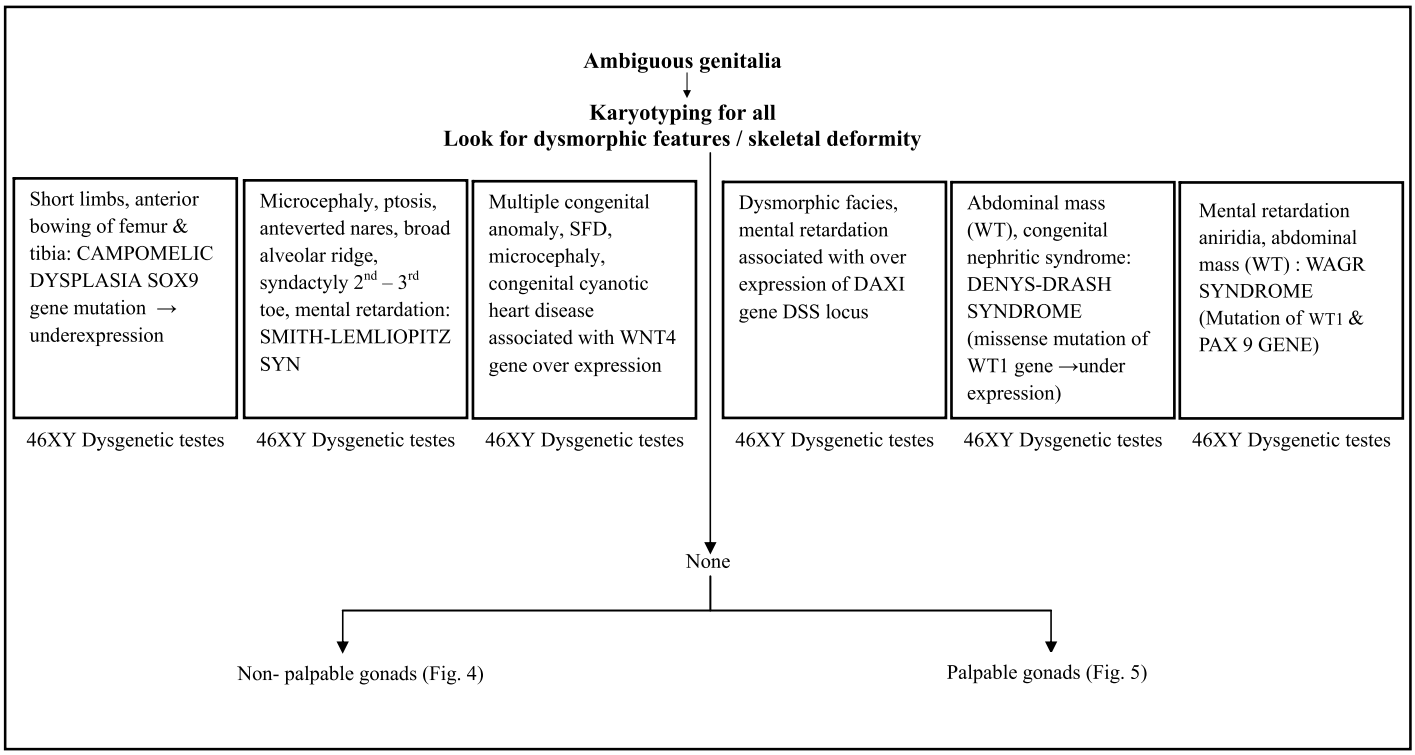

Fig.3. Approach to child with DSD

Laparoscopy[10] and gonadal biopsy should always be done in presence of Y chromosome material and genital ambiguity. Molecular genetic studies can help to identify the cause of DSD in patients whose etiological diagnosis remains unknown even after extensive work up.

Figs. 3, 4 and 5 depict a stepwise diagnostic approach to child with DSD.

Management

Assignment of gender: The most challenging and controversial aspect of management of DSD is the assignment of appropriate sex at the appropriate time. The psychosexual development which starts before 3 yrs of age has three aspects, viz., gender identity, gender role and sexual orientation. It depends not only on chromosomal sex, but also on exposure to androgen, brain structure and social and cultural background. Recently it has become apparent that testosterone imprinting of the fetal brain may play a role in determining male sexual orientation.[11] On the other hand, patients with CAIS inspite of high testosterone level usually do not exhibit male sexual orientation. Hence, caution should be exercised while assigning sex of rearing different from the chromosomal sex.

Factors that should be considered for assigning sex of rearing are chromosomal sex, etiology of DSD, potential for fertility, reproductive anatomy, malignant potential of gonads and family and social circumstances.[3,12,13] Potential for fertility is seen in virilized females due to CAH, 5α reductase deficiency, true hermaphrodites with compatible external and internal genitalia. At present there is insufficient evidence to support male sex rearing in a 46 XX infant with CAH even with Prader stage V virilization as these patients show behavioral masculinization more predominant in gender role behavior, less prominent in sexual orientation and rarely in gender identity.[14] Complete androgen insensitivity syndrome and 46 XY complete gonadal dysgenesis has a complete female phenotype, hence reared up as female.

Sex assignment is particularly difficult in partial androgen insensitivity syndrome, 46 XY partial gonadal dysgenesis, mixed gonadal dysgenesis, 5α reductase deficiency, 17 ketoreductase deficiency and ovotesticular DSD, because they may have a predominantly female phenotype at birth followed by virilization at puberty. Hence, whatever the initial sex assigned, genital surgery is best avoided till adolescence when the patient also can take part in making a decision. The size of the phallus and its potential to develop at puberty into a sexually functional penis can help in initial sex assignment in these patients. A trial of testosterone injection should be given in equivocal cases and the infant raised as a boy only when there is a very good response.[13]

Malignant potential of gonads: Streak gonads in patients with a 46XY gonadal dysgenesis, 46XO/XY mixed gonadal

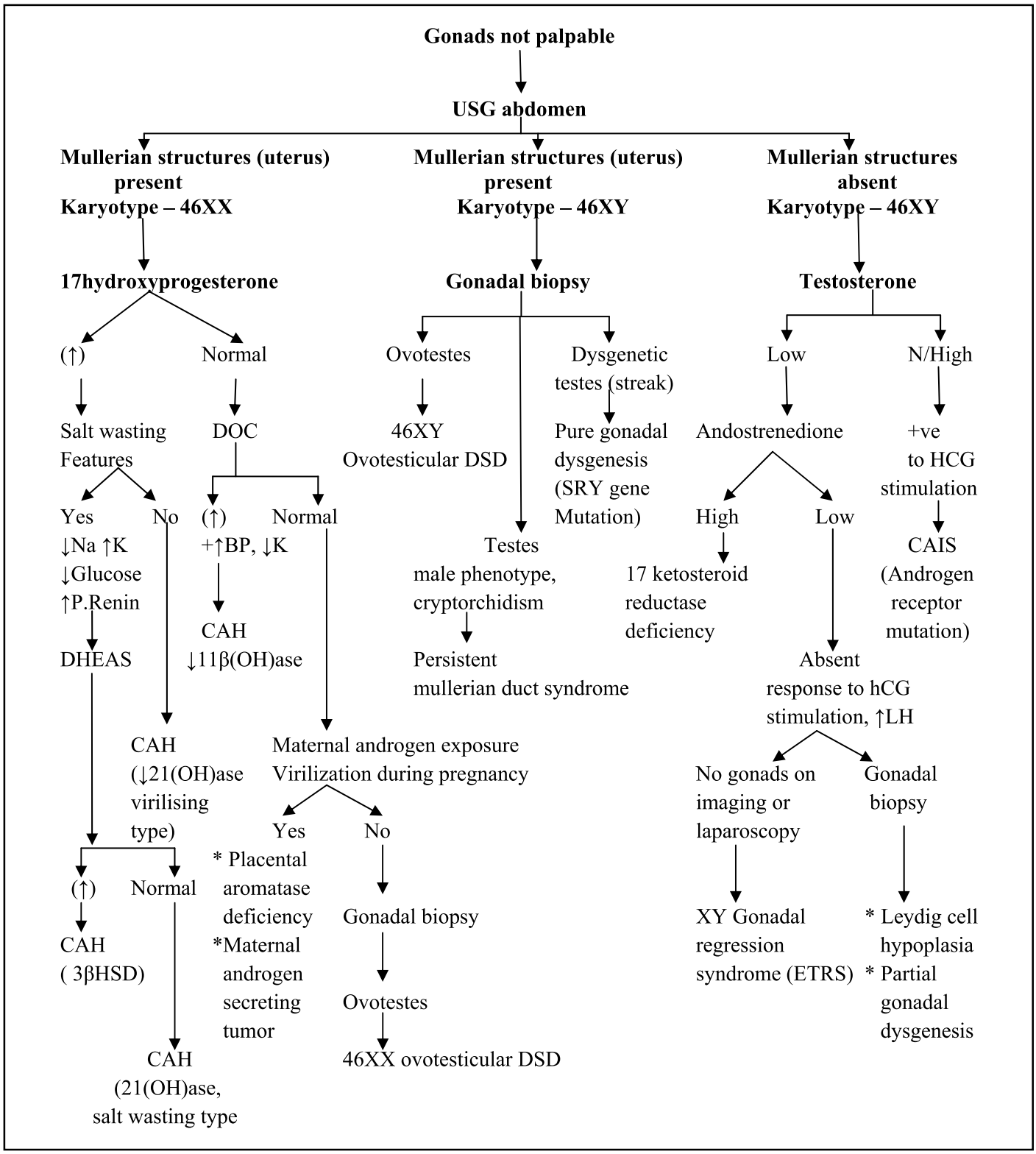

Fig.4. Algorithm for non palpable gonads

dysgenesis, undescended testes in CAIS or PAIS, scrotal testes in gonadal dysgenesis and gonads in true hermaphrodites are potentially malignant, hence removed immediately at the time of diagnosis if streak or brought down to the scrotum if normal or dysgenetic and followed up by periodic clinical assessment and biopsy at puberty to look for carcinoma in situ.

Hormonal management: The principle of hormonal management is to replace the deficient hormone and suppress the excess hormone by negative feedback.

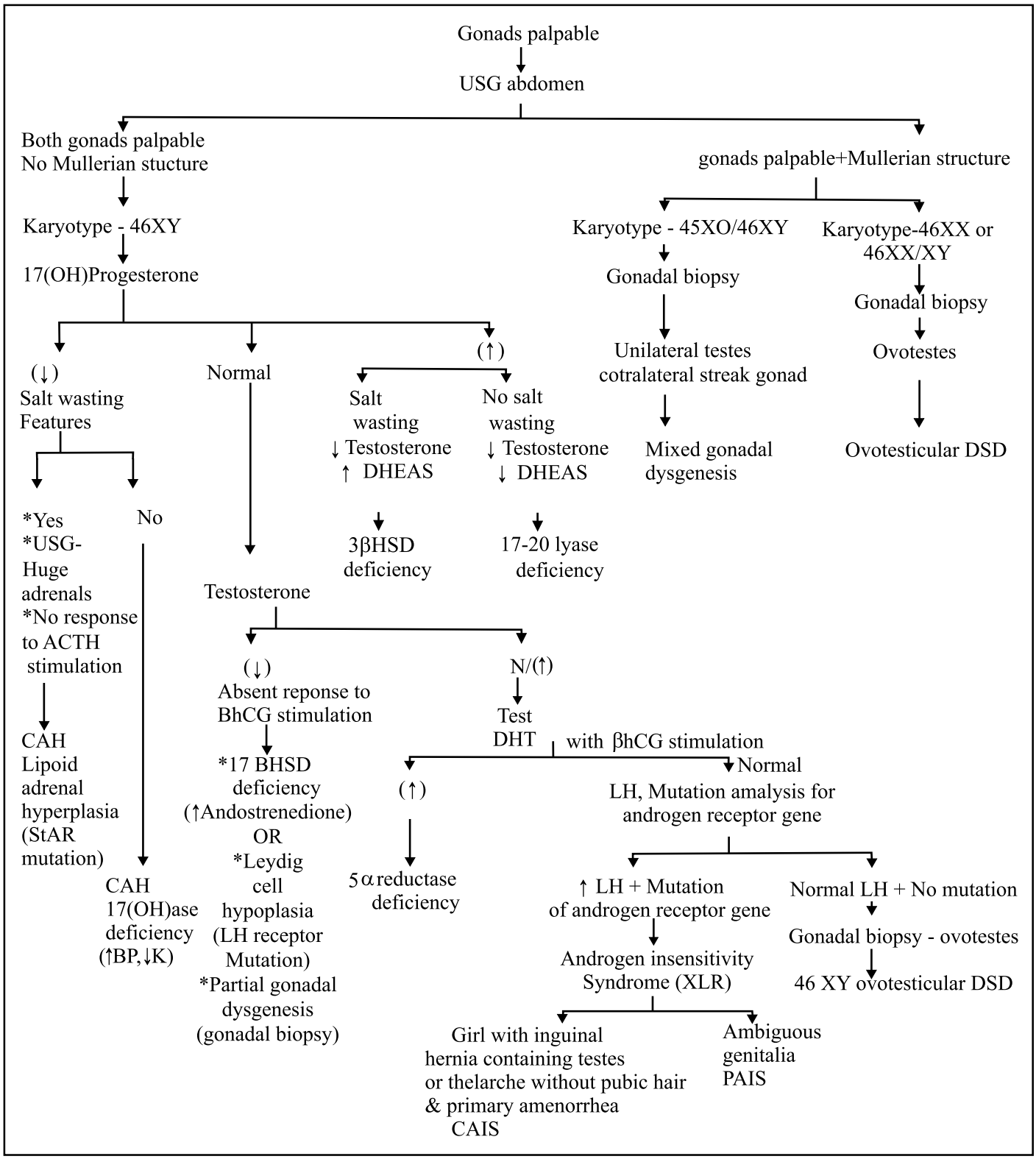

Fig.5. Algorithm for palpable gonads

For CAH, hydrocortisone 10–15 mg/m^2/day is recommended in childhood which is followed by dexamethasone after completion of linear growth.[14] Fludrocortisone 0.05–0.3 mg/day should be added in salt wasting types. 2–3 times the maintenance dose of hydrocortisone should be administered during periods of physical stress. All patients should be monitored for physical and hormonal status once in 3 months in infancy and once in 4–12 months thereafter.

Patients whose gonads are removed or hypofunctioning

are treated with estrogen or testosterone depending upon the sex assigned to induce puberty and secondary sexual characteristics. A progestogen is added with estrogen when uterus is present to induce cyclical bleeding.[15]

Prenatal treatment of pregnant woman with dexamethasone can be used to prevent genital ambiguity in a female fetus with '21 hydroxylase deficiency'.

Surgical management and timing of surgery: The ideal timing and nature of surgical reconstruction in DSD is again a highly controversial issue. The current recommendation is that, for virilized female with CAH,[14] feminizing genitoplasty with appropriate repair of the common urogenital sinus should be done within 12 months when there is high proximal junction between vagina and urethra. Total removal of clitoris is contraindicated. The neurovascular bundle, glans and preputial skin related to glans should be preserved. Revision vaginoplasty may be needed during adolescence. Surgery may not be necessary in the case of less virilized females with minimal clitoromegaly.

Early gonadectomy should be done for infants with testicular dysgenesis and androgen insensitivity assigned female sex. In boys with undescended testes and hypospadias orchidopexy and hypospadias, repair with urethroplasty should ideally be done between 6 and 18 months[13] followed by gonadal biopsy at puberty. Phalloplasty can be done for micropenis. For ovotesticular DSD with uterus, minimal testicular function and mild virilization optimal management is removal of testes, feminizing genitoplasty followed by hormone replacement therapy (HRT) at puberty.[13]

Points to Remember

- ***A child with genital ambiguity is an enormous stress to the family. Parents should be counseled to accept that it is not a matter of shame and these children can lead a functional and meaningful life in the society.***
- ***The principal emphasis should be on avoiding gender dissatisfaction and gender dysphoria in adolescence as far as possible.***
- ***A proper evaluation to arrive at the etiological diagnosis can help in deciding the appropriate sex to be assigned.***

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DRUG PROFILE

PREBIOTICS AND PROBIOTICS IN CHILDREN

Jeeson C Unni

Abstract: *Pre and probiotics help by altering the microflora of the host. Probiotics are foods or live organisms mostly bacteria or yeast contributing to healthy microbial flora suppressing harmful microbes. They play a main role in prevention and management of gastroenteritis, especially antibiotic associated diarrhea. Other less common indications are inflammatory bowel disease, necrotizing enterocolitis, constipation, etc. Few more indications for preventive therapy in pediatrics are being explored.*

Keywords: *Probiotics, Prebiotics, Gastroenteritis, Children.*

Intentional manipulation of host microbes with a therapeutic objective of treating many diseases is an area of great interest. Probiotics and prebiotics have the potential benefits of altering the microflora of the host potential for beneficial health. The characteristics of these agents and the differences between them are given in (Table I).

More than 400 distinct species of microorganisms, some harmful and some useful, inhabit the GI tract. **Probiotics** are foods or concentrates of live organisms, mostly bacteria and occasionally moulds or yeast - that contribute to a healthy microbial environment and suppress the potential harmful microbes.[1] Among bacteria, strains of lactic acid bacilli are more popular. The first recorded probiotic was fermented milk. Diametrically opposite effect may occur in the body in comparison with the lab for a given strain of probiotic. The effects demonstrated by one strain cannot be extrapolated to other strains, even if they belong to the same species. It is also noted that the various dosages and duration of therapy may have opposite effects.[2] The classification of different probiotic products and minimal requirements for these products have been formulated.[3]

* Editor-in-Chief, IAP Drug Formulary,
Consultant Pediatrician,
Dr.Kunhalus Nursing Home,
Cochin.

Prebiotics are usually available naturally in the form of oligosaccharides and can be added to infant formulas, food and beverages as supplements. In infant formula, generally galacto-oligosaccharides (GOS) and/or fructo-oligosaccharide (FOS) are used. Many studies of prebiotics are based on full-spectrum prebiotics, e.g, a mixture of short-chain and long-chain prebiotics.

The benefits of both prebiotics and probiotics are being extensively researched and both need to be ingested in sufficient quantity to have an impact. Further, the preparations should not contain excessive amounts of calories in the form of sugar, carbohydrates or fats.

Probiotic (usually multiple strains) available in combination with prebiotics that support their growth are called 'synbiotics'. These products are marketed highlighting the advantages of each component in the combination. The correctness of this approach needs to be studied. The strains of probiotics used are not specified for products available in India and there is ample evidence that the efficacy of probiotic is strain-specific. Some lactobacillus species need prebiotics for their activity while some do not. This article will review recent evidence for the use of these agents in pediatrics.

Prevention of acute gastroenteritis

RCTs show modest effect with doubtful clinical relevance.[4, 5, 6] These studies addressed the role of various species of probiotics including (a) Lactobacillus reuteri, L. rhamnosus GG and Bifidobacteria lactis, alone or in combination with Streptococcus thermophilus and L. reuteri, (b) L. rhamnosus (not GG), and L. acidophilus, either alone or in comparison with each other and (c) L. reuteri DSM 17938. Infant formulae enriched with probiotics have also been marketed in the West to promote GI health in infants but the European Society for Paediatric Gastroenterology, Hepatology and Nutrition that studied the products felt that there was insufficient evidence to recommend its use.[7]

Treatment of acute gastroenteritis

The Cochrane review of 63 studies, on use of probiotics for treatment of acute gastroenteritis, which met inclusion criteria concluded that alongside rehydration therapy, probiotics appear to be safe and have clear

Table I. Characteristics of prebiotics and probiotics

Prebiotics	Probiotics
Prebiotics are a form of dietary fiber: non-digestible substances that pass through the stomach and small intestine unchanged. The most widely accepted prebiotics are the FOS (fructo-oligosaccharides) and GOS (galacto-oligosaccharides). FOS and GOS occur naturally in foods such as asparagus, garlic, artichoke, onion, wheat and oat, as well as soybean. The compound created from merging these two prebiotics together is called Oligofructose-Enriched-Inulin and is considered a 'full-spectrum' Prebiotic.	Probiotics are living bacteria intended to benefit colon health. They usually contain one to a few strains. Once consumed, the bacteria are just 'bacteria' no longer 'probiotics'.
Prebiotic fiber is not affected by heat, cold, acid or time	Probiotics can be killed by heat, acid or simply the passage of time. They must not be subjected to excessive heat during transport and warehousing. They should typically be refrigerated to ensure the bacteria remain relatively dormant and do not die simply from 'old age'. The bacteria can also be killed by acid, such as found in the human stomach.
Prebiotics nourish the trillion good bacterial species that are part of the diverse array of commensal microbes in the GI tract that act as a separate ecosystem (each person's colon microflora is as unique that of individual's fingerprint)	Probiotics contain from one to a few species of bacteria which are added to the colon when they are ingested.
Prebiotic fiber is a naturally-occurring substance, found in thousands of plant species (though mostly in very small amounts)	Probiotics occur naturally in fermented foods like yogurt
Prebiotics foster an environment in the colon which is hostile to bad bacteria	Probiotics may impact bad bacteria by crowding them out

beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea.[8] Many studies using various probiotics such as L. rhamnosus GG, L. acidophilus, L. reuteri, L. bulgaricus, L. reuteri DSM 17938, Lactobacillus paracasei strain ST11 and Bifidobacteria longum subsp. infantis CECT 7210[9, 10, 11], have been carried out on children with acute diarrhoeal disease showing some beneficial effect; maximum effect was observed when Lactobacillus GG was used.[12, 13] A subgroup analysis for different probiotic strains concluded that both Lactobacillus GG and L. reuteri significantly reduced the duration of diarrhea as compared to the placebo.[14] A small study done in North Bengal using Lactobacillus GG for treating persistent diarrhea in children demonstrated that it decreased the frequency and duration of diarrhea and vomiting and reduced hospital stay.[15] Lactobacillus GG and L. reuteri are not available in the Indian market. They are very expensive. IAP National Task Force for use of probiotics in diarrhea therefore recommended that there is presently insufficient evidence to recommend probiotics in the treatment of acute diarrhea in our settings.[16] Further, the Task Force felt that it may not be possible to extrapolate the findings of studies in developed countries to the Indian setting where the breast feeding rates are high and the microbial colonization of the gut is different. However, there is some initial evidence of a role for Saccharomyces boullardi in acute diarrhoea in Indian children.[17] A very recent review of RCT's or their meta-analyses published after 2008 suggested L. rhamnosus GG and S. boulardii as first choice probiotics in therapy of acute diarrhoeal illness.[18]

Prevention of antibiotic-associated diarrhea

Prescribing probiotics with antibiotics could

significantly reduce diarrhea associated with its use.[19] The majority of the studies in the meta-analysis used Lactobacillus-based interventions alone or in combination with other genera; strains were poorly documented, but the best results were with L. rhamnosus GG, S. boulardii, B. lactis and Str. thermophilus. However, all ages were included and the number of children studied is not mentioned. Therefore, more child-centric research is needed to determine which probiotics are most effective, and with which specific antibiotics maximum affect could be expected.

Recommendations: Usage of pre- and probiotics may extend beyond the clinical sciences as they are used in alternative and complementary forms of medicine for many years. Studies done on this subject are few and have methodological limitations; hence it is difficult to make unequivocal conclusions and recommendations. They are not considered as standard of care or primary treatment for any of these diseases. In general they are found to be safe and used in the prevention of antibiotic-induced diarrhea and the treatment of infectious diarrhea, particularly lactobacillus GG and sacharomyces boulardii.

Other off-label indications

Antibiotic-associated diarrhea - There have been no randomized controlled trials with probiotics in the treatment of antibiotic-associated diarrhea in children.[20]

Inflammatory bowel disease - Limited studies in children; some strains may be effective for ulcerative colitis[21]; nil data for crohn's disease even in adults.[22]

Irritable bowel syndrome - More studies required to define role; though some strain specific and symptom specific effects may be expected.[23]

Helicobacter pylori - The adjuvant effect of adding probiotics to regimens for treatment of H pylori in children has not been conclusively proved.[24, 25]

Necrotizing enterocolitis - Some experts suggest that evidence for use is insufficient while others feel it is unethical to withhold an intervention that may save life. However, though a Cochrane review suggests effect[26], some researchers express uncertainity.[27]

Constipation - Probiotics added to formula feeds act as stool softners in non-constipated children but it has no role in the treatment of habitual constipation.[28]

Allergy and Atopic Dermatitis - The effect is inconclusive[29]

The following are the safety concerns of prebiotics and probiotics. These products appear to be safe in healthy infants and children. However there are rare reports of sepsis due to endogenous flora as well as probiotic bacteria in high risk children such as immunocompromised, ill preterms and those with intravenous catheters or indwelling medical devices.[30]

Conclusion

Probiotics and prebiotics do have an influence on gut flora. However, as discussed in this article, innumerable studies of their use have not been able to conclusively prove their use as a first line 'drug' for prevention therapy of any pediatric illness. They have thus far not been included in the IAP Drug Formulary. They are used in the treatment of acute viral diarrhea and in the prevention of antibiotic associated diarrhea with some supportive evidence, though more robust studies are needed.

Points to Remember

- ***Pre and probiotics have the potential to alter the microflora of host leading to a healthy microbial environment and suppression of harmful microbes.***
- ***Using probiotics with antibiotics could significantly reduce antibiotic associated diarrhea.***

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DERMATOLOGY

MANAGEMENT OF ULCERATED INFANTILE HEMANGIOMAS

*** Jayakar Thomas**
**** Kumar Parimalam**
***** Devaraj Kumar Dinesh**

Abstract: *During the past several years, there have been new advancements in the management of infantile hemangiomas (IHs). In many patients, no treatment is ever necessary, because IHs are well known for their natural history of spontaneous involution. However, a significant minority of hemangiomas do require treatment. Moreover, they are very heterogeneous, making the decision of when, how and why to intervene quite variable. The least common but the most important rationale for intervention is the presence of a life- or function-threatening complication, where prompt therapeutic intervention is a necessity. A much more common scenario is ulceration, where appropriate management is needed to expedite healing and control pain. Increasingly, the life-altering aspects of hemangioma are being recognized as a rationale for treatment because permanent scarring and disfigurement can result even if involution is complete. Treatments for IHs currently include topical, intralesional and systemic therapies. Laser and surgical modalities are also sometimes used depending on the clinical scenario. In the absence of rigorous evidence based studies, clinicians must carefully weigh the risks and benefits of medical or surgical treatments versus observation alone in tailoring the management to the specific clinical situation at hand.*

Key words: *Hemangioma, Infantile, Ulcerating, Management.*

* Professor of Dermatology,
Department of Dermatology,
Sree Balaji Medical College,
Chennai.

** Professor of Dermatology,
Department of Dermatology,
Government Villupuram Medical College,
Villupuram.

*** Department of Dermatology,
Kanchi Kamakoti CHILDS Trust Hospital, Chennai.

Infantile hemangiomas (IHs) are the most common, benign vascular tumors of infancy, present in 4% to 5% of the population.[1] Hemangiomas have a characteristic clinical appearance and predictable natural history. Most are not present, or, present only as a precursor lesion at birth. Most IHs go on to proliferate rapidly for the first several months of life, followed by a period of gradual involution. In most patients with IHs, no treatment is necessary because most lesions regress over years without leaving significant scarring.

However, for some patients, hemangiomas can be complicated by ulceration, leave permanent anatomic distortion or scars, or impair function. In these cases (or where such complications are anticipated) prompt intervention is often required.[2]

Although the rationale for treating IHs are quite diverse, they are best separated into 3 distinct categories: a) to prevent or improve functional impairment or pain, b) to prevent or improve scarring and/or disfigurement, and c) to avoid life-threatening complications.

Current management of ulcerated hemangiomas

Ulceration is the most common complication of IH. Like other aspects in the management of IH, there is no 'gold standard' therapy for ulceration, and a lack of evidence-based studies to support specific interventions. In general, topical modalities, such as barrier emollients like petrolatum in conjunction with non-adherent dressings, such as thin hydrocolloid dressings or petrolatum impregnated gauze are used as first line therapies. An important practical point is that the fibrinous or hemorrhagic crust at the surface of ulcerated IH blocks reepithelialization and can be a source for bacterial superinfection. Removal of the crust with dilute hydrogen peroxide soaks is recommended. Ulcerated hemangiomas should not be assumed to be infected (although most often colonized). Anecdotally, metronidazole gel has been reported to be effective as an adjunctive treatment particularly in perioral, neck fold and perianal ulceration. Overt bacterial infection is uncommon but if heavy or malodorous exudates, pustules or erythema along with induration of surrounding skin is present, bacterial cultures should be obtained and appropriate systemic antimicrobials initiated.

Topical Therapy (Corticosteroids, Imiquimod, Timolol)

No large clinical trials exist in support of any topical therapy in the management of IH. Some case reports/series demonstrate some evidence for certain modalities, mainly during the early proliferative phase of growth of very superficial IH, but mixed or deep IH typically does not respond to topical therapies. The advantage of topical therapies are their lack of systemic effect, although when used in larger amounts (in larger hemangiomas), significant systemic absorption remains a real possibility. Their disadvantage is limited penetration that may preclude effectiveness for thicker or deeper lesions, including those which may appear to be superficial but have an occult or emerging deeper component. Super potent topical steroids, particularly clobetasol, have shown some benefit in treating relatively small, superficial IH particularly in the periorbital distribution.[3] Potential side effects include possible systemic absorption, cutaneous atrophy and striae and hence close follow-up is warranted.

Topical imiquimod has also been reported to be safe and effective in treating some small superficial lesions and could be considered as a treatment option in patients presenting in the early proliferative phase with IH on visible locations. Crusting and theoretically, ulceration, are possible complications.[4]

A topical beta-blocker, timolol 0.5% gel or solution, has been reported to be effective in treating ulcerating IH.[5]

Intralesional steroids for IH on other sites (nasal tip, lip, and other sites) can be effective, particularly when administered during the proliferation phase and in small tumors where the medication will be more likely to be distributed evenly. The dose of steroid, usually triamcinolone, should not exceed a maximum of 1 to 2 mg/kg per treatment (to a maximum of 10 mg).[6]

Systemic Therapy (Systemic Corticosteroids, Propranolol, Interferon, Vincristine)

Systemic therapies are needed in cases in which hemangiomas cause life- or function-threatening complications, providing us with a rationale for treatment. At this time, the mainstay of treatment is still systemic corticosteroids,[7] but recently, oral propranolol[8] has shown great promise as an effective systemic therapy. In addition, vincristine and alpha interferon can also be considered in certain cases or added in conjunction with other modalities.[9,10]

Oral propranolol is the most recent of the systemic therapy for treating IH. Preliminary reports of efficacy are extremely promising, with more predictable shrinkage of hemangioma tissue, even after the growth phase is completed. Propranolol is a non-selective beta adrenergic blocker. It has been used in infancy in the management of certain cardiac conditions and also for neonatal hyperthyroidism. There are many potential side effects of propranolol, including hypoglycemia, hypotension and bradycardia.

Recombinant interferon alpha (2a and 2b) has known antiangiogenic properties, and many reports attest to its efficacy in treating IH, particularly in complicated hemangiomas which have failed to respond to oral corticosteroids. However, since the recognition of serious neurologic sequelae (spastic diplegia, up to 20% of treated patients), most authors have reserved this as a second- or even third-line treatment.[9]

Vincristine is a vinca alkaloid microtubule inhibitor that is used primarily by oncologists to treat hematologic and solid tumor malignancies. There are several case reports documenting the benefit of vincristine for the treatment of life- or function-threatening IH. In this setting, vincristine is given intravenously at a dose of 1.0 to 1.5 mg/ m^2 weekly. Vincristine has many known side effects when used at high doses as a chemotherapeutic agent, including immuno-suppression, neuropathy and alopecia. However, in most of the cases reported, there was good response to treatment with a favourable safety profile in most patients.[10]

Physical Treatment (Lasers, surgery)

The flash lamp pumped pulse dye laser (PDL) initially at wavelengths of 585 nm and at 595 nm is the most common laser modality employed in the treatment of IH.[11] It is best viewed as a 'local therapy' as its efficacy is generally limited to superficial aspects of the disease. It is useful in lightening the brightly erythematous superficial component of IH or residual telangiectasias left behind after involution. In addition, PDL can be very helpful in expediting healing of ulcerated hemangiomas. The bare-fiber neodymium-yttrium–aluminium-garnet (Nd:YAG) laser has been reportedly effective in treating subglottic and mixed or deep cutaneous hemangiomas. Nd-YAG laser is more effective in deeper lesions as it has a greater depth of penetration. This method may be particularly effective in rapidly proliferating periorbital hemangiomas causing visual compromise, but it has not gained wide acceptance as a standard modality of treatment.[12]

Surgical management of IH should be considered depending on the specific case and anticipated complications. Some IH are amenable to early excision,

whereas for others, waiting several years until involution is complete may be more appropriate. Surgical intervention is best performed by an experienced surgeon with a good knowledge of the natural history of IH. Like the medical therapies discussed previously in this article, there is no 'gold standard' for when and how surgical intervention should be performed; it depends on the specific clinical situation at hand. Some patients may require surgery early during the proliferative phase, such as in ulcerated or bleeding IH, or in those in whom surgical excision may help to decrease the likelihood of visual complications. Surgical management of disfiguring hemangiomas should be considered before the patient reaches school age.[13]

Conclusions

Though IHs are very common their complications depend on the size, location and growth characteristics of the particular lesion. Given their inherent heterogeneity, developing a rationale for interventions can be challenging; however, management of individual lesions should ultimately be determined on the basis of an in-depth knowledge of their natural history. In cases in which the rationale for treatment is unclear, seeking consultation with multidisciplinary vascular anomalies teams, if available, can be extremely helpful, particularly in life-threatening cases. Although most hemangiomas never require intervention, when needed, there are many therapeutic options available. We are optimistic that with more experience and recent advances in our therapeutic armamentarium, future management of IH will be more successful in preventing scarring, disfigurement and life- or function-threatening sequelae.

Points to Remember

- ***A minority of infantile hemangiomas do require treatment.***
- ***Making the decision of when, how, and why to intervene is quite variable.***
- ***The most important rationale for intervention is the presence of a life- or function-threatening complication, where prompt therapeutic intervention is a necessity.***
- ***A common scenario is ulceration, where appropriate management is needed to expedite healing and control pain.***
- ***Treatments for IHs currently include topical, intralesional, and systemic therapies. Laser and surgical modalities are also used depending on the clinical scenario.***
- ***In the absence of robust evidence-based studies, clinicians must carefully weigh the risks and benefits of medical or surgical treatments versus observation alone.***

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SURGERY

MANAGEMENT OF VASCULAR ANOMALIES

*Sushmita N Bhatnagar

Abstract: *The term hemangioma as referred to most commonly in the past for all types of vascular lesions, has been redefined. In this era a lot of research and understanding of these lesions has provided the latest terminology for vascular lesions as vascular anomalies which could be either hemangiomas (vascular tumors) or vascular malformations. This review article aims at an in-depth discussion of all the modalities of management of the vascular lesions excluding the lymphatic malformations and provide a ready reference to the practicing pediatrician and surgeon who encounter these conditions on a regular basis.*

Keywords: *Vascular anomaly, Hemangioma, Vascular malformation, Management.*

The pioneers of an in-depth pathological study, classification and directing the course of management of vascular lesions are Dr. John B. Mulliken (Co-Director, Vascular Anomalies Center and Director, Craniofacial Centre at the Plastic and Oral surgery department at Boston Children's Hospital) and Dr. Julianne Glowacki, Professor of Orthopedic Surgery at Harvard Medical School and Professor of Oral and Maxillofacial Surgery at the Harvard School of Dental Medicine. The classification described in 1982 by them[1,2] has been the basis of continued study on this subject. A decade later the International Society for the Study of Vascular Anomalies (ISSVA) was formed in 1992.[3] ISSVA has revised the classification and has been continuously working on improving the classification system based on the original research of Mulliken and Glowacki. Almost during the same period, Hamburg in 1993[4] classified the congenital vascular malformations as per the site of occurrence as truncular and extratruncular vascular lesions based on embryology, anatomy, histology and pathophysiology.

* Head,
Department of Pediatric Surgery,
B.J.Wadia Hospital for Children,
Mumbai.

Understanding the terminologies and type of anomaly is of utmost importance for appropriate management of the lesion. Most of these can be diagnosed clinically; nevertheless investigations such as ultrasonography, MRI and angiograms are occasionally needed to establish the diagnosis.[5] Whilst some of the hemangiomas need no treatment due to spontaneous resolution, a myriad of medical and surgical modalities are available for the treatment of all types of vascular lesions. Discussed herein are the various treatment options and their indications, contraindications and complications.

Management

Vascular anomalies require multidisciplinary treatment. Ideally these conditions are best managed by a team comprising the pediatric surgeon, plastic surgeon, orthopedic surgeon, dermatologist and an interventional radiologist. Though the philosophies of treatment differ from one institute to another and from one culture to another, the guidelines of management remain the same for lesions of the face, those which are complicated with pain, bleeding, etc. and those which are rapidly growing. The lesions which are life threatening have to be managed on an emergency basis as per the type of lesion with the appropriate modality as per availability. There is an immense variability in the presentation of lesions from one patient to another based on the site, size, extent, complexity and complications. Hence the treatment should be individualized rather than protocol-based.

The 5 main modalities of treatment available are:

1. Medical
2. Surgical
3. Lasers
4. Sclerotherapy
5. Embolization

Medical and surgical management and sclerotherapy will be discussed more in detail in the subsequent part of this review. But before discussing the treatment modalities, let us review the goals and principles of treatment of vascular anomalies. The principles of treatment are categorized into 5 groups such as ameliorating the symptoms (pain, infection,

ulceration, bleeding), clinical regression or arrest of growth for rapidly growing lesions, cosmetic – to prevent or minimize disfigurement, saving life for life threatening vascular anomalies, and complete cure - eradication of the lesion.

Medical treatment

Medical management includes systemic and topical therapies.Systemic therapy includes corticosteroids, propranolol, interferon, vincristine and cyclophosphamide. Topical therapy includes topical creams and ointments such as steroids, propranolol, imiquimod and timolol.

Systemic therapy[6]

Corticosteroids: Several corticosteroids have been used for treatment of hemangiomas. Triamcinolone acetate and dexamethasone are the most commonly used and the most efficacious steroids. Others such as methylprednisolone, betamethasone,hydrocortisone do not seem to control capillary growth as efficiently. Inspite of this fact, there are reports of benefits of oral prednisolone with 90% of the patients showing excellent response.[7] The doses recommended have been 2–4 mg/kg/day. Greene et al used oral prednisolone in the dosage of 3mg/kg/day in single dose long term therapy and found that all patients with infantile hemangioma responded to oral prednisolone.[8] The complications have been variably reported by several authors such as hypertension, Cushingoid appearance, reflux, growth suppression, behavioral changes and infections.[7-9]

Propranolol: Propranolol had been accidently discovered for the treatment of hemangiomas which revolutionized the treatment of infantile hemangiomas. In routine situations, a dose of 2mg/kg/day is recommended, though for large and rapidly growing lesions the dose can be increased upto 5mg/kg/day. The duration for propranolol therapy is not yet clear. As per the study done by Hong et al[10], 6 months on an average is appropriate for upto the age of 12 months. Propranolol has been recommended as the first line treatment in infantile hemangiomas and has superseded the use of corticosteroids due to clinical effectivity more than steroids, cost-effectiveness, negligible side effects and better tolerance.

Interferon[11,12]: There are three main types of interferons - alpha, beta and gamma. Interferon-alpha 2a and 2b have been proposed in life threatening and deep visceral hemangiomas which do not respond to any other form of treatment. Rarely is interferon therapy used as first line therapy for treatment of hemangiomas. It is administered subcutaneously in a dosage between 1–3 million U/m^2/day. Interferon alpha has a serious though uncommon adverse effect of irreversible spastic diplegia. Hence, the use of this therapy must be restricted and when utilized should be accompanied by close and meticulous neurological examinations of the children during and post-treatment.

Vincristine[11]

Vincristine is a vinca alkaloid and a chemotherapeutic drug used for several malignancies in children. Its use in the management of vascular lesions is reserved for complicated, extensive, rapidly progressing life threatening hemangiomas. Vincristine is given as a weekly and strictly intravenous dose of 0.05 mg/kg/m^2 for children weighing less than 10 kg and 1.5 mg/kg/m^2 for children more than 10 kg. Vincristine is used in combination with other modalities of treatment especially in Kasabach Merritt syndrome.[13]

Cyclophosphamide[11]

Cyclophosphamide is again a chemotherapeutic drug and an immunosuppressant used for leukemia, lymphoma some malignant solid tumors as well as autoimmune diseases such as systemic lupus erythematosus, lupus nephritis, etc. In vascular tumors, the indication for its use is limited to those lesions which are diffuse and extensive such as diffuse infantile hemangiomatosis and those vascular tumors which are life threatening. It is administered intravenously in a dosage of 10 mg/kg/day given on 3 consecutive days. It can be used alone or in combination with mesna. Reports of use of cyclophosphamide are anecdotal, but have shown good response to life threatening situations.

Topical agents

Topical creams and ointments are usually effective in superficial vascular lesions. Till date, few topical agents have been reported but no large clinical trials have been done which prove the efficacy of topical therapy in the management of hemangiomas. Corticosteroids have been used as topical creams either as a sole agent or in combination with other agents. Topical potent cortico-steroids can improve thin superficial hemangiomas but not their deep component.Topical mometasone has also been tried with a reasonably good response. The adverse reactions of steroids with or without combinations include atrophy and hyperpigmentation. Imiquimod as a topical agent has also been reported to be safe and effective in treating small superûcial lesions,[14,15,16] along with other agents such as steroids, but crusting and ulceration are possible complications. Beta blockers such as propranolol, timolol, etc. have been recently used as topical agents in superficial facial hemangiomas. Propranolol has shown promising

results as both topical[17] and systemic therapy (as discussed earlier). Timolol maleate, a hydrophilic non-selective beta-blocker was reported to treat periocular hemangiomas successfully without adverse events.[18] Very recently, timolol in combination with brimonidine has been tried on 3 children with a promising response and no adverse effects.[19]

Surgical treatment

In the past, surgical intervention was considered a mainstay in the treatment of vascular anomalies as other modalities of treatment were not developed well. In the present era, surgery is considered as the last option and is not even required in a majority of cases. Though some authors recommend surgery in the proliferative phase of hemangioma, with the use of systemic and local treatment forms, surgical excision is not the routine practice now. The proponents of surgery who take up patients for upfront surgery for all types of vascular anomalies, whether hemangiomas or vascular malformations including AVM[20,21], may not find acceptance in present times wherein non-surgical modalities work wonders in curing the patients. Surgery should be considered as an adjunct to other modalities such as sclerotherapy and in specific situations to improve function or for cosmetic reasons. However, the limitations of upfront surgical management such as surgical scar, massive blood loss and large tissue defects requiring skin grafts or reconstruction with flaps, have to be taken into consideration before opting for surgical intervention. The most appropriate indication for surgical intervention is for post-treatment residual lesions or for excision of fibro fatty remnants of involuted hemangiomas.

Lasers

Lasers, in the management of vascular lesions, were limited to capillary hemangiomas, cavernous hemangiomas, vascular malformations wherein argon lasers for superficial lesions, Nd:YAG laser for deeper and thicker lesions, and CO_2 laser for excision or vaporization have been used.[22] With the introduction of pulsed dye lasers and photodynamic therapy, port wine stains, residual erythema and telangiectasia, and ulcerative lesions during proliferation phase can be treated. The argon, KTP, and Nd:YAG and 755 nm lasers[23] have also been used as surface lasers for capillary and venous malformations. Recently, introduction of intralesional laser therapy for the treatment of vascular malformations has revolutionized the treatment of vascular malformations. Intralesional Nd:YAG or diode lasers and KTP–potassium titanyl phosphate have been shown to be an effective form of treatment for voluminous deep venous lesions.

Sclerotherapy[24]

Sclerotherapy is a technique by which a sclerosing substance is injected into the lesion percutaneously either blindly or under ultrasonographic or CT guidance depending on the site, size and the type of lesion. Sclerotherapy is most commonly used for hemangiomas and slow flow vascular malformations.

Various sclerosants are available worldwide. The choice of the sclerosant varies from one institute to another, differs with the choice of the specialist treating the condition and depends on the availability of the sclerosant. Traditionally, hypertonic saline, absolute alcohol, 5% sodium morrhuate were being used which are now outdated due to the severe post-injection reactions. Gliadin, diatrizoate acid, quinolone and hypertonic glucose are also described in the literature, but with limited usage in clinical practice.

The various sclerosants still in use are as described in the following list:

1. Sodium tetradecylsulphate[25]
2. Ethanol (anhydrous)[26]: 95%–98% forms only are suitable for sclerotherapy. Multiple injections are needed with the dose not exceeding 1ml/kg due to risk of cardiovascular collapse. Though it is easily accessible the procedure is painful, post-procedure complication rate is high and the deep vascular layer is affected adversely.
3. Ethanolamine oleate[27]: is a detergent sclerosant with an excellent thrombosing effect but may cause acute renal failure due to hemolytic effect.
4. Poppy oil[28]: Iodised poppy seed oil is known commonly as lipiodol. This agent is used for high flow vascular malformations and usually via intra-arterial route.
5. Polidocanol[29]: Also termed as aethoxysclerol or Lauromacrogol, it is a local anaesthetic and has antipruritic properties. When injected into the vessels it causes fibrosis in the vessels due to irritant properties. This agent is used for low flow vascular malformations and the procedure of sclerotherapy can be performed either blindly or under ultrasound guidance.The serious side effect of this sclerosant is cardiac arrest which is reversible. Polidocanol is available in the concentration of 0.25% to 3%.
6. Bleomycin[30]: is a glycopeptide antibiotic produced from the bacteria Streptomyces verticelli. The anti-cancer forms are expressed as Bleomycin A2 and B2 anti -

Table I. Selection of treatment modality as per the type of lesion

Type of lesion	Subtype	Treatment
Hemangioma	Massive,Life-threatening,Disfiguring	Systemic therapy – Corticosteroids Interferon Vincristine Propranolol
	Localized	Injection sclerotherapy Surgical excision FPDL
Vascular malformation	Capillary	FPDL argon, potassium-titanyl-phosphate (KTP) lasers, and 755nm laser
	Venous	Sclerotherapy
		Laser therapy – Nd-YAG, KTP
		Surgery
	Arteriovenous	Embolization
		Surgery
Multi-organ involvement	Mixed lesions	Combination therapies—both systemic and local.

cancur forms which are used for treatment of various malignancies in children. When injected intravascularly, it causes endothelial damage and thus fibrosis of the vascular lesion.

Sodium tetradecylsulphate (STD) and hypertonic saline were used earlier but did not provide satisfactory results for vascular anomalies. This could be attributed to the fact that the differentiation of hemangiomas from vascular anomalies was not very clear and patient selection was probably not as per criteria. The results were found to be better with lymphatic malformations as compared to the vascular anomalies. Moreover the tissue response to these agents was much more in terms of inflammatory response presenting as pain, swelling, fever, etc. With better understanding of the terminologies and the use of bleomycin since 2005, an excellent response was noted by the author (unpublished data) in 78 patients given bleomycin sclerotherapy till date. Two patients had exaggerated inflammatory response with sudden increase in size of swelling, severe pain and fever which was taken care of by intravenous antibiotics. Almost 60% of the children developed a few scattered hyperpigmented patches over the body which spontaneously resolved on completion of therapy. No other complication, especially the dreaded pulmonary fibrosis occurred in any of the children. The dose of bleomycin used was as per recommendation-1unit/kg over the body and extremities and 0.66 units/kg over the face and genitals. Overall results were satisfactory in terms of response to the sclerosant.

7. Pingyangmycin (PYM)[31]: Very similar to bleomycin, PYM is an antitumor antibiotic and is derived from Streptomyces. PYM gets its name from the area where it was discovered in Pingyang, China. Its major component is bleomycin A5. Therapeutic effect is again due to endothelial damage and toxicity. As a sclerosant for vascular lesions, the results of treatment are considerable with few side effects such as bradycardia, skin fibrosis/necrosis and scar contracture as in with any other sclerosant.

8. Intralesional steroids[32]: These steroids have been the most commonly used agent in the past and still remain the preferred sclerosant in some centers. Their use gives best results only in the proliferative phase and for small lesions and was first described by ophthalmologists in the treatment of peri-orbital infantile hemangiomas. Subsequently they were used for lesions at other sites with variable responses. The agent most often used is triamcinolone in the dose of 1-3mg/kg/ treatment and should not exceed 10mg/kg.

The injections are spaced at 3-6 week intervals. Bleeding, skin atrophy, skin necrosis, infection, anaphylaxis and adrenal suppression are potential complications.

The above sclerosants can all be used in combinations and apparently provide an added advantage over a single agent.

Embolization

For arteriovenous malformations/fistula (AVM/AVF) and high flow venous malformations, the treatment of choice is embolization of the abnormal feeder vessel(s) preserving the normal vessels. The procedure depends on location, severity, extent of vascular malformation and on availability of embolising agent. All these agents cause direct mechanical obstruction and induces foreign body reaction.

Various agents are available for embolization.[33] These are:

1. N-butyl cyanoacrylate (Histacryl): Most commonly used as it causes permanent mechanical block.
2. Coils: Available in various sizes from 2–30 microns and can be acquired either of stainless steel or platinum with or without Dacron mesh woven into the coil.
3. Polyvinyl alcohol (PVA) foam particles: Available in sizes from 50 to 2000 microns. PVA is more commonly used for tumor embolization and devascularization of the tumor.
4. Superabsorbent polymer microspheres: Mainly used for arterial embolization.
5. Onyx: This embolic system has non-adhesive properties, hence has better handling than the glue.
6. Other agents such as gelfoam, balloons, microfibrillar collagen, autologous material, etc.

Summary

The selection of the treatment modality as per the type of the lesion is summarized in Table I.

Conclusion

Vascular anomalies represent a wide spectrum of conditions related to the blood vessels and the lymphatics. Whilst some do not require treatment, the others should be studied in detail and establishment of an appropriate diagnosis is crucial to successful outcome. The outcome is also dependant on appropriate selection of treatment modality. Erroneous treatment can lead to complications such as ulceration, skin necrosis, wide areas of skin loss and disfigurement as well as adverse effects of treatment modality.

Points to Remember

- ***Vascular anomalies require multidisciplinary treatment.***
- ***Treatment modalities include medical, surgical, LASER, sclerotherapy and embolisation.***
- ***Management outcome depends on the correct selection of treatment modality.***

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NEWS AND NOTES

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Email : drvikastaneja@yahoo.co.in, krishan.chugh@fortishealthcare.com

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RADIOLOGY

DEVELOPMENTAL DYSPLASIA OF THE HIP

*** Vijayalakshmi G**
**** Natarajan B**
**** Jeya Rajiah**
***** Kasivisalakshi KP**
**** Balan MP**

Developmental dysplasia of the hip is an important condition that needs early and accurate diagnosis. Expert hands can detect DDH during routine examination of newborns. In case of doubt, a positive family history, or when documentation is required, ultrasound is an excellent modality in the newborn period. In the newborn and young infant the head of the femur is entirely cartilaginous. Therefore a plain X-ray cannot visualise actual dislocation. Fig.1. is a plain X-ray of an older child where the head is seen because it is ossified. The head of the left femur is clearly outside the acetabulum. In the newborn where the head is not ossified we use certain lines. A horizontal line drawn through both triradiate cartilages is called the Hilgenreiner line. Another vertical line, the Perkins line, is dropped down from the outer edge of the acetabulum. Normally the head of the femur or the upper edge of the metaphysis lies in the lower inner quadrant. In dislocation it is displaced and lies in the upper outer quadrant. Ultrasound allows us to not only visualise the head but also the acetabulum deep to the head. The age at which the ossification centre of the proximal femur appears is highly variable but is usually 2 to 8 months. As the ossification centre grows it masks the acetabulum.

Many ultrasound methods have been put forth by various workers. Some do not assess the acetabulum, while others do not stress on angle measurement and instead study the percentage coverage of the femoral head. Some scan from the anterior aspect.

* Professor
** Asst. Professor
Department of Radiology
Institute of Child Health and Hospital for Children,
Chennai.

In our hospital we routinely follow the method first described by Reinhard Graf. Fig.2. is an ultrasound picture of the hip of a newborn obtained from the lateral aspect in the coronal plane. The iliac bone is seen as a white horizontal line that sharply dips inferiorly as it forms the superior part of the acetabulum. The acetabulum continues as a curved line forming a cup. The central break in the curved line of the acetabulum (T) is the triradiate cartilage. Within the curve of the acetabulum is the black cartilaginous head with white stippling (H). The labrum (L) is a triangular white structure that overhangs the head of the femur and thus deepens the acetabulum. As we study the morphology of the hip we can also assess how much of the head is covered by the bony acetabulum. This is the Morin's method and assesses femoral head coverage. Graf's reference line which is a horizontal line drawn along the lateral iliac border is used. Normally 2/3 of the femoral head should lie internal to the line. Less than one third coverage means a shallow acetabulum. This way of assessment correlates very well with an abnormal acetabular index in the X-ray. The acetabular index is the angle between the Hilgenreiner line and a line through the acetabulum and should normally be less than 20°.

While most methods do not assess acetabular morphology, the angles described by Graf are very useful in describing the extent of acetabular dysplasia. DDH includes hips that are immature, unstable, subluxed or dislocated. To measure the angles, (Fig.3.) the reference line is a straight horizontal line drawn along the ilium. Another line is drawn along the lower limb of the ilium as it turns downward to form the superior part of the acetabulum. The alpha angle is the angle made by this line with the reference line and should normally be greater than 60°. The beta angle is the angle between the same reference line and a line along the labrum. It should be less than 55°. In high dislocation these angles may not be measurable. Fig.4. shows a dislocated head. The labrum is everted.

In the immature hip the alpha angle is 50° to 60°. When less than 50° the acetabulum is deficient with or without subluxation. If less than 43° there is subluxation. The measurement of the beta angle has shown a lot of variability. However it is less important as treatment does not depend on the beta angle alone. Stress testing can also

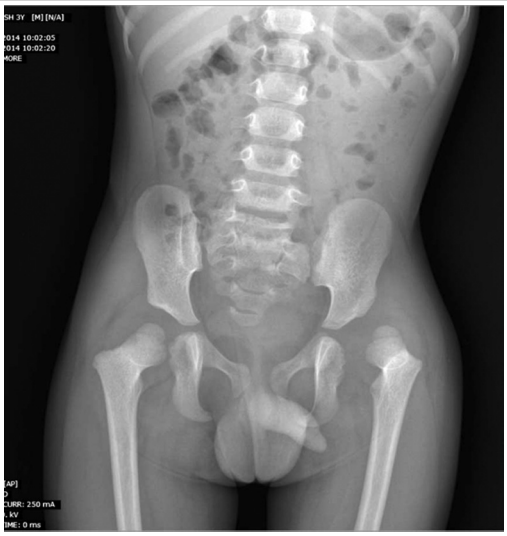


Fig.1. X-ray – DDH

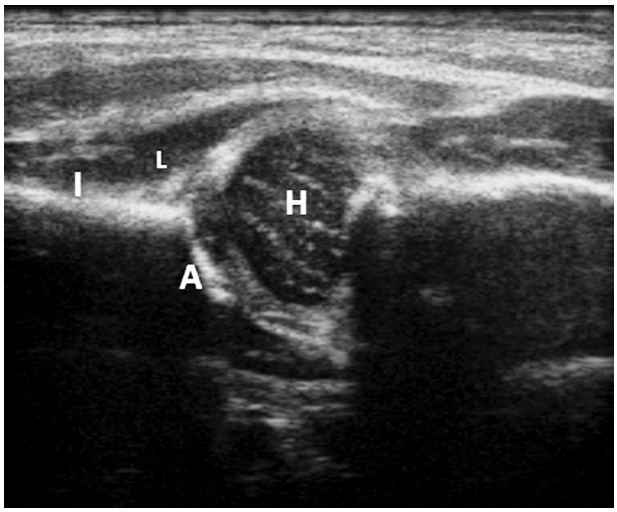


Fig. 2 Measurement of angles

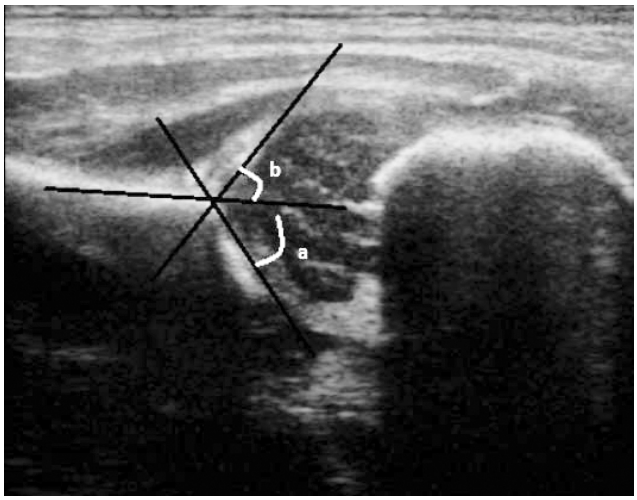


Fig.3. Normal hip - US

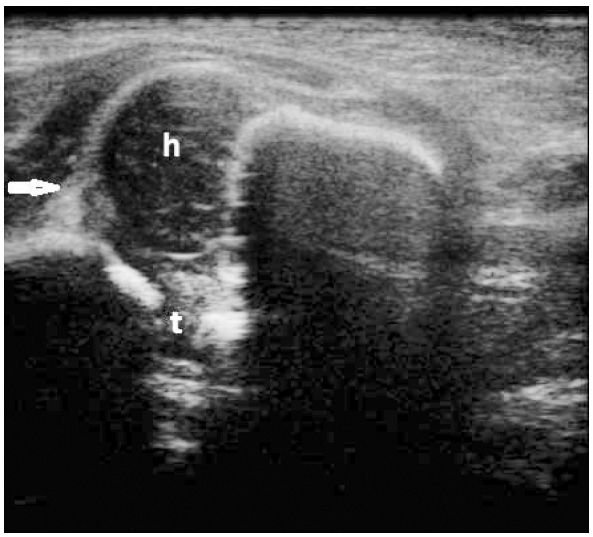


Fig.4. Dislocated head: arrow points to everted labrum.

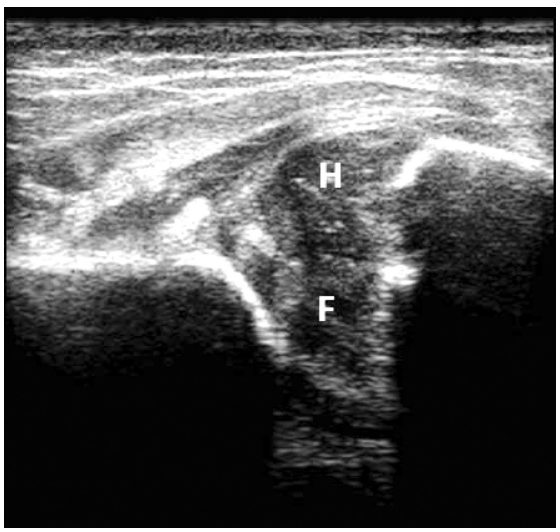


Fig.5. Septic arthritis: F is the joint fluid

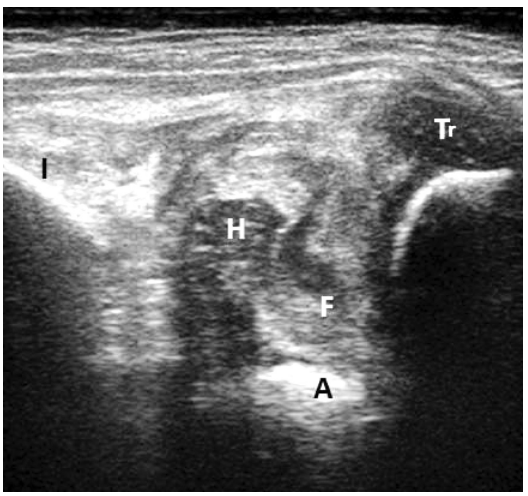


Fig.6. Transverse section showing thick synovium around black fluid: Tr is the greater Trochanter, A is the acetabulum

be done while imaging. The hip is held in 90° degree flexion and pressure is applied pushing the femur posteriorly to provoke dislocation. This is analogous to the Barlow manoeuvre and indicates a shallow acetabulum. DDH needs to be diagnosed in the neonatal period so that complete reduction is done and maintained with a simple harness or splint device. This provides the acetabulum with a chance for development by remodelling.

Ultrasound is also useful in septic arthritis of the hip (Fig.5). The head is dislocated because the joint cavity is filled with fluid. Fig.6. is another view showing inflamed thickened synovium around black joint fluid.

BOOK REVIEW

Recent Trends in Paediatrics, Paediatric neurology

Editors: B.D.Gupta,R.k.Maheswari,M.Parakh,A.Purohit,Mukesh kumar

Published by IAP Barmer Branch, RAJ PEDICON 2013

The speciality of Pediatric Neurology has seen tremendous advancement in the past 2 decades.Only a few books on paediatric neurology from our country are available.This multiauthored book dealing with basics and latest concepts is one more addition. The Book consists of 322 pages and 27 chapters.The book is very handy but at the same time, highly informative. The book is written in simple language. Another highlight of this book is that, the first few chapters on developmental aspects and developmental disorders in which milestones, developmental assessment, IQ, ADHD, autism are well dealt with in depth and they cover almost one third of the book. Every paediatric resident must go through these chapters.

Chapters on neurocysticercosis and cerebral malaria are much relevant to our country. Chapter on hypotonic infant dealing with clinical and investigatory approach has a lot of practical utility. In chapter on neonatal seizures, authors have given a good algorithim for weaning AED.

A few modifications will add to the quality of book. Common neurological problems like headache, meningitis,tics may be included in subsequent edition. More illustrations and clinical photos may be added. Picture and photo quality may be improved. Salient points may be highlighted at the end of the chapter. Meticulous proof reading has to be done to avoid typographical errors, especially in chapter on cerebrovascular diseases. Too much emphasis on cerebrovascular malformations may be avoided. Rather, approach and evaluation of stroke may be discussed for the benefit of paediatric residents and pediatricians. It may be more appropriate that the chapter on global developmental delay follows the chapter on development assessment. Usefulness of MR imaging and MRS in Neurometabolic disorders may be included.

Overall, this book is worth possessing by all pediatric postgraduates and it also serves as a ready reference book for practising pediatricians and other physicians involved in child care.

Reviewed by: S. Velusamy, Professor of Pediatric Neurology, Stanley Medical College, Chennai.

CONTRIBUTORS TO CORPUS FUND OF IJPP

Dr.V.Arumugam, Tiruvarur

Dr.P.Ramachandran, Chennai

CASE REPORT

EOSINOPHILIC CHOLANGIOPATHY IN A VERY YOUNG CHILD – A RARE CASE OF RECURRENT ABDOMINAL PAIN

*Sumathi B
**Nirmala D
***Bhaskar Raju B
****Sankarabharathi CS
*****Rajalakshmi V

Abstract: *Recurrent abdominal pain is a common problem in pediatric gastroenterology practice. Rarely, eosinophilic involvement of the hepatobiliary system can present as recurrent abdominal pain. Peripheral blood eosinophilia and eosinophilic infiltration of the tissues such as gastrointestinal tract and hepatobiliary system may be seen in association with a number of conditions,[1, 2] but may occasionally occur in isolation. We report a rare case of eosinophilic cholangiopathy presenting as recurrent abdominal pain. The child had peripheral eosinophilia, distal common bile duct narrowing and tissue eosinophilia. She was managed surgically along with oral steroids.*

Keywords: *Eosinophilic cholangiopathy, Benign biliary stricture, Children, Recurrent abdominal pain.*

Eosinophilic cholangiopathy is an unusual and benign form of biliary disease characterized by peripheral blood eosinophilia and cholangitis. Pain and jaundice may be the presenting complaints in majority of these patients. Response to steroids is often seen and other modalities such as endoscopic stent placement and surgery may benefit some. Biliary strictures can occur either in isolation involving any segment or with involvement of liver and gall bladder. Clinical and imaging studies, tissue eosinophilia with or without peripheral eosinophilia are the basis to diagnose this rare condition. There were a few reported cases where surgery was done due to suspected malignancy.

* Asst. Professor, Department of Pediatric Gastroenterology
** Professor & Head, Department of Pediatric Gastroenterology
*** Professor & Head (Retd.), Department of Pediatric Gastroenterology
**** Asst. Professor, Department of Pediatric Surgery
***** Professor & Head (Retd.), Department of Pathology.
Institute of Child Health & Hospital for Children, Chennai.

Case Report

A six year old female child born of non-consanguineous parents was admitted in July 2008 with history of recurrent episodes abdominal pain and fever since the age of three years. Pain was predominantly in the upper abdomen, with nocturnal exacerbations of varying severity associated with jaundice requiring hospitilisation on two occasions. When she was referred to pediatric gastroenterology clinic she was stooping forward with severe pain. There was no history of trauma, worm infestation, drug intake, food allergy or family history of allergy. Clinical examination revealed mild scleral icterus and anemia. Systemic examination showed moderate hepatomegaly which was tender on palpation with bilateral wheeze on auscultation. Perusal of earlier medical records revealed raised leukocyte count with polymorphonuclear leukocytosis, peripheral eosinophilia and elevated serum amylase (486 IU/L). There was minimal dilatation of intrahepatic biliary radicles with bulky pancreatic head without gall stones or sludge on abdominal sonograpy. CECT abdomen showed bulky pancreatic head with minimal dilatation of intrahepatic biliary radicles without biliary calculi. Current investigations showed hemoglobin 9gm/dL, total WBC count of 18,200 /mm^3 with 54% polymorphs, 24% lymphocytes and 22% eosinophils. Serum bilirubin was 3.6 mg/dl, SGOT 26 IU/L, SGPT 84 IU/L, SAP 246 IU/L, serum amylase 288 U/L (normal 90). Microscopic examination of stool was normal on three consecutive days. X-ray chest and abdomen were normal. Mantoux test and HIV were negative. Upper GI endoscopy and echocardiogram were normal. Magnetic resonance cholangiopancreatogram showed smooth tapering of distal part of common bile duct. (Fig.1.) with proximal dilatation of bile duct. The pancreatic duct was normal. The child was treated with a course of antibiotics and bronchodilators. As endotherapy was not feasible in our center and as the child had significant abdominal pain with recurrent bouts of cholangitis requiring hospitalisation, surgery was contemplated. Intraoperative findings showed bulky, firm pancreatic head. There was smooth distal tapering of common bile duct with proximal minimal dilatation without evidence of choledochal cyst or distal common channel. Hepaticojejunostomy with Roux-en-y anastomosis was done and the resected segment consisting of gall bladder, cystic duct, proximal common bile duct (CBD) was sent for

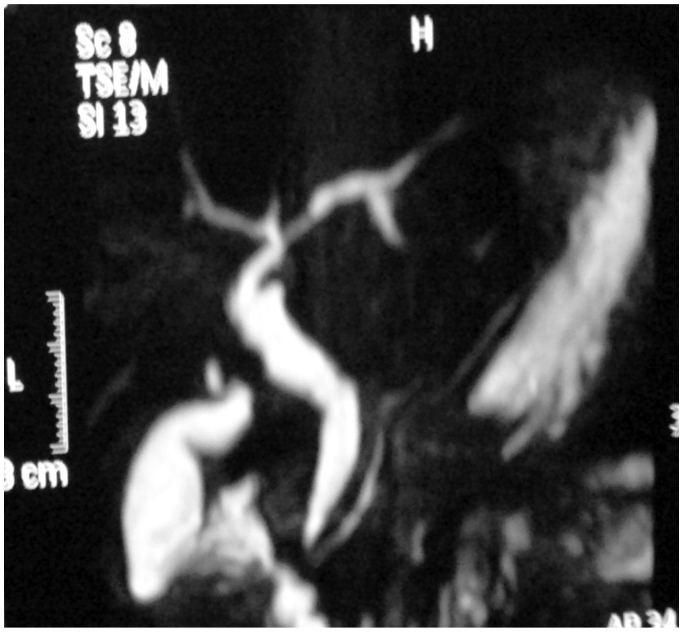
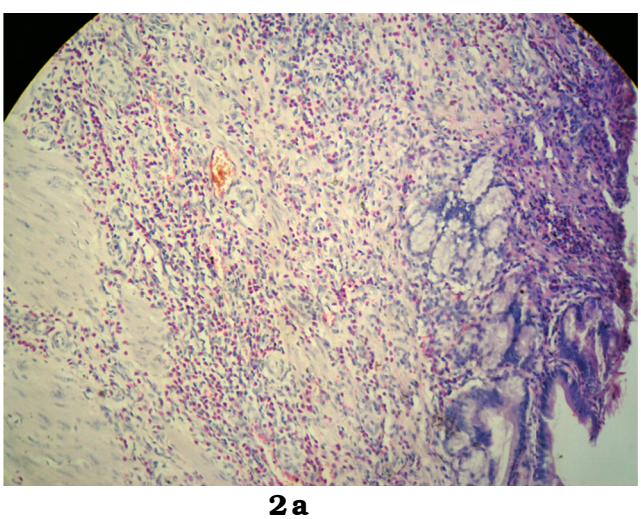


Fig.1. Magnetic resonance cholangiopancreatography showing smooth tapering of the common bile duct distally

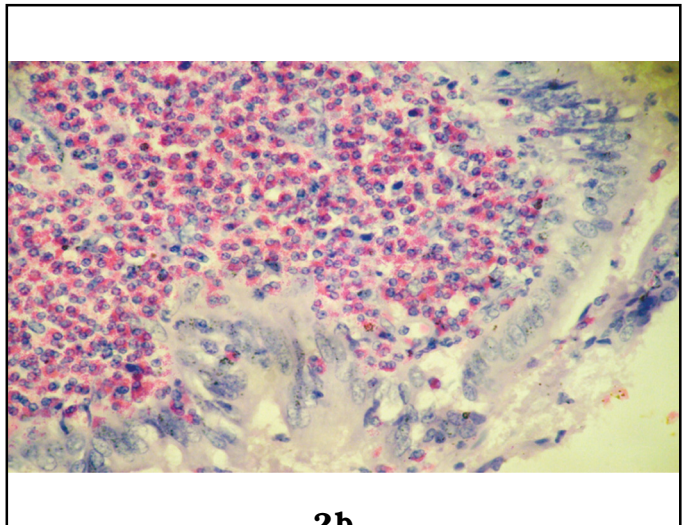
histopathology. Histopathology of cystic duct and proximal CBD showed intense tissue eosinophilia, with fibrosis (Figs 2a and 2b). The final diagnosis of eosinophilic cholangiopathy presenting as distal CBD stricture was made post-operatively. She was started on oral prednisolone at 1mg/kg per day for twelve weeks, then gradually tapered and maintained on low dose 5mg per day for six months. She was followed up three years and she was asymptomatic.

Discussion

Eosinophilic cholangiopathy is a rare benign cause of biliary obstruction causing obstructive jaundice. Very few cases have been reported in literature both in adults and children. Eosinophilic cholangiopathy is part of a spectrum of diseases defined by eosinophilic infiltration of tissues and organs with or without peripheral eosinophilia. These patients have in common an unexplained eosinophilic proliferation, with varying severity and prognosis. Peripheral blood eosinophilia and eosinophilic infiltration of the gastrointestinal tract and hepatobiliary system may be seen in association with a number of conditions.[1] Clinically it is characterized by recurrent wheeze and intermittent cholangitis. The exact cause is unknown. Regardless of the clinical presentation, the pathogenesis of eosinophilic infiltration is poorly understood. Patients with a more benign presentation tend to have immunologic abnormalities indicative of hypersensitivity. Pathologically this is characterized by dense transmural eosinophilic infiltration of the biliary tract. Tissue eosinophilia can affect only the gallbladder (i.e., eosinophilic cholecystitis), the gallbladder and bile ducts simultaneously or only the bile ducts (i.e., eosinophilic cholangitis).[3-5] Eosinophilic infiltration may not be limited to the biliary tract but can affect other organs or various layers of the GI tract. The difficulty may be compounded if there is gastrointestinal tract involvement, which indicates the possibility of ulcerative colitis or Crohn's disease associated with primary sclerosing cholangitis. With eosinophilic cholangiopathy, the bile duct wall is thickened, with or without biliary dilatation at CT or US. Tenner et al[6] reported a case with an isolated stricture



2a



2b

Fig.2a and 2b. Histopathology of the excised segment of the bile duct showing dense infiltration with eosinophils with fibrosis.

of the common bile duct. Irregularities of the wall of the common bile duct and intrahepatic ducts are seen at endoscopic retrograde cholangiography or transhepatic cholangiography. Most of these patients show dramatic response to steroids which is the hallmark of the disease. The treatment of eosinophilic cholangitis varies from conservative watchful waiting to the use of steroids and hydroxyurea.[7] The treatment of eosinophilic gastroenteritis is varied from short repeated courses of steroids to long-term low-dose steroid therapy or the use of steroid-sparing agents such as montelukast, ketotifen or sodium cromoglycate.[8] Other modalities of treatment include stent placement in biliary system. Hepaticojejunostomy has also been carried out in a few cases.[9]

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CLIPPINGS

Use of vitamin A and fish oils for retinitis pigmentosa

Retinitis pigmentosa (RP) comprises a group of hereditary eye diseases characterized by progressive degeneration of retinal photoreceptors. It results in severe visual loss that may lead to legal blindness. Symptoms may become manifest during childhood or adulthood and include poor night vision (nyctalopia) and constriction of peripheral vision (visual field loss). This field loss is progressive and usually does not reduce central vision until late in the disease course.The worldwide prevalence of RP is one in 4000, with 100,000 patients affected in the USA. At this time, there is no proven therapy for RP.

Objectives of this review was to synthesize the best available evidence regarding the effectiveness and safety of vitamin A and fish oils (docosahexaenoic acid (DHA)) in preventing the progression of RP.

Selection criteria: We included randomized controlled trials (RCTs) evaluating the effectiveness of vitamin A, fish oils (DHA) or both, as a treatment for RP. We excluded cluster-randomized trials and cross-over trials.

Authors' conclusions: Based on the results of three RCTs, there is no clear evidence for benefit of treatment with vitamin A and/or DHA for people with RP, in terms of the mean change in visual field and ERG amplitudes at one year and the mean change in visual acuity at five years follow-up. In future RCTs, since some of the studies in this review included unplanned subgroup analysis that suggested differential effects based on previous vitamin A exposure, investigators should consider examining this issue. Future trials should take into account the changes observed in ERG amplitudes and other outcome measures from trials included in this review, in addition to previous cohort studies, when calculating sample sizes to assure adequate power to detect clinically and statistically meaningful difference between treatment arms.

Rayapudi S, Schwartz SG, Wang X, Chavis P. Vitamin A and fish oils for retinitis pigmentosa. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD008428. DOI: 10.1002 14651858.CD008428.pub2. Assessed as up to date: August 20, 2013.

CASE REPORT

STAPHYLOCOCCAL OSTEOMYELITIS WITH DEEP VEIN THROMBOSIS

*Gayathri S
**Karthika S
***Gowrishankar NC
***Thangavelu S

Abstract: *Acute osteomyelitis is a severe form of staphylococcal infection. Deep vein thrombosis (DVT) with septic pulmonary embolism (PE) has been described as a rare association with disseminated staphylococcal disease (DSD) especially when associated with osteomyelitis. The authors describe a 7 year old child affected with acute osteomyelitis with DVT. All cases of acute osteomyelitis/DSD warrant a high index of suspicion for DVT as there can be a clinical overlap and if not recognized early can adversely affect the outcome.*

Key words: *Osteomyelitis, Deep vein thrombosis*

A 7 year old previously healthy boy was admitted with history of high grade fever, pain around the left hip joint and inability to walk since 5 days. There was no history of trauma. Except for a furuncle over the face 10 days prior, the past history was unremarkable. Examination revealed a sick looking febrile child with left lower limb flexed and abducted at the hip. There was warmth and fullness around the left hip with pain on minimal movement. Plain radiograph of the left lower limb was normal. Ultrasound left hip showed no effusion. The hemogram showed neutrophilic leukocytosis (TC: 15,500/cu.mm, polymorphs: 79%) with elevated CRP (78mg/L).The child was empirically started on antibiotics (Ceftriaxone and Cloxacillin) with the clinical suspicion of osteomyelitis/pyomyositis. On day 3 the swelling in the left lower limb increased extending down to the feet with a positive Homan's sign. An ultrasound Doppler showed thrombosis of the left external iliac vein, common femoral vein extending up to the distal part of the superficial femoral vein. The child was screened for prothrombotic conditions (Protein C, S, Antithrombin III, antiphospholipid antibody levels, homocysteine levels) which were negative and was started on low molecular weight heparin (LMWH). An MRI of the left lower limb showed diffuse osteomyelitis involving the entire shaft of the left femur. CXR was normal. There was no echocardiographic evidence of pulmonary embolism/endocarditis. Surgical drainage was done and traction given. Both blood culture and pus from the infected site grew methicillin sensitive Staphylococcus aureus. Child was continued on antibiotics and warfarin started after 1 week of LMWH. He became afebrile in a week. Antibiotics were continued for 6 weeks. Follow up Doppler showed recanalization of the thrombosed veins and he was continued on warfarin for 6 months.

Discussion

DVT is rare in children and occurs mostly secondary to central line catheters, trauma, surgery, malignancies and congenital heart disease.[1] The association of DVT with staphylococcal musculoskeletal sepsis and osteomyelitis has been reported in several case series recently.[2,3,4] In a study by Crary et al[5] nearly 23% of the cases of osteomyelitis had DVT at the site of infection, proven by imaging. The high incidence of DVT in staphylococcal septicaemia is due to the action of various exotoxins. Staphylococcal alpha toxin acts on cell membranes and produces aggregation of platelets and spasm of vascular smooth muscles. Coagulase interacts with fibrinogen and causes plasma to clot.[6] Organisms with Panton-Valentine leukocidin gene that encodes an exotoxin with pore forming activity which destroys leucocytes have increased propensity for DVT.[7]

There can be a clinical overlap between the findings of osteomyelitis and DVT. This condition should be suspected when edema is severe, as in the above case. In the case report by Ali et al[4] two children had DVT recognized earlier with the diagnosis of osteomyelitis delayed, because of overlapping symptoms. Infected DVT in the setting of osteomyelitis can lead to showering of septic thromboemboli causing pulmonary embolism and dissemination to distant organs adversely affecting the outcome.[8]

* Junior Consultant, Department of Pediatrics
** Post Graduate, Department of Pediatrics
*** Senior Consultant,
Department of Pediatrics,
Mehta's Children's Hospital,
Chennai.

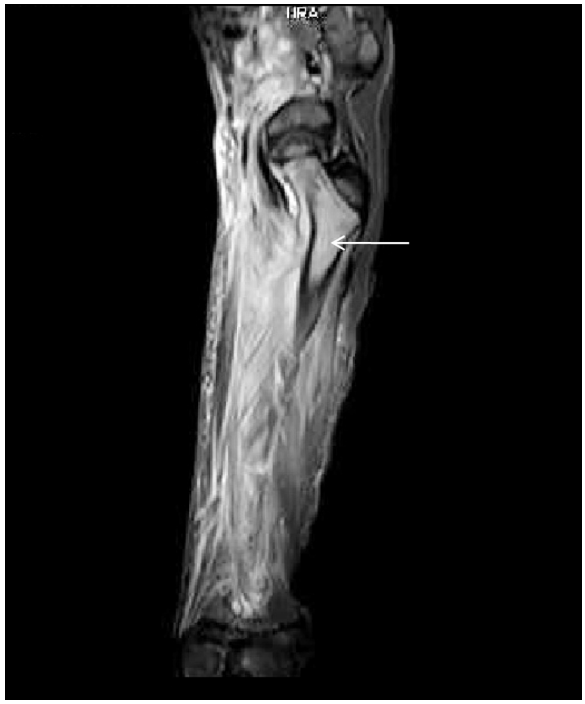

Fig.1. MRI left lower limb sagittal view (T2 weighted image) showing increased signal intensity in the upper femoral shaft (white arrow) suggestive of osteomyelitis.

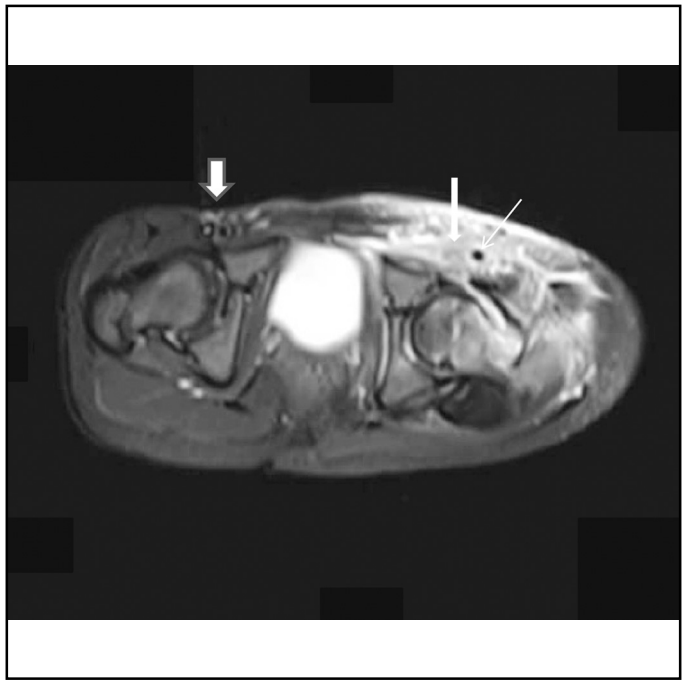

Fig.2. MRI showing cross section of both lower limbs through upper end of femur (T2 weighted image) showing thrombosed left common femoral vein(thick white arrow). Patent left femoral artery seen lateral to it (thin white arrow). Normal vein and artery seen on the right side (thickest arrow).

MRI is more sensitive than CT or radionuclide imaging in diagnosing acute osteomyelitis as well as identifying contiguous septic arthritis, pyomyositis and venous thrombosis.[9]

Initial therapy with unfractionated heparin (75U/kg loading dose followed by 20U/kg/hr to maintain APTT 1.5 times normal) or LMWH (to maintain anti FXa 0.5-1U/ml) is given for 5-10 days. Pediatric experience is maximum with Enoxaparin given at a dose of 1mg/kg/dose subcutaneous twice daily. Vitamin K antagonists (Warfarin) can be started as early as Day 1 and are continued for 6 months monitoring the PT-INR (range between 2-3).Thrombolytic therapy is not routinely recommended due to the risk of bleeding and should be individualized.[1]

Conclusion

Thromboembolic complications can occur in the setting of staphylococcal musculoskeletal sepsis. It is one of the important causes of DVT outside the intensive care setting. Early imaging and commencement of anticoagulation and antimicrobials can be life saving.

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CLIPPINGS

Postnatal parental education for optimizing infant general health and parent-infant relationships

Many learning needs arise in the early postpartum period, and it is important to examine interventions used to educate new parents about caring for their newborns during this time.

Objectives: To assess the effects of structured postnatal education delivered to an individual or group related to infant general health or care and parent-infant relationships.

Selection criteria: Randomized controlled trials of any structured postnatal education provided to individual parents or groups of parents within the first two months post-birth related to the health or care of an infant or parent-infant relationships were included.

Authors' conclusions: The benefits of educational programs to participants and their newborns remain unclear. Education related to sleep enhancement appears to increase infant sleep but appears to have no effect on infant crying time. Education about infant behaviour potentially enhances mothers' knowledge; however more and larger, well-designed studies are needed to confirm these finding

Bryanton J, Beck CT, Montelpare W. Postnatal parental education for optimizing infant general health and parent-infant relationships. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD004068. DOI: 10.1002/14651858.CD004068.pub4. Assessed as up to date: September 17, 2013

Maternal oxygen administration for fetal distress

Maternal oxygen administration has been used in an attempt to lessen fetal distress by increasing the available oxygen from the mother. This has been used for suspected fetal distress during labour and prophylactically during the second stage of labour on the assumption that the second stage is a time of high risk for fetal distress.

Objective of this review was to assess the effects of maternal oxygenation for fetal distress during labour and to assess the effects of prophylactic oxygen therapy during the second stage of labour on perinatal outcome.

Selection criteria: Randomized trials comparing maternal oxygen administration for fetal distress during labour and prophylactic oxygen administration during the second stage of labour with a control group (dummy or no oxygen therapy).

Authors' conclusions: **Implications for practice-** There is not enough evidence to support the use of prophylactic oxygen therapy for women in labour, nor to evaluate its effectiveness for fetal distress.

Implications for research - In view of the widespread use of oxygen administration during labour and the possibility that it may be ineffective or harmful, there is an urgent need for randomized trials to assess its effects.

Fawole B, Hofmeyr GJ. Maternal oxygen administration for fetal distress. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD000136. DOI: 10.1002/14651858.CD000136.pub2.Assessed as up to date: November 12, 2012.

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09.10-09.30 hrs	Equipments in office practice	Dr.Raju Subramaniam
09.30-09.40 hrs	Discussion	
09.40-10.50 hrs	**SESSION II**	
09.40-10.00 hrs	Refractory anemia – Evaluation	Dr.Aruna Rajendran
10.00-10.20 hrs	Vitamin D - Deficiency to toxicity	Dr.M.Vijayakumar
10.20-10.40 hrs	Approach to bleeding PR in an infant	Dr.Malathi Sathiyasekaran
10.40-10.50 hrs	Discussion	
10.50-11.00 hrs	**TEA / COFFEE BREAK**	
11.00-11.30 hrs	**INAUGURATION**	
11.30-12.25 hrs	**SESSION III**	
11.30-12.00 hrs	Antibiotic stewardship	Dr.Y.K.Amdekar
12.00-12.20 hrs	Infantile wheeze	Dr.D.Vijayasekaran
12.20-12.25 hrs	Discussion	
12.25-13.15 hrs	**SESSION IV**	
	Panel Discussion	Moderator: Dr.Jayakar Thomas
	"Pediatric dermatology in office practice"	Panelists : Dr. Parimalam Kumar Dr.V.Anandan Dr.C.Vijayabhaskar Dr.R.Madhu
13.15-14.00 hrs	**LUNCH**	
14.00-15.00 hrs	**SESSION V** Panel discussion	**Moderator : Dr.P.Ramachandran**
	"Newer vaccines: Jap B, Typhoid conjugate, Meningococcal conjugate, Influenza"	Panelists : Dr.V.V.Varadarajan Dr.T.N.Manohar Dr.L.N.Padmasani Dr.C.V.Ravisekar
15.00-16.10 hrs	**SESSION VI**	
15.00-15.20 hrs	Acute encephalitis syndrome	Dr.Y.Sangeetha
15.20-15.40 hrs	Management issues in tuberculosis	Dr.N.C.Gowrishankar
15.40-16.00 hrs	Pediatric cardiac emergencies	Dr.K.Sasidaran
16.00-16.10hrs	Discussion	
16.10-17.00 hrs	**SESSION VII**	
16.10-16.30 hrs	Point of care testing in ER	Dr.Radhika Raman
16.30-16.50 hrs	Fever with jaundice – Approach	Dr.S.Thangavelu
16.50-17.00 hrs	Discussion	

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