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CONTENTS

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CHANGING TRENDS IN INTRAVENOUS MAINTENANCE FLUID THERAPY

**** Thangavelu S***

Abstract: *Present concept about intravenous maintenance fluid is sixty years old and was introduced by Holliday and Segar. Recent understanding about fluid electrolyte balance and antidiuretic hormone has questioned the validity of this concept. Reporting of more than fifty cases of hyponatremic encephalopathy caused by hypotonic intravenous maintenance fluid, has raised many arguments for using isotonic fluid as maintenance. Another group of researchers favors reduction in volume rather than increasing the sodium concentration in the maintenance fluid. Opinion for and against as well as the acceptable guidelines are discussed in this article.*

Keywords: *Intravenous maintenance fluid, Isolyte P, Hyponatremic encephalopathy, Hospital acquired hyponatremia.*

Most common medication used in any hospital is intravenous (IV) fluid. Paradoxically this is the medicine least understood, highly controversial and prescribed imprecisely. Major constituent of our body is water. Like other nutrients, water and electrolytes are essential daily needs. This is regulated by thirst and the various hormones like aldosterone, antidiuretic hormone (ADH) and natriuretic peptide. In a normal child they are consumed in the form of water and other liquid preparations of diet. In a hospitalized child IV maintenance fluid is started for different indications. The concept of maintenance fluid therapy is six decades old and currently many new recommendations have evolved. Evolution of new specialties like pediatric emergency, critical care and nephrology which focus on fluid electrolyte status closely has shown the way to this change. Though all the new recommendations are not fully accepted by pediatric community, most recent guidelines emphasize on avoiding hypotonic fluid for maintenance.

* Former Reader in Pediatrics,
Pediatric Intensive Care Unit,
Institute of Child Health, Madras Medical College,
Currently, Pediatric Consultant,
Mehta Children Hospital, Chennai.

Fluid electrolyte physiology[1]

It is interesting to note that two thirds of earth as well as human body is made up of water. In infants and children total body water (TBW) is 65%, while in a term and preterm newborn, it is 70% and 80% respectively. As the child grows older, TBW decreases to 60% in adult male and 55% in adult female. But percentage of intracellular fluid compartment remains the same in all age groups at 40%. Fall in TBW with growing age is reflected in shrinkage of extracellular fluid compartment (ECF) (Table I).

In a child, TBW is two thirds of body weight (Figs.1 & 2). In TBW, one-third is ECF and two-thirds is ICF. In ECF, one-quarter is plasma (Intravascular fluid) and three-quarters is interstitial fluid.

Table I. Body water compartments in various ages (% age of body weight)

Preterm	Term	newborn	Infant and child	Adult	
				Male	Female
ICF	-	40	40	40	40
ECF	-	30	25	20	15
TBW	80	70	65	60	55

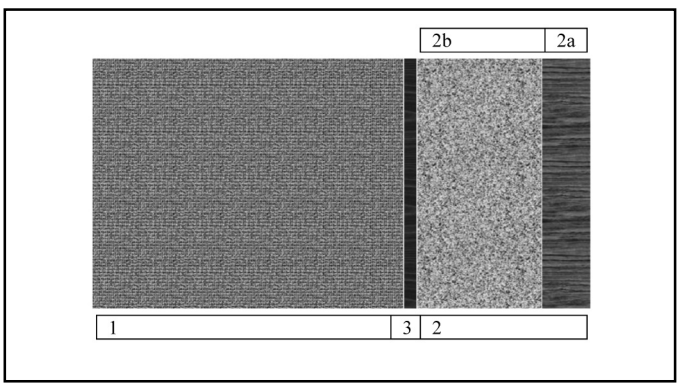

Fig. 1. Body fluid compartments (Graphical representation)[2]

TBW: 60-70% of Body Weight (BW), 1. ICF: 40% of BW, 2. ECF: 20% of BW, a. Intravascular-fluid: ¼ of the ECF (5% of BW), b. Interstitial Fluid (ISF) surrounds the cells, but does not circulate. About ¾ of the ECF. (15% of BW), 3. Transcellular fluid: CSF, pleural, peritoneal (1.5% of BW)

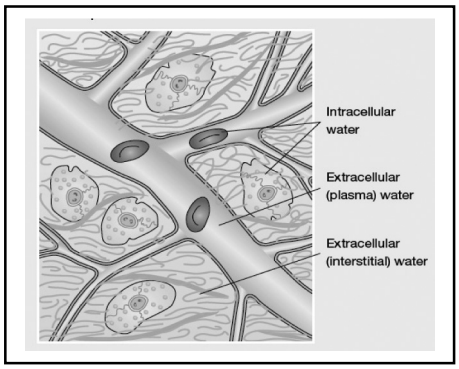

Fig.2. Body fluid compartments (Pictorial representation)[2]

Tonicity of the infused fluid decides the distribution of fluid among the various volume compartments

The objective of IV fluid therapy is to fill the intravascular compartment. Isotonic fluid like normal saline (NS) or Ringer's lactate (RL) will stay in the intravascular compartment better than other IV fluids. When hypotonic fluids like G5 ½ NS, G5 ¼ NS or G5 1/5 NS are administered, only a small quantity stay in the intravascular compartment. Hence, isotonic fluids are preferred in the correction of shock and deficit.

Definitions

Osmolality: This is the measure of the number of osmotically active particles present in a solution per kilogram of solvent.

Osmolarity: This is the number of osmotically active particles present per litre of solution. Osmolality is commonly used in practice. For practical purposes both are nearly equal and the terms are often used interchangeably.

Tonicity: It is the effective osmolality of a solution and is equal to the sum of the concentrations of solutes that have the capacity to exert an osmotic force across a semi-permeable membrane, i.e impermeable solutes like sodium. Tonicity is a property of a solution with reference to a membrane. But osmolality or osmolarity is the property of a solution independent of any membrane, because it includes both impermeable and permeable solutes like urea. For example, glucose 5% is initially iso osmolar with plasma but, in normal conditions, glucose is a permeant and ineffective solute which readily enters cells. Glucose 5% is therefore isosmolar with plasma but hypotonic with reference to the cell membrane.

Objective of IV fluids

Intravenous fluids are commonly used with four objectives.

1. Isotonic fluid bolus to correct shock. eg, Septic shock, Dengue shock, Hypovolemic shock.

2. Deficit replacement eg. Diarrheal dehydration.

3. For maintenance fluid eg. Preoperative IV fluids when the child is kept fasting.

Everyday fluids are lost through normal physiological activities, such as respiration, perspiration and urination. This is called as physiological water losses. This loss should be constantly replaced. Maintenance fluid is provided with this objective, when there are no pathological fluid losses. Out of 100 mL/kg lost, urinary loss is approximately 50mL/kg (40-70 mL) and stool 5 mL/kg. Sweat is 0-20 mL/kg. These three routes are considered as 'sensible' water losses. Insensible water loss means loss of water through skin which is lost by evaporation and also from respiratory tract. It is not measurable and usually we are not aware of it. This is isolated water loss without loss of solutes. Skin loss of 30 ml/kg and breath loss of 15ml/kg are included in this (Fig.3).

4. Replacement of ongoing losses eg.loss of water in diarrheal stools, polyuria, loss through ostomies.

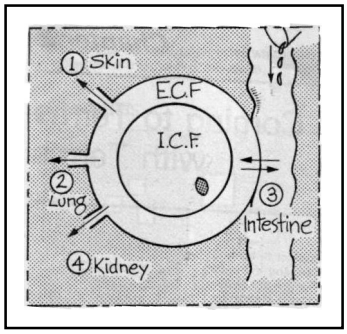

Fig. 3. Physiological water losses 100 mL/kg

Insensible water loss: Lungs – 15 mL/kg, Skin – 30mL/kg; Sensible water loss: Urine – 50 mL/Kg (40-70), Stool – 5 mL/kg, Sweat – 0-20mL/kg

Indications

Enteral feeds are the ideal and practical choice for every child. IV maintenance fluid (IVMF) is indicated only when enteral feeds cannot be given or should not be given. Oral feeds cannot be given for a child with acute respiratory distress for the fear of aspiration as in bronchiolitis, bronchopneumonia, cardiac failure or in children with altered level of consciousness. Later, this can be switched over to

nasogastric feeds. In preoperative and post operative states where child cannot be given oral feeding, IV fluids are needed particularly in preschool children.

Composition of maintenance fluid

Water, glucose, sodium and potassium are the standard constituents. Apart from water, glucose is added to supply energy and to increase the osmolarity, sodium and potassium to replace the normal requirements. Other minerals and electrolytes like calcium, bicarbonate and phosphate are not included as the child can manage without them for few days.Ideal IV maintenance fluid should be cheap, easily available, should have long shelf life and free from complications.

Limitations of IV maintenance fluid[4]

1. It provides only 20% of energy requirements and if IVMF is needed for more than 3-5 days, TPN or enteral feeding should be started as nasogastric tube feeds.

2. In a normal child with intact compensatory mechanisms any excess or deficit can be compensated, but in a sick child with compromised physiology compensatory mechanisms may not work well. Hence, close clinical watch and biochemical monitoring of electrolytes are mandatory prior to starting IV maintenance fluid and every 24 to 48 hours thereafter.

3. Calcium, magnesium, bicarbonate and phosphates are not routinely included in the usual fluid meant for short term use. But they may have to be supplemented if parenteral fluids are needed for a longer period.

4. In a child with related specific abnormalities monitoring and appropriate correction is needed eg. children with diabetes insipidus may require increased volume of fluid with low sodium, child with renal tubular acidosis may need supplementation with sodium bicarbonate and in a child with ventilator support phosphate supplementation may be needed as hypophosphatemia will lead to weaning failure.

Limitations of hypotonic IV maintenance fluid

Problem of the currently used hypotonic IVMF is hospital acquired hyponatremia. Volume and osmolality of the ECF is finely balanced by the interaction between various hormones- vasopressin, aldosterone and natriuretic peptides and renal system. Both hypovolemia and increase in osmolality stimulates vasopressin secretion and thirst . But the thirst threshold is approximately 10 m.osm higher than the osmotic threshold for vasopressin release. As a result, vasopressin is released prior to initiation of thirst, so that the ingested water is retained. This is comparable to a simple analogy that hole in the pot is sealed before pouring in water. Water balance is closely related to sodium balance. Hypovolemia stimulates aldosterone secretion which in turn stimulates renin angiotensin and retains sodium and water. This delicate mechanism maintains sodium and water balance despite gross variation in water and salt intake by a normal, active child. This balance may be upset in a hospitalized child. Despite absence of fluid loss or serious renal impairment, hyponatremia can occur. This is because of non osmotic stimulation of ADH by the factors like anxiety, pain, stress caused by surgery and hospitalization. Inappropriate vasopressin secretion despite absence of increase in osmolality and reduction in volume status leads to retention of water and hyponatremia. This is aggravated by infusion of hypotonic IVMF like isolyte P leading to expansion of ECF volume. This causes dilutional hyponatremia. End result is the development of serious complication like hyponatremic encephalopathy. Hyponatremic encephalopathy is caused by influx of water into the intracellular space resulting in cellular swelling, cerebral edema, seizures and brain stem herniation. This happens in previously healthy kids.

Hot debate over the sodium content and volume of IVF maintenance fluid

Present concept about IVMF is 60 yrs old and concerns have been raised from many quarters in the last few years. More than 50 cases of hyponatremic encephalopathy in previously well children have been reported in the world literature which was associated with use of hypotonic IVMF solution such as 0.15% sodium chloride with 5 % Dextrose (Isolyte P in our part of the country).[5] This practice of using hypotonic solutions like 0.15% sodium chloride Dextrose was proposed by Holliday and Segar in the 1950s and are still used.All critics agree among themselves that this practice need to be changed. But they disagree on how this change can be implemented. One group argues for substituting isotonic fluid like NS or RL with appropriate glucose and potassium instead of isolyte P as IVMF Second group debates against isotonic fluid, but they want to retain the same hypotonic fluid at a reduced volume at 2/3 maintenance. As the debate still continues, no consensus has been arrived at. The following recommendations have been taken from two standard references.

Nelson text book of Pediatrics 19th edition, recommends 5%glucose with 0.2 NS as IVMF for children below 10 kg body weight and 5% glucose with 0.45 normal saline beyond10 kg with appropriate potassium. But preparing 5% G 0.2NS is cumbersome and might

Table II. Choice of maintenance intravenous fluids in different clinical states

Clinical condition	Sodium content of IVMF	Volume of IVMF	Comments
All hospitalized children who are not critically ill	G 5 ½ NS with Potassium 20 mmol/L	Normal	Monitor clinically and daily electrolytes
Pre operative	GNS with potassium 20 mmol/L	Normal	
Post operative	GNS with potassium after voiding urine	2/3 of normal	
Acute respiratory conditions	G5 ½ NS with Potassium 20 mmol/L	Normal	Check potassium and correct if low
CNS infection, head injury, Neurosurgery	NS with potassium 20 mmol/L	Normal or 2/3 of normal, if SIADH suspected	Add glucose if hypoglycemia
Dengue	NS with potassium 20 mmol/L	2/3 of normal	Add glucose if hypoglycemia
Cardiac conditions	G5 ½ NS with potassium 20 mmol/L		Check sodium, potassium and correct if low
Renal	G5 ½ NS with no potassium unless hypokalemic	IWL + Previous day urine output	Monitor electrolytes

complicate the regular practice. The second is from National Health Service, United Kingdom which has issued a patient safety alert **"Reducing the risk of hyponatremia when administering IV infusions to children"** to their pediatricians and hospitals. This advice appears to be simple to execute and may be considered as a practical guideline till the controversy is resolved. Both the arguments and the current advice by NHS UK are given below.

Viewpoint favouring normal saline as IVF maintenance solution beyond neonatal period: (more salt, same volume)[6,7]

Isotonic solutions with 5% dextrose should be used as the IVMF solution, because of the following reasons.

- Though Holliday and Segar formula is simple, it has overestimated energy expenditure and thereby IV maintenance fluid requirement.
- Insensible water loss (IWL) in acutely ill kids and those in PICU is almost half of what is recommended. Again thermo neutral environment and humidifiers in ventilated patients further reduce the IWL. Hence ,total daily physiological water loss may be only less than half in acutely ill children or after surgery
- Overriding influence of ADH was not recognized when Holliday Segar formula was conceived. Increased ADH secretion is commonly observed in acutely ill children because of non osmotic stimulation such as stress due to hospitalization, fever, vomiting, surgery, pain and use of NSAID. This reduces urine output and leads frequently to hyponatremia as the kidneys are unable to excrete the excess free water infused by the hypotonic fluids. ADH concentration was found to be reduced after usage of normal saline and not with 5% dextrose.

Viewpoints against isotonic fluid for maintenance[6,8,9] (Same amount of salt, less volume)

The group arguing against isotonic fluid quote studies in surgical patients who developed hyponatremia even after administration of isotonic fluid. In the absence of a RCT comparing the current standard of using hypotonic fluid with 1. Isotonic fluid in standard volume 2.Isotonic fluid in reduced volume 3.Hypotonic fluid in reduced volume, it is difficult to say whether increasing the sodium content or reducing the volume is going to be useful or not. Therefore, if the problem is antidiuresis, rather than natriuresis, then the principle of treatment should be less fluid, not more salt.(using ¼ or 1/5 normal saline (Isolyte P) as IV maintenance solution, but 50 – 60% of the total volume

currently used. Singhi and M.Jayashree in their studies concluded that use of conventional hypotonic maintenance fluids is not the main cause of hyponatremia in critically ill children. There may be an alternative mechanism such as translocation and/or redistribution of sodium contributing to hyponatremia in sick children which needs further investigation.[9]

Current recommendations

(NHS UK Patient safety alert 22: "Reducing the risk of hyponatremia when administering intravenous infusions to children". National Patient Safety Agency no 22. 28 March 2007)

1. Wherever possible oral fluids are preferable
2. For majority of the children, half normal saline with 5% dextrose (Sodium chloride 0.45% with 5% dextrose) is the safe IV maintenance fluid.
3. In the following circumstances isotonic fluids are needed which are normal saline (0.9% Sodium chloride) or 5% Dextrose with normal saline (5% Dextrose with 0.9% Sodium chloride) with appropriate potassium or Ringer's lactate
    a. Serum sodium is in the lower range of normal < 135 mmol/L
    b. Peri and postoperative states
    c. CNS infection, head injury, neurosurgical post operative patients
    d. Bronchiolitis
    e. Excessive gastric and diarrheal losses, salt wasting syndromes, those requiring replacement of ongoing loss,. eg. Severe vomiting and diarrhea including cholera, diabetic ketoacidosis
    f. Children with hypernatremia > 160 mmol/L to prevent rapid fall in serum sodium causing neurological injury
4. Volume of the IVMF: wherever excess ADH secretion is expected, this can be reduced to 2/3 of normal recommended IVMF volume

Kannan L et al, compared the effect of three IV fluid regimes on the incidence of hyponatremia in their study. They observed that incidence of hyponatremia was lowest (1.72%) when0.9% saline in 5% dextrose at the standard maintenance rate was used. Incidence was 3.8% when 0.18% saline in 5% dextrose at two-thirds of the standard maintenance rate was used and highest (14.3%) was seen with 0.18% saline in 5% dextrose at the standard maintenance rate.[10] Based on these results, they concluded that the administration of 0.9% saline in 5% dextrose as IV maintenance fluid helps in reducing the incidence of hospital-acquired hyponatremia among children.

In different clinical conditions, sodium content of IVMF and the volume varies [11] (Table II).

Caution

Readymade commercially available IV solutions are convenient to use in various situations. Currently recommended IVMF is G5 ½ Normal Saline which is commercially available but without potassium. Potassium has to be added to this solution by mixing 5 ml (10 mmol) of potassium chloride solution (15%) to 500 ml of G5 1/2NS. But this process should be done by an experienced nurse who is aware of the fact that it is a high risk medication and should not be injected directly. It should be always given as infusion and after adding the KCl to the IVF bottle or bag, it must be thoroughly mixed for uniform distribution. The bottle needs to be labelled as potassium containing fluid. Mishaps and fatal medication errors have occurred at all levels when right procedure was not followed. If G5 ½ NS with 20 mmol of KCl is commercially made available, many serious medication errors.

Practical aspects

1. Prescription for IVF should contain proper description of the type of fluid, volume, duration and rate of flow.

2. Clinical monitoring for vital signs includes, pulse rate, pulse volume, respiratory rate, work of breathing, liver span, signs of dehydration or overload, blood pressure, oxygen saturation, weight and urine output. Laboratory monitoring includes serum electrolytes, urea, creatinine and HCT every day or atleast on alternate days will be useful.

3. Daily needs of IV maintenance volume as per Holliday Segar formula and rate of flow per hour are given in the Table III. Flow rate is well controlled when infusion pumps or syringe pumps are used. In resource poor settings, pediatric IV maintenance set should be used to properly regulate the flow as well as to avoid inadvertent fluid overload. When adult IV infusion set is used it is called as mega drops and 15drops comprise one ml in this set. eg. If 2000 ml/day is to be given over 24 hrs, remove the last two digits, leaving behind 24. ie 24 drops/minwill deliver 2400 mL in 24hrs. When pediatric IV maintenance set is used the drops are smaller and are called as micro drops. Here 60 micro drops make one mL. eg If 2400 ml is to be delivered over 24 hrs, calculate for hourly rate of flow which

Table III. Maintenance fluid (water) requirement(Holliday Segar formula)

BW in Kg	Volume per 24hours	Volume per hour
Upto 10 Kg	100 mL/kg	4mL/kg/hour
11 – 20 kg	1000mL plus 50mL/kg for each 1 Kg>10	40mL/hour plus 2mL/kg for each 1 Kg>10
21 Kg and above	1500mL plus 20mL/Kg for each 1 Kg>20	60ml/hour plus 1 mL/Kg/hour for each 1 Kg >20

Eg. Wt 10 kg – 40 mL/hr; 15 kg – 40+10=50 mL/hr; 25 kg – 40+20+5=65 mL/hr

The maximum total fluid per day is normally 2400ml and per hour is 100ml.

is 2400/24=100 mL/hr and set at the rate of 100 drops per minute, 100 mL per hour and 2400 mL/day will be delivered. Nurses should be taught to adjust the rate of flow by simple drop counting.

Points to Remember

- ***Traditional calculation of IVMF needs to be revised with respect to type of fluid and volume***
- ***Though there are two options such as, 1. Using G5 ½ NS or GNS or NS or RL with appropriate potassium in standard maintenance volume.and 2. Reduction of volume by 2/3 maintenance, former is accepted in standard guidelines***
- ***Based on underlying condition, IVMF is modified***
- ***If G5 ½ NS with 20 mmol of KCl is commercially made available, many serious medication errors can be avoided***
- ***IVF is a medication needing correct prescription mentioning the type of fluid, volume, duration and correct rate of flow.***

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CHANGING TRENDS IN THE ROLE OF VITAMIN D IN CHILDREN

** Sangeetha G*
** Shweta Priyadarshini*
*** Prahlad N*
*** Vijayakumar M*

Abstract: *Vitamin D is not an essential dietary vitamin in a very strict sense. 25(OH) vitamin D is produced in the liver and is converted to 1,25 $(OH)_2$ vitamin D (calcitriol) in the kidney. Serum calcium, phosphorous, PTH and fibroblast growth factor (FGF-23) play a major role in the regulation of vitamin D. Production of 1,25 $(OH)_2$ vitamin D locally in various non-renal tissues is being increasingly documented with its various advantages. The optimal intake of vitamin D for neonates, children and adolescents is 400 IU/day. Previously vitamin D levels were considered as sufficiency, insufficiency, mild deficiency and severe deficiency if the levels were more than 30, 16 to 30, 5 to 15 and less than 5 ng/mL respectively. According to changes in the recent literature, the levels have been modified to more than 20, 12 to 20, 8 to 12 and less than 8ng/mL respectively. Treatment of vitamin D deficiency is based on vitamin D levels. Usage of vitamin D2, vitamin D3 as well as alfa calcidol and 1,25 $(OH)_2$vitamin D is decided by the vitamin D deficiency state, severity of hypocalcemia and the associated renal disorders like chronic kidney diseases. Hypercalcemia and hypercalciuria are the important toxic effects of vitamin D chronic intoxication affects various tissues of the body including the kidneys, heart and blood vessels. Rickets other than due to vitamin D deficiency needs careful attention and the usage of vitamin D should be monitored carefully. Changing trends in vitamin D usage has made us reconsider its use in other conditions also.*

Keywords: *Vitamin D optimal need, Vitamin D levels, Extra skeletal effects, Changing trends in usage.*

* Fellow in Pediatric Nephrology

** Consultant Pediatric Nephrologist,
Mehta Children's Hospital,
Chennai - 600 031.

Vitamin D is a fat soluble 'secosteroid', a steroid in which one of the bonds in steroid ring is broken. Vitamin D can be synthesized in mammals from sunlight endogenously in the skin; hence it is not an essential dietary vitamin in a very strict sense. The knowledge about vitamin D and its analogues have increased significantly over the past 10 years giving an insight into effect of Vitamin D on various other tissues in the body apart from skeletal system.Vitamin D has an endocrine and an autocrine mode of action. Endocrine action helps in calcium regulation through calcitriol. Autocrine function which comes in effect by degradation of calcitriol intracellularly, facilitate gene expression in various tissues and thus their function.[1]

Vitamin D metabolism

Vitamin D can be endogenously synthesized in the skin when exposure to sunlight is adequate. Ultraviolet B radiation from sunlight converts 7-dehydrocholesterol in skin to pre-vitamin D3 which gets converted to vitamin D3. Vitamin D can be ingested from plant source (ergocalciferol or vitamin D2) or animal source (cholecalciferol or vitamin D3).

Vitamin D, obtained from the above sources, enters the circulation and goes to liver bound to vitamin D binding protein(VDBP). Here a cytochrome P450 enzyme 25-hydroxylase, converts vitamin D to 25-hydroxy vitamin D (25(OH) D). This step is substrate dependent and hence reflects the nutritional status of an individual. 25-hydroxy vitamin D, which is the specific vitamin D metabolite, is measured to determine a child's vitamin D status.[2] 25-hydroxy vitamin D is then transported to kidney, bound to vitamin D binding protein. In proximal renal tubular cells, the mitochondrial P450 enzyme 1-alpha-hydroxylase, converts 25(OH)D to its active metabolite 1,25-dihydroxy vitamin D (1,25 $(OH)_2D$), calcitriol.[3] The 1-alpha-hydroxylase enzyme is also present in various other tissues like macrophages, breast, skin, large intestine, muscles, etc leading to production of 1,25$(OH)_2D$ locally in these tissues. It also contributes to the non-skeletal functions of the vitamin D. However this fraction does not significantly contribute to the serum level. The above step in renal tissue is highly regulated. Increased PTH, calcitonin and hypophos phatemia stimulate the enzyme 1-alpha hydroxylase and enhance 1,25$(OH)_2D$ production, while high calcium,

hyperphosphatemia, calcitriol and phosphaturic hormone fibroblast growth factor 23(FGF-23) inhibit this enzyme and is under negative feedback loop by 1,25$(OH)_2$D. Calcitriol binds to vitamin D receptor (VDR) in the nuclei of the target cells to exert its biological effect. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins [such as Transient receptor potential cation channel protein, sunfamily V, number 6 (TRPV6) and calbindin], which are involved in calcium absorption in the intestine.[4]

Optimal requirement and intake of vitamin D

According to the recommendations in 2008 by the American Academy of Pediatrics, all infants including those who are exclusively breast fed should be given 400 IU of vitamin D per day and this should be continued unless the infant is weaned to at least 1 L per day of vitamin D-fortified formula or fortified whole milk. Vitamin D levels in breast milk range from less than 25 to 78 IU/L, putting exclusively breast-fed infants at greater risk for vitamin D deficiency.[5] The intake of vitamin D for children and adolescents is also 400 IU/day.[2] Universal recommendations for high-dose vitamin D supplementation during pregnancy are not currently standardized, however, various studies have found the intake of 1500-2000 IU to have beneficial fetal outcome.[6] Very few foods naturally contain vitamin D (Table I) and most of the required vitamin D is synthesized by cutaneous exposure to sunlight[7].

Ideal vitamin D levels

Vitamin D deficiency is quite prevalent in India. A study showed 90% prevalence in adults and 24% prevalence in pregnant women.[6] It is quite common in children also.

Table I. Vitamin D content of common foods

Cow's milk	3-40 IU/L
Fortified infant formula	400 IU/L
Butter	35 IU/100g
Egg yolk	20-25 IU/yolk
Cod liver oil	400 IU/tsp.
Fish	44-624 IU/100g
Yoghurt	89 IU/ g
Cheese	12-44 IU/ 100g

Optimal level of 25(OH)D is defined as the level which causes maximal suppression of PTH and maximum calcium absorption. The optimal 25(OH)D concentration may also be defined clinically, such as level needed for fracture reduction. There is no consensus on the optimal 25(OH)D concentration for skeletal health. Currently accepted standards for defining vitamin D status in children and adolescents are as follows; vitamin D sufficiency: 25(OH)D ≥ 20ng/mL, vitamin D insufficiency: 25(OH)D between 15 to 20ng/mL, vitamin D deficiency: 25(OH)D between 5 to 15ng/mL and severe deficiency: 25(OH)D < 5ng/mL. Individuals with 25(OH)D levels above 100ng/mL have been arbitrarily designated as having vitamin D excess and above 150ng/ml is considered to be intoxicated.[6]

Previously vitamin D levels were considered as sufficiency, insufficiency, mild deficiency and severe deficiency if the levels were more than 30, 16 to 30, 5 to 15 and less than 5ng/mL respectively. The recent 2011 Institute of Medicine(IOM) report has come out with different cut offs.[8] According to this, the levels have been modified to more than 20, 12 to 20, 8 to 12 and less than 8ng/mL respectively. Unfortunately this has become a debatable issue in literature. Dibas B and Srivastava T state that what sufficiency, insufficiency and deficiency are at skeletal and non-skeletal sites for physiological functions of vitamin D will have different cut offs.[9]

Vitamin D assays

Vitamin D assays are available to measure the levels of serum 25(OH)D, serum 1,25$(OH)_2$D and total vitaminD which is both vitamin D2 and D3 derivatives of 25(OH)D.25-hydroxy vitamin D has a long half-life of 2-3 weeks. Hence, it is the major circulating form of vitamin D which makes it the best indicator of vitamin D levels in an individual.[6] Also as discussed earlier, the synthesis of 25(OH) D is a substrate dependent step and not under any feedback loop. It is a measure of total vitamin D from dietary and sunlight sources and from adipose tissue. 1,25dihydroxy vitamin D is regulated by PTH, calcium and phosphate and hence its levels are maintained till vitamin D deficiency is severe. Also the half-life of it is short, being about 4 hours. Hence levels of 1,25$(OH)_2$ vitamin D is not a reliable indicator of vitamin D status and stores of an individual.Total vitamin D assay which measures both D2 and D3 should ideally be done as both the fractions are active after 1 alpha hydroxylation.Total 25 (OH) vitamin D levels can be measured by high performance liquid chromatography (HPLC), tandem mass spectrometry method and various binding assays like immunoassays and protein binding assays. Assays with HPLC and liquid

chromatography-mass spectrometry (LC-MS)are the gold standard methods.[6] It is a regular practice for the patient to have been fasting 8 to 12 hours before the sample collection. The volume of sample needed is 0.25 ml which should be at room temperature.

Causes of vitamin D deficiency

Major source of vitamin D for our body is obtained from cutaneous synthesis. Vitamin D deficiency contributes to various skeletal and extra- skeletal morbidities. There are many causes of vitamin D deficiency. There are various factors that can contribute to decreased cutaneous synthesis of vitamin D. Ultraviolet B(UV-B) rays are having shorter wave length, tend to scatter earlier or later in the day and hence cutaneous vitamin D synthesis is maximum between 10 AM to 3 PM. Skin pigment melanin absorbs the UV-B rays and hence dark skinned people make less vitamin D.[10] Dark skinned people need 8-10 times more exposure to sunlight to make the same amount of vitamin D as their fair counterparts.[11] Sunscreens with sun protection factor (SPF) of 8 to 15 also inhibit vitamin D synthesis in skin by 95 to 98%. Sunscreens with SPF of 15 can reduce cutaneous vitamin D synthesis by upto 99 %.[10] Season and latitude of a place also play a role in vitamin D synthesis in its inhabitants. In Atlanta which is above 35 degree north, cutaneous vitamin D production during the month of November to April is highly deficient as less solar UVB rays reach the earth during these months.[10]

Infants who are exclusively breast fed are at increased risk of vitamin D deficiency as unfortunately breast milk is a poor source of vitamin D. Mothers who have vitamin D deficiency have been found to give birth to vitamin D deficient infants.[11] Premature infants do not have adequate vitamin D stores and are at increased risk for vitamin D deficiency. Malabsorption resulting from celiac disease, cystic fibrosis, gastric bypass surgeries reduces the absorption of vitamin D by the body.[10] Obese patients typically have levels in the range of 10-20 ng/mL. This may be due in part to lower levels of exercise and sunlight exposure in obese persons than lean persons. So the body mass index is inversely related to the serum 25(OH)D levels.[10] Liver disease leads to reduced formation of 25(OH)D and severe liver failure can lead to complete impairment of its production.[10]

Etiology of vitamin D deficiency is multifactorial in renal diseases.Nephrotic syndrome leads to significant urinary loss of 25(OH)D and VDBP. In chronic glomerular disorders, reduction in the functional mass causes reduction in 1-alpha hydroxylase levels and thereby reduces active vitamin D levels. Reduction of GFR to < 70% causes retention of phosphate and reciprocal lowering of serum calcium. This stimulates PTH release, causing further renal damage;PTH levels progressively increases leading on to osteoclastic osteolysis, osteitis fibrosa cystica and epiphyseal stippling. In tubulo-interstitial diseases, metabolic acidosis is an added factor. Normal acid base status is an important factor for mineralisation. Chronic metabolic acidosis results in resorption of bone as bone minerals particularly $CaCO_3$ are potent biological H+ ion buffers, which can be accentuated by high PTH levels. Metabolic acidosis also interferes with collagen turnover and conversion of 25 (OH)D to 1,25$(OH)_2$D by blunting the action of 1alpha-hydroxylase.[12] Adequate levels of serum phosphate are important as serum calcium in bone mineralisation. Inappropriately increased excretion of phosphate is the cause of hypophosphatemia in familial hypophos phatemic rickets (FHR) and Fanconi syndrome. In children with chronic kidney disease (CKD), many factors operate like anorexia, diet restriction causing negative calcium balance, uremic toxins inhibiting mineral absorption, mineralisation and collagen formation.[13] One should remember that reduced levels of both 25(OH)D and 1,25$(OH)_2$D are noted in CKD.

Treatment of vitamin D deficiency

Once vitamin D deficiency is documented treatment is given using vitamin D2 or vitamin D3. The dosage recommended is 1000 IU/day for infants <1 month old, 1000 to 5000 IU/day for infants 1 to 12 months old and 5000 IU/day for children >12 months old.[14] Treatment with above dosage is continued till radiological healing is seen which usually takes about 2-3 months. This is followed by a maintenance dose of 400 IU of vitamin D per day. Calcium intake should be maintained at approximately 30 to 75mg/kg/day to avoid "hungry bone" syndrome (worsening hypocalcemia after starting vitamin D therapy). Calcium supplements are not usually necessary after serum 25(OH)D levels are normalized.[15]

An alternative form of vitamin D therapy wherein high dose rather than daily small dose of vitamin D is given, is called the 'Stoss therapy' (3 lakhs to 6 lakhs IU of vitamin D are administered orally as 2 to 4 doses over 1 day or single intramuscular injection), the name being derived from a German word 'stossen', which means, to push. This form of therapy eliminates the compliance issue that might exist with daily dosing schedule. However this high dose therapy can lead to hypercalcemia.[16]

In children with CKD the recommended supplementation for vitamin D deficiency is well defined.[17] For insufficiency level(15-30ng/dL) 50,000IU of vitamin D

is given once a month for three months; for mild deficiency (5-15ng/dL) same dose is given once in 2 weeks for 3 months; for severe deficiency (<5ng/dL), same dose of 50,000IU of vitamin D is given once a week for first four doses and then every alternate week for next four doses. Active vitamin D should be initiated in CKD when phosphorus restriction, calcium supplementation and vitamin D replacement are not sufficient to reduce PTH to target levels.[18] Vitamin D analogue like paricalcitol is preferred over calcitriol, because calcitriol stimulates gut absorption of both calcium and phosphorous along with PTH suppression. Some children demonstrate increase in calcium and phosphorous as a result of calcitriol treatment. In this context, active vitamin D analogues are compounds designed to interact with vitamin D receptors in the parathyroid glands, suppressing PTH secretion as calcitriol does, but which also have been designed to have reduced affinity for vitamin D receptors in the gut. As a result, the analogues in general, cause less of an increase in serum calcium and phosphorus while still maintaining effective suppression of PTH.[18]

Adverse effects of vitamin D

Vitamin D can adversely affect an individual in case of inadvertent ingestion of high doses of vitamin D. The adverse effects seen after acute intoxication are hypercalcemia and hypercalciuria. The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia, which include nausea,vomiting, poor feeding, constipation, abdominal pain, pancreatitis, lethargy, hypotonia, disorientation, polyuria and dehydration. Hypercalcemia can also lead to acute renal failure and if persistent can lead to nephrolithiasis and nephrocalcinosis which may result in chronic renal insufficiency. These adverse effects are usually seen at levels not below 88ng/ml.[6] 25-hydroxy vitamin D level of >100ng/mL is considered to be excess and can be associated with features of vitamin D toxicity. Hypercalcemia is usually seen at serum level >150ng/mL of 25OH Vitamin D. Chronic hypervitaminosis D occurs after ingestion of large quantities of vitamin D over weeks or months and can lead to malignant calcifications in various soft tissues of the body. Calcification of heart valves can cause aortic valvular stenosis; calcification of blood vessels can lead to systemic hypertension; calcification of renal tubules can cause nephrocalcinosis, secondary nephrogenic diabetes insipidus or Fanconi syndrome.[16]

Rickets other than due to vitamin D deficiency

Normal bone growth and mineralization require adequate calcium and phosphorus, the two major constituents of the crystalline component of bone. Rickets refers to deficient mineralization at the growth plate, whereas osteomalacia refers to impaired mineralization of the bone matrix. Rickets usually occur as long as the growth plates are open and hence seen in children. Osteomalacia occurs after the growth plates have fused, hence commonly seen in adults.Common form of rickets is still due to vitamin D deficiency. Failure to induce healing with adequate doses of vitamin D is called rickets other than due to vitamin D deficiency and can be calcipenic or phosphopenic as mineralization defects are classified according to the predominant mineral deficiency.

Calcipenic (hypocalcemic) rickets is primarily caused by reduced serum calcium levels.Calcipenic rickets resistant to vitamin D therapy is essentially caused by a defect in the enzyme 1 alpha hydroxylase. This disorder is commonly called vitamin D dependent rickets type1(VDDR type 1), or pseudo vitamin D deficiency, because its clinical manifestations mimic those of vitamin D deficiency. In addition, calcipenic rickets can be caused by a mutation in the gene that encodes the vitamin D receptor, leading to hereditary vitamin D resistant rickets (old minology was vitamin D dependent rickets type 2,VDDR type 2).[9] Both diseases are rare autosomal recessive disorders. VDDR type 1 is characterized by hypocalcemia, hypophos phatemia, elevated alkaline phosphatase, normal 25(OH)D level, low to undetectable $1,25(OH)_2D$ level, secondary hyperparathyroidism and early onset of severe rickets. VDDR type-1children respond to long-term treatment with calcitriol. Initial doses are 0.25 to 2microgram/day, with lower doses used once the rickets has healed. When children fail to respond to active vitamin D, intensive calcium therapy is used.Children with VDDR type-2 have severe rickets, alopecia and extremely elevated levels of $1,25(OH)_2D$. Some children may respond to extremely high doses of vitamin D(20 to 200 mcg/day of ergocalciferol or 50 to 60 mcg/day of calcitriol).[9] Children who donot respond to high dose vitamin D can be treated with long term intravenous calcium, with possible transition to very high dose oral calcium supplements. This response is due to partially functioning vitamin D receptors.Other conditions producing calcipenic rickets are chronic renal failure and distal renal tubular acidosis.

Phosphopenic (hypophosphatemic) rickets is primarily caused by reduced phosphate levels, almost always caused by renal phosphate wasting, which may be isolated as in familial hypophosphatemic rickets, tumour induced osteomalacia conditions or part of a generalized renal tubular disorder such as Fanconi syndrome and Dents disease. The cause can be distinguished by checking the

acid base status, serum electrolytes, urinary glucose and amino acids. Therapy relies on oral phosphorus replacement (1 to 3 g/day of elemental phosphorus in 4 to 5 divided doses orally). Along with this, replacement of fluids, bicarbonates, potassium and active vitamin D supplements on a long-term basis form the principles of treatment in Fanconi syndrome. In renal tubular acidosis, need for active vitamin D therapy is only transient as the suppression of 1-alpha hydroxylase by metabolic acidosis will be eliminated by correction of acidosis with alkali therapy. In Dents disease, oral phosphate therapy and active vitamin D supplementation result in improvement of bone disease. Treatment of hypercalciuria is done with dietary sodium restriction and thiazide diuretics. Dietary calcium restriction though scientific, is not recommended because it may exacerbate the risk of bone disease. Monitoring the serum calcium, phosphorous and alkaline phosphatase along with urine calcium creatinine ratio estimation is needed frequently to avoid exacerbation of hypercalciuria via increased intestinal calcium absorption.[12] Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare disorder characterised by hypophosphatemia, renal phosphate wasting, elevated serum alkaline phosphatase and $1,25(OH)_2D$ levels. Treatment of hypophosphatemia decreases serum levels of $1,25(OH)_2D$ and corrects the hypercalciuria. The response to therapy is usually excellent, with resolution of pain, weakness, and radiographic evidence of healing rickets.[16] There is no role for calcitriol in HHRH, which may worsen hypercalciuria and increases the predisposition for nephrocalcinosis. Routine use of calcitriol has to be avoided in this condition as $1,25(OH)_2$ vitamin D levels are high. Removal of tumor is curative in tumour induced conditions.[7]

Changing trends in vitamin D usage

Vitamin D is synthesized in the kidney through activation of 25(OH) D to $1,25(OH)_2$ D. A non-classical way of this activation process exists in various non-renal tissues. These peripheral non- renal tissues have intracellular vitamin D receptors(VDR). By binding with its intracellular VDR in these tissues, calcitriol can regulate cellular proliferation and differentiation, inflammation, the immune and the endocrine system, including renin angiotensin aldosterone system(RAAS), insulin resistance and lipid metabolism.[19]

The non-classical pathway has an effect on the RAAS pathway whose activation in CKD leads to elevated blood pressure and thereby left ventricular hypertrophy. Administration of vitamin D has modulatory effect on RAAS pathway, thus, reducing blood pressure and left ventricular hypertrophy (LVH). Administration of vitamin D may decrease proteinuria through modulation of RAAS.[19] Evidence from clinical studies and association data from the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated an inverse relationship between the level of vitamin D and degree of albuminuria.[20] Nuclear factor kappa B (NF-kB) pathway which is regulated by the non-classical mode of vitamin D action has a role in CKD. Activation of the NF-kB pathway triggers a cascade of events yielding cytokines, chemokines and other inflammatory factors, which exacerbate tissue injury, inflammation and interstitial fibrosis in the renal disease process.[19] Vitamin D inhibits NF-kB, thereby reducing interstitial fibrosis and tissue injury in the form of glomerulosclerosis. These findings emphasize the importance of vitamin D supplementation in CKD.Vitamin D has been studied and found to decrease blood pressure in hypertensive patients, thus decreasing cardiovascular morbidity. Calcitriol suppresses fibrosis by inhibiting interstitial myofibroblast activation, thus preventing cardiomyocyte hypertrophy.[21]

Many tissues in the body have vitamin D receptors including brain, colon, breast, prostrate and immune cells. These cells also express 1-alpha-hydroxylase and hence respond to therapy with 25(OH)D and therapy with active form of vitamin D might not be required unless indicated. In case of any infection like Mycobacterium tuberculosis, wherein monocyte-macrophage system is stimulated, it leads to up regulation of vitamin D receptor and 1-alpha-hydroxylase. The active form of vitamin D produced in such situations induces formation of cathelicidin, which is a promoter of innate immunity and thus helps to fight against the tubercle bacilli.[7] Vitamin D also acts on T-lymphocytes which regulate cytokine synthesis and B-lymphocytes which regulate immunoglobulin synthesis.[6] Risk of many cancers is reduced if 25-OH-vitamin D level is >30 ng/mL.[6] Vitamin D has a role in inhibiting cell proliferation and angiogenesis. It has also been found to promote apoptosis and differentiation. Thus, when cells become malignant, it induces apoptosis and inhibits proliferation of cancerous cells, thus keeping the malignancy in check.According to various studies, vitamin D supplementation in pediatric age group helps to bring down the incidence of type 1 diabetes mellitus in children.[22] In another study, vitamin D deficiency was found to be associated with increased insulin resistance and decreased insulin production.[22] Vitamin D deficiency has also been found to be associated with psychiatric manifestations of depression and schizophrenia. Adequate vitamin D levels during pregnancy maybe important for brain development in utero and mental health later on.[6]

Points to Remember

- ***Previously vitamin D levels were considered as sufficiency, insufficiency, mild deficiency and severe deficiency if the levels were more than 30, 16 to 30, 5 to 15 and less than 5 ng/ml respectively. But, according to 2011 Institute of Medicine (IOM) report, the cut off levels are more than 20, 12 to 20, 8 to 12 and less than 8ng/ml respectively.***
- ***Total vitamin D assay which measures both D2 and D3 should ideally be done as both the fractions are active after 1-alpha hydroxylation.***
- ***Causes of vitamin D deficiency are many including insufficient exposure to sunlight as well as deficient skin entry of UVB rays due to melanin content of the skin. Infants who are exclusively breast fed are at increased risk of vitamin D deficiency as unfortunately breast milk is a poor source of vitamin D.***
- ***According to the recommendations established in 2008 by the American Academy of Pediatrics, all infants including those who are exclusively breast fed should be given 400 IU of vitamin D per day. The intake of vitamin D for children and adolescents is also 400 IU/day.***
- ***Hypercalcemia and hypercalciuria should be monitored while using all forms of vitamin D and chronic vitamin D intoxication can cause calcification of heart valves, blood vessels and renal tubules.***
- ***Vitamin D is useful in extra-skeletal tissues due to its local formation of 1,25 $(OH)_2$ vitamin D and its use in various cardiovascular diseases, immunological dysfunctions, cancers and chronic infections is increasingly noted. One should remember that vitamin D acts on bones and also beyond bones.***

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NUTRITION SUPPLEMENTS IN VERY LOW BIRTH WEIGHT AND PRETERM BABIES

** Durai Arasan G*

Abstract: *Most preterm infants, especially VLBWs accumulate significant energy, protein, mineral and other nutrient deficits by the time they are discharged from hospital. At the time of discharge, many preterm infants are significantly growth restricted, the risk increasing with lower birth weight and gestational age. Following discharge from the hospital, preterm infants fed on demand may consume greater volumes of milk than term infants of the same post menstrual age in order to attain some "catch up" growth. Despite this, growth deficits can persist through infancy and beyond. Slow postnatal growth in preterm infants is associated with neurodevelopmental impairment in later childhood and with poorer cognitive and educational outcomes. Preterm infants who have accumulated deficits in calcium and phosphate by the time of hospital discharge have a higher risk of low bone mineralisation, metabolic bone disease and slow skeletal growth compared to infants born at term. There is also some concern that nutritional deficiency and growth restriction both in utero and in the early postnatal period may have consequences for long term metabolic and cardiovascular health.*

Although human milk is the recommended nutritional source for newborn infants for at least first six months of postnatal life, exclusive breast milk may not meet the recommended nutritional needs of growing preterm infants. There is a need for continued nutritional supplementation for preterm infants in the post hospital discharge period of early infancy. Higher levels of nutritional input during this period is very much important to meet the additional metabolic requirements.

Keywords: *Preterm, VLBW, HMF*

* Senior Asst. Prof of Pediatrics
Department of Neonatology
ICH and HC, Chennai.

Optimal nutrition during the neonatal period is essential for growth and development throughout infancy and into childhood. Nutritional needs of infants vary based on gestational age, metabolic state and physiological complications. The postnatal growth of very low birth weight (VLBW) infants during initial hospitalization remains extremely poor, with the vast majority suffering profound growth retardation.In a recent review from the neonatal network of the National Institute of Child Health and Human Development, 83% to 100% of VLBW infants underwent significant growth retardation between birth and discharge, an effect that was greater in the smaller, more immature infants (ie, almost 100% of infants weighing ≤1000 g at birth had a birth weight of ≤10th percentile at 36 weeks corrected age).[1] Given the potentially lifelong effects of growth retardation during a critical time of development, considerable effort has been expended on improving growth after discharge in these undernourished infants.

Why supplements in VLBW babies ?

These infants who are usually born before 32-34 weeks gestation have inadequate body stores of most of the nutrients. To understand why we need to consider providing nutritional supplements to babies less than 1500 gm, we should understand what our target growth is for these babies and what are the nutritional requirements suggested by various bodies like European Society for pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), American Academy of pediatrics (AAP) Committee on nutrition, etc., to achieve this target. The most commonly accepted goal of provision of enteral nutrition to premature infants is to achieve growth comparable to the fetus.

Macronutrient requirements in premature

Proteins

At 26 weeks' gestation, the fetus accretes approximately 2.2 g/kg per day of protein; by term, this amount declines to approximately 0.9 g/kg per day. Protein losses are inversely related to gestational age, providing an explanation for higher protein requirements in extremely premature neonates (Table I). Protein and energy needs should be considered hand in hand, because protein synthesis requires energy. Extremely premature infants require a higher protein to energy ratio for optimal growth (Table II).

Energy

If energy intake is not adequate, protein utilization is not efficient, resulting in lower retention of nitrogen. The recommended energy intake for enterally fed premature infants ranges between 110 and 135 kcal/kg per day.[2] The optimal ratio of enteral protein to energy intake must be defined in terms of optimizing weight gain and also by what is required to an optimal body composition (Table II). Changes in body composition in response to energy intake are important consideration, because excessive energy intake can contribute to excessive fat deposition and recent studies have suggested that rapid weight gain may be associated with adverse outcome.

Carbohydrates

The main carbohydrate in human milk is lactose, supplying nearly half of the total calories. Lactase (β-galactosidase) is an intestinal enzyme that hydrolyzes lactose to glucose and galactose in the small intestine. Despite lower levels of intestinal lactase activities in premature infants, premature infants are able to efficiently digest lactose. Recommended carbohydrate intake for premature infants is 11.6 to 13.2 g/kg per day.[2] This amount of intake will provide sufficient glucose to meet the needs for total energy expenditure.

Fat

Fat provides a substantial source of energy for growing premature infants. Premature infants have low levels of pancreatic lipase, bile acids and lingual lipase. Human milk, however, supplies a variety of lipases, including lipoprotein lipase, bile salt esterase and non activated lipase. The composition of dietary fat affects absorption and digestion. The absorption of fatty acids increases with decreasing chain length and with the degree of unsaturation. Consequently, medium-chain triglycerides (6- to 12-carbon chain length) are hydrolyzed more readily than long-chain triglycerides. Human milk supplies 8% to 12% of fat as medium-chain triglycerides. Recommended intake for lipid in enterally fed premature infants ranges between 4.8 and 6.6 g/kg per day. Of this amount, medium-chain triglycerides should be less than 40% of total intake.[2]

Table I. The recommended enteral protein intakes for very low-birth weight infants by various bodies

Recommending bodies	Recommended protein intake
Canadian Pediatric Society, 1995	Birth weight <1000 3.5-4.0g/kg/d Birthweight ≥1000 3.0-3.6 g/kg/d
Life Sciences Research Office, 2002	3.4-4.3 g/kg/d
AAP Committee on Nutrition, 2004	3.5-4.0 g/kg/d
ESPGHAN, 2010	Weight up to 1000 g 4.0-4.5 g/kg/d Weight 1000-1800 g 3.5-4.0 g/kg/d

Table II. Estimated protein and energy requirements to achieve fetal growth[3]

Weight (g)	Protein (g/kg/d)	Energy (kcal/kg/d)	Protein:Energy(g/100 kcal)
500–700	4.0	105	3.8
700–900	4.0	108	3.7
900–1200	4.0	119	3.4
1200–1500	3.9	125	3.1
1500–1800	3.6	128	2.8
1800–2200	3.4	131	2.6

Though breast milk is the preferred source of enteral nutrition for premature infants, by looking at the composition of breast milk and the requirements of the VLBW babies to achieve their target growth it is understood that the breast milk has inadequate amounts of protein, energy, calcium, phosphorus, trace elements (iron, zinc) and vitamins (D, E & K) that are unable to meet their daily recommended intakes (Table III & IV). Hence, these infants need multi-nutrient supplementation till they reach term gestation (40 weeks postmenstrual age).

Multi-nutrient supplementation can be ensured by one of the following methods:

1. Supplementing individual nutrients - eg., calcium, phosphorus, vitamins, etc.
2. By fortification of expressed breast milk:

   a. Fortification with human milk fortifiers (HMF)

   b. Fortification with preterm formula

Table III. Recommended enteral intake of minerals and trace elements for preterm infants

Mineral/Trace Element(per 100 kcal)	AAP [4]	ESPGHAN [2]	Preterm Human Milk[5] (1 week) per 100 kcal
Protein, g			2.1
Fat, g			5.8
Carbohydrate, g			9.9
Calcium (mg)	67–200	110–130	37
Magnesium (mg)	5.3–13.6	7.5–13.6	4.6
Phosphorus (mg)	40–127	55–80	19
Potassium (mEq)	1.3–2.7	1.5–4.1	2.17 mL
Sodium (mEq)	2–4.6	1.7–2.7	1.60 mL
Iron (mg)	1.33–3.64	1.8–2.7	0.18
Chromium (µg)	0.07-2.05	0.027-1.12	
Copper (µg)	80-136	90-120	96
Fluoride (µg)		1.4-55	
Iodine (µg)	6.7-54.5	10-50	16
Manganese (µg)	0.5-6.8	6.3-25	
Molybdenum (µg)	0.2-0.27	0.27-4.5	
Selenium (µg)	0.9-4.1	4.5-9	
Zinc (mg)	0.34-2.7	1-1.8	0.5 mg

Table IV. Recommended oral intake of vitamins for preterm infants

Vitamin (per 100 kcal)	AAP [4]	ESPGHAN [2]	Preterm Human Milk[5] (1 week) per 100 ml
Fat Soluble			
Vitamin A (IU)	467–1364	1210–2466	560
Vitamin D (IU)	100–364	100–350 (800–1000/d)	4
Vitamin E (IU)	4–10.9	3-15	1.5
Vitamin K (µg)	5.3-9.1	4-25	

Supplementing individual nutrients: Practically it is difficult to supplement a wide range of nutrients separately where composition, bioavailability, compatibility with other nutrients and palatability of each one have to be considered. The question of supplementing good quality protein with adequate energy separately is one main issue in individual nutrient supplementation.

Fortification with HMF: Fortification of expressed breast milk with HMF increases the nutrient content of the milk without compromising its other beneficial effects (such as reduction of NEC, infections, etc.). Experimental studies have shown that the use of fortified human milk results in net nutrient retention that approaches or is greater than expected intrauterine rates of accretion in preterm infants.[6] Though there are concerns about the increase in osmolality, clinical studies have not shown any significant adverse effects following fortification of human milk. The Cochrane review on fortification found short term improvement in weight gain, linear and head growth without any increase in adverse effects such as NEC.[7] The standard preparations of human milk fortifiers (HMF) used in developed countries are not available in India. The only preparation available (Lactodex-HMF, Raptakos, Brett & Co. Ltd; Rs.10/- per sachet) has some limitations. Short of other options, it may still have to be used in VLBW infants. One study from Chandigarh has reported better growth with its use.[8] VLBW infants on expressed breast milk fortified with HMF do not require any supplementation except for iron.HMF fortification should beconsidered for all preterm (<32 weeks) VLBW infants. It is started once they reach 150 mL/kg/day of enteral feeds in the dose recommended by the manufacturer [4g (2 sachets) /100mL of expressed breast milk] and starting iron at 4-6 weeks in the dose of 2mg/kg/day.

Fortification with preterm formula: The other option available for fortification is preterm formula. The recommended concentration is 0.4g per 10mL of breast milk. Though more economical than fortification by HMF, this method has two major drawbacks - it is difficult to measure such small amounts of formula powder and the RDA of some minerals and vitamins (e.g. calcium, phosphorus, vitamin D, folic acid) are not met even after fortification. While the former problem can be managed to a certain extent by using a small scoop of 1g size for 25mL of milk, the later is circumvented by additional supplementation.

If HMF is unavailable or parents could not afford it, fortify EBM with preterm formula (0.4g/10 mL). Since calcium, phosphorus and vitamin D intakes are low even after fortification with formula, supplement these nutrients additionally. Add iron as mentioned before.

NNF clinical practice guidelines 2010[9]

For Indian scenario, the National Neonatology Forum of India which is the apex body for neonatal recommendations in India gives the following guide lines

Recommendations (Grade A):

- Mother's milk is the best feeding option for LBW infants
- In case breast milk feeding is not possible, it may be preferable to use pre-term infant formula for Pre-term infants (< 2000 grams)
- Considering the weak evidence of benefits and substantially higher costs of nutrient enriched formula, its routine use cannot be justified in developing country settings.
- Routine use of the multicomponent fortification of the breastmilk should be avoided. This option is best reserved for preterm infants <32 weeks gestation or <1500 g birth weight who fail to gain weight despite full volumes of breast milk feeding (NNF)

From these recommendations it is very clear that these babies need to be followed up closely and multinutrient fortification to be considered at appropriate time when growth faltering occurs.

Growth monitoring

Growth parameters include the infant's weight, length and head circumference and should be monitored on a weekly to biweekly basis for the first four to six weeks after hospital discharge. After this initial period of close observation, infants who are growing normally can be followed on a monthly and then every two month schedule. Regular growth monitoring helps in assessing the nutritional status and adequacy of feeding; it also identifies those infants with inadequate weight gain. After discharge the weight gain should be at least 15-20g/kg/day till a weight of 2-2.5 kg is reached. After this, a gain of 20 to 30 g/day is considered appropriate.

Growth charts: Using a growth chart is a simple but effective way to monitor the growth. Serial plotting of weight and other anthropometric indicators in the growth chart allows the individual infant's growth to be compared with a reference standard. It helps in early identification of growth faltering in these infants.

Two types of growth charts are commonly used for growth monitoring in preterm infants: intrauterine and

postnatalgrowth charts. Both types of charts have merits and limitations. There are no comparative studies establishing superiority of one over the other. The postnatal growth chart allows for the initial weight loss that occurs in the first two weeks of life. The two postnatal charts that are most commonly used for growth monitoring of preterm VLBW infants are: Wright's and Ehrenkranz' charts.[10,11] Fenton's growth charts is the commonly used intrauterine growth chart.[12] Once the preterm LBW infants reach 40 weeks PMA, WHO growth charts should be used for growth monitoring.

Points to Remember

- ***Majority of the NICU (VLBW Babies) graduates are growth restricted at the time of hospital discharge.***
- ***Human milk though the best does not meet the RDA of most of the nutrients for VLBW babies.***
- ***Close monitoring of NICU graduates after discharge need to be done***
- ***Multi nutrient fortification is to be used judiciously.***

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CLIPPINGS

Christopher D, Smyser Hiroyuki Kidokoro, Terrie E Inder. Magnetic resonance imaging of the brain at term equivalent age in extremely premature neonates: To scan or not to scan? Journal of Paediatrics and Child Health, September 2012.

In the last decade, the role of magnetic resonance imaging (MRI) in neonatal care for prematurely born infants has rapidly expanded and evolved. Recent investigations addressed many of the practical issues pertaining to image acquisition and interpretation, enabling high-quality MR images to be obtained without sedating medications in preterm infants at any institution. Expanded application has demonstrated that MRI provides superior ability to assess cerebral development and identify and define cerebral injury in comparison to other imaging modalities. Term equivalent MRI results have been shown to correlate with neurodevelopmental outcomes, providing improved predictive ability over other neuroimaging, clinical or physical examination measures.

IAP - IJPP CME 2012

USE OF ANTIPYRETICS - DO's AND DONT's

** Ramesh S*
** Sudharsana S*

Abstract: *Fever is the commonest symptom seen in any pediatric outpatient department. Hence, a knowledge about the choice of appropriate antipyretic, its dose, adverse effects and toxicity is essential for all practitioners. Fever must be differentiated from hyperthermia as the management differs. This article deals with the mechanism of fever and various antipyretics used in pediatric practice.*

Keywords: *Fever, Hyperpyrexia, Antipyretic*

Fever is defined as rectal or core body temperature above 100.4°F or 38°C. The most common indication for initiating antipyretic therapy in children is a temperature higher than 101°F (38.3°C).[1] Temperature above 107°F can be lethal and must be managed aggressively.

Fever versus hyperthermia

What is fever ?

Elevation of the thermoregulatory set point in the hypothalamus by immunoregulatory proteins - cytokines results in fever. These cytokines are also referred to as endogenous pyrogens.The notable cytokines involved in febrile response are interleukin 1β, interleukin 6, interferon α and tumour necrosis factor.[2] It is proposed that these pro inflammatory cytokines stimulate central production of cyclo-oxygenase-2 (COX-2) and subsequent production of prostaglandin E series which in turn raises the thermoregulatory set point. A number of exogenous substances or exogenous pyrogens can evoke fever by inducing the production of cytokines. These exogenous pyrogens may be infectious agents, toxins and tumors.

Fever which is produced by elevation of thermoregulatory set point can be lowered by antipyretics.

* Consultant in Pediatrics,

* Consultant Pediatrician,
BRS Hospital Private Limited,
Chennai.

What is hyperthermia?

When the core body temperature is raised without any rise in hypothalamic temperature set point, hyperthermia is said to occur. Antipyretics would not lower temperature in hyperthermia. External cooling methods are required to bring down body temperature in these situations.

Hyperthermia occurs by two mechanisms

1. When heat production exceeds heat loss, as in thyroid storm and salicylate poisoning.
2. When there is defective heat loss or when heat loss mechanisms are overwhelmed, as in heat stroke and iatrogenic hyperthermia of neonates under the radiant warmer.

What is hyperpyrexia?

Hyperpyrexia refers to any excessive elevation of temperature more than 104°F.

Measurement of body temperature

When measuring body temperature at different sites in different age groups, we must remember the following:

1. Oral temperature is less than the rectal temperature by 0.5 to 1°F.
2. Axillary temperature is lower than the oral temperature by 0.5 to 1°F and
3. Tympanic membrane temperature measures core body temperature.

In the ICU setting, rectal temperature would be preferable in view of the highly critical nature of children admitted.

Should fever be treated ?

Fever is a physiological mechanism beneficial in fighting infection. Fever retards the growth and reproduction of bacteria and viruses. It enhances neutrophil production and T- lymphocyte proliferation. It also aids in the body's acute-phase reaction.

Prof Frank Shann states not to routinely give paracetamol/antipyretics for the treatment of fever unless

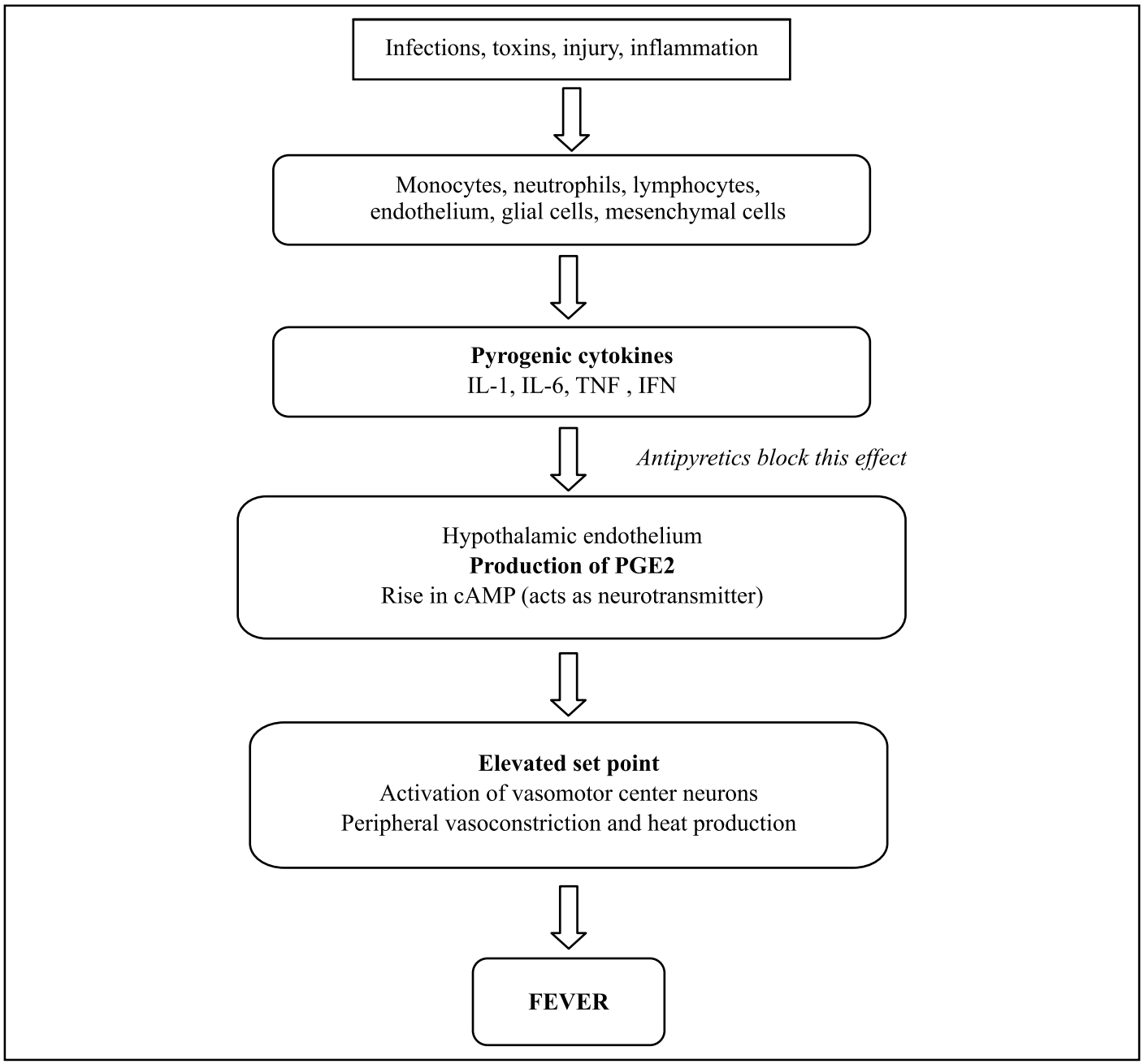

Fig.1.Pathogenesis of fever (http://www.sharinginhealth.ca, March 2010, David LaPierre, KathrynDorman)

it is contributing to respiratory or cardiac failure, causing an arrhythmia or there is traumatic or hypoxic brain injury. Studies have shown that i) antipyretics increase mortality in mammals with severe infection, ii) antipyretics prolong illness in influenza,chickenpox, malaria and probably measles, iii) antipyretics increase viral shedding and diminish antibody response and iv) paracetamol does not prevent febrile seizures.[3]

A. Antipyretics for children

Paracetamol and ibuprofen are the two antipyretics approved to be used in pediatric age group.

Paracetamol

The antipyretic mechanism of paracetamol is not clearly understood. Though many biochemical studies suggest that the antipyretic mechanism of paracetamol is due to the inhibition of cyclo-oxygenase-2 (COX-2), there may be a separate COX activity that is specifically susceptible to paracetamol (? COX 3).[4]

Oral Paracetamol: The dose is 10-15mg/kg/day given 4-6 hourly not to exceed 90mg/kg/day in children and 4 grams in adults. An initial dose of 15mg/kg can be given

if an immediate response is needed. Intramuscular paracetamol injections are no more used and must be avoided because not only they are not more effective than oral dose, but are also extremely painful.

Rectal paracetamol: Same dose as oral is recommended. Studies done have shown no difference in decrement of temperature between oral paracetamol 15mg/kg, same dose rectally and double dose of 30 mg/kg rectally.[5]

However a higher loading dose of rectal paracetamol can be given for analgesia 30-45mg/kg stat and 15mg/kg 6 hourly for 24 hours.

Intravenous paracetamol: At present the labelled use is for post operative analgesia. It can be given as IV infusion over 15 minutes and can be used in neonates too. Available as 1gram in 100 ml solution. Irrespective of dose the dosing schedule is up to 4 infusions/day with a minimum of 4 hours between each administration (Table I).

Paracetamol and hepatotoxicity: Paracetamol is metabolised by conjugation with sulfate and glucoronide and oxidation. 5-10% of the drug is oxidised to a toxic metabolite NAPQ1. NAPQ1 is detoxified by glutathione and eliminated in urine or bile. NAPQ1 which is not detoxified may bind to hepatocytes and produce cellular necrosis. Hepatotoxicity occurs at doses exceeding 150mg/kg/day single dose. Sustained supratherapeutic doses exceeding 90mg/kg/day for one day has been described as a risk factor for hepatotoxicity in infants less than 2 years of age.[6] Paracetamol in pediatric practice is predominantly prescribed as drops or suspension. The concentration of these preparations vary from 100 mg/mL to 250 mg/5mL. It is possible for confusion to arise in the minds of the parents and hence one may be used instead of the other ie. drops given mistakenly in the quantity of the prescribed suspension. Hence a prescription for paracetamol must also contain the concentration of the drug and explained to the parents. Other risk factors for developing paracetamol toxicity are malnutrition, fasting, drugs (isoniazid, rifampicin, phenobarbitone, carbamazepine), intercurrent illness and inherited glutathione synthetase deficiency.

Ibuprofen[7]

Ibuprofen is a propionic acid derivative. It is widely used in arthritis and musculoskeletal conditions where pain is more prominent than inflammation. It has been rated as the safest conventional NSAID by the spontaneous adverse drug reaction reporting system in U.K. Ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic and anti-inflammatory activity of NSAIDs appear to operate mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for unwanted effects on the gastrointestinal tract. A combination of ibuprofen and paracetamol is additive (not supra additive). There is no evidence that such combinations are superior to single agents, either in safety or in efficacy. The antipyretic dose is 10mg/kg/dose given 6 hourly and can be used from the ages of 6 months to 12years.

However, there is risk of gastritis and nephrotoxicity. As it increases the risk of bleeding manifestations it is not advisable to use ibuprofen as as an antipyretic in dengue endemic areas like India.[8]

B. Unlabelled antipyretics popularly used

1. Mefenamic acid
2. Nimesulide

1. Mefenamic acid: There is very little literature evidence to support the use of this drug as an antipyretic. Most reviews for mefanamic acid as an antipyretic quote an article by Weiss published in 1968. It is known to cause

Table I. Intravenous paracetamol dosage

Term newborn and infants < 10kg	7.5mg/kg/dose q6h (0.75mL/kg) Maximum daily dose 30mg/kg i.e 3mL/kg
10kg-33kg	15mg/kg/dose q6h (1.5mL/kg) Maximum daily dose 60mg/kg i.e 6ml/kg not exceeding 2gram
33kg-50kg	15mg/kg/dose (1.5mL/kg/dose) Maximum daily dose 60mg/kg i.e without exceeding 3grams (300mL)
> 50kg / Adult	IV infusion 1gram (100mL) must not exceed 4gram/day

colitis, non oliguric renal failure, hemolytic anemia and generalized tonic clonic seizures in over dose. The indications of mefanamic acid are for pain relief rather than as an antipyretic.[9]

2.Nimesulide: Popularly used antipyretic in the late 90's, fell into disrepute because of the reports of hepatic toxicity.[10] Use of nimesulide in small children or in any age group who have mild liver or kidney impairment can rapidly worsen the liver and kidney function. In viral infections and fever in all age groups it causes platelet dysfunction and acute bleeding. It should never be used in pregnancy because it causes permanent damage to fetal kidney. The health ministry of India banned the use of nimesulide under 12 years of age early last year following the advice of Drug Technical Advisory board (DTAB).

Nimesulide is still licensed for use above twelve years of age and is available for over the counter sale in India. The Drug Controller of India has asked the drug manufacturers to include a box label on the cover, carton,promotional material and package insert to state the following "use of nimesulide should be ordinarily restricted to 10 days ,if longer clinical use is warranted, liver function test should be assessed periodically".[11]

External cooling

External cooling is the treatment of choice in hyperthermia. The thermoregulatory set point is not altered in hyperthermia and therefore antipyretics would be ineffective.

Methods of external cooling are

1. Evaporation and convection- Wetting the skin surface with lukewarm water (tepid water sponging) and blowing warm air across the body.

2. Conduction by a) cooling blanket, b) immersion water bath and c) placing ice in axillae and groin.

External cooling does have its adverse effects. It causes shivering and cutaneous vaso constriction and also increases core body temperature and oxygen consumption.

External cooling in fever: Antipyretics are superior to tepid water sponging in reducing temperature in fever. Traditionally tepid water sponging has been used as an adjunct along with antipyretics to bring down body temperature in fever especially when temperature is above 104°F. Antipyretics with tepid water sponging brought down the temperature faster in the first thirty minutes while causing more discomfort. This effect would be useful if it reduced the incidence of febrile seizures. This effect has never been demonstrated.[12] External cooling can be considered in fever when it is associated with brain injury, meningitis, encephalitis or cardiac failure in mechanically ventilated patients. In view of the deleterious effects of shivering in these critically ill patients they should be paralysed before external cooling methods are adopted.

Points to Remember

- ***The dose of paracetamol is 10-15 mg/kg q4-6hour and its toxic dose is 150mg/kg/dose.***
- ***Paracetamol hepatoxicity may be more prevalant than imagined.***
- ***Ibuprofen though an approved antipyretic may not be safe in the Indian context.***
- ***Mefanamic acid is not an approved antipyretic.***
- ***External cooling methods are primarily meant for hyperthermia.***
- ***Tepid sponging may not prevent febrile seizures.***

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TRAUMA RESUSCITATION

* ***Shanthi S***

Abstract: *Trauma is an important cause of morbidity and mortality in children. Blunt injuries are the predominant mechanism of injury in children. The most common preventable cause of death in trauma is failure to secure the airway. Head injury is responsible for most pediatric trauma deaths. The initial assessment and management at the time of presentation to the emergency department decides the outcome. Hence the initial golden hour management of the trauma victim is emphasized. This article will elaborate only on trauma resuscitation which is often needed in severe polytrauma victims.*

Keywords: *Polytrauma, Primary survey, Secondary survey, Golden hour management.*

Trauma causes injuries that can range from minor injury to fatal injury. Falls account for the majority of all pediatric injuries. Trauma is categorized as local or multiple, based on extent. Multiple trauma refers to significant injuries to two or more body areas. In a child multisystem injury is the rule rather than exception. More than 50% of major injuries are associated with injuries of the head, chest and musculoskeletal system.[1] Trauma is classified as severe when vital signs are abnormal. Polytrauma requires a multi-disciplinary approach. Emergency departments of tertiary care hospitals who cater to trauma victims must have a trauma team in place. The trauma team should comprise of a pediatric ER physician who will act as the leader, pediatric surgeon, right and left hand nurses, an intensivist and one person exclusively to document all the events. In addition the orthopedician and neurosurgeon should be readily available if there is a need.[2]

There are certain unique features of a pediatric trauma victim which need consideration as some management decisions have to be modified based on these features.

* Associate Professor of Pediatrics
Chengalpattu Medical College
Chengalpattu, Tamil Nadu.

1. The larynx is cephalad and more anteriorly placed. The tongue is relatively large. Hence it may be difficult to visualize the glottis.
2. Head injuries are more common in children as the head is proportionately larger. Most serious pediatric trauma is blunt trauma that invoves the brain. Apnea, hypoventilation and hypoxia occur five times more commonly than hypovolemia with hypotension in seriously injured children. Therefore management protocols for the pediatric trauma victim include greater emphasis on aggressive management of the airway and breathing.
3. Hypothermia is common in the pediatric trauma victim as thermal energy loss may be significant in a child because of the large body surface area. The young child should preferably be resuscitated under a warmer. The child should be covered with blankets.
4. Spinal cord injury without radiological abnormality (SCIWORA) is more common in children due to lack of muscular development of the neck and elasticity of spine. A normal cervical spine X-ray does not rule out SCIWORA.
5. Injuries in children can have long term effects on growth and development. Social,affective and learning disabilities are present in half of seriously injured children. Injuries through growth plates may result in growth abnormalities of the injured bone.

The goals of trauma management include rapid assessment of the injuries, determining the management priorities and providing critical intervention. It is important to do the assessment and management simultaneously. The emphasis is on aggressive support of vital functions during what has been called the " platinum half hour" of early pediatric trauma care.[3]

The American College of Surgeons Committee on Trauma in their advanced trauma life support program has formulated a systematic approach to a severely injured patient.[4]

The initial assessment and management include

1. Primary survey(ABCDE)

2. Resuscitation
3. Secondary survey.
4. Triage/referral to definitive care
5. Imaging, lab studies

Primary survey has been considered as a critical element to proper trauma care.[5,6] It comprises of quick assessment for any life threatening injury and simultaneous treatment. It involves the ABCDE approach. A cardiopulmonary cerebral assessment helps to identify the physiological status and life threatening problems.

Airway and cervical spine immobilisation: In pediatric trauma victims airway and breathing abnormalities are more common than abnormalities of circulation.[7] The airway which may be obstructed by falling back of the tongue in an unconscious victim, blood and debris, secretions, foreign body and broken teeth presents as snoring, gurgling and stridor. Immediate attention to the airway is essential. The airway is positioned using the jaw thrust maneouver with out head tilt with concurrent spinal stabilization and immobilization to prevent secondary cervical spine injury. The airway should be suctioned using a yankauer suction catheter to suck out large particulate matter and vomitus which may contain foodparticles. All children should receive 100% oxygen. If the child is bradypneic, bag and mask ventilation should be initiated after introducing an orogastric tube to decompress the stomach. The child should be connected to a cardiopulmonary monitor.

Cervical spine stabilization and immobilisation: It is an important component of trauma management. This should be done preferably in the field and should continue during transport to and stabilization in the advanced life support facility and till the spine is cleared. Initially a manual inline cervical stabilization is initiated and later maintained by a semirigid collar and head immobilizer. The goal is to maintain the cervical spine in a neutral position and avoid any movement of the spine which may result in paralysis. In cases where the c-spine can not be cleared clinically or with plain radiographs, maintaining spinal precautions until a MRI can be obtained is prudent.Indications for cervical spine immobilization are given in Table I.[8]

Tracheal intubation

If the airway remains compromised or the respiratory efforts are inadequate despite after positioning and suctioning or if the victim is unconscious tracheal intubation will be needed. The indications for intubation are given in Table II. A rapid sequence intubation is often necessary especially when there is associated head trauma to prevent increase in intracranial tension which can occur following awake intubation. However, if difficult intubation is anticipated as in significant facial, head ,neck and or airway injury neuro paralytic drugs should not be used. Intubation should always be performed by a person who has advanced airway expertise like an anesthesiologist, ER physician or an intensivist. Manual cervical spine immobilization should be maintained through out the intubation. Orotracheal intubation is preferred to nasotracheal intubation because the latter requires excessive manipulation of the neck. Nasotracheal intubation is contraindicated in patients suspected to have base of the skull fractures or maxillofacial injury as the endotracheal tube can migrate into the cranium.

Difficult intubation

Be prepared for a difficult intubation in severe maxillofacial injuries, laryngo tracheal injuries, obese patients, those with short neck, narrow receding mandible and a small mouth. In children less than ten years an emergency needle cricothyroidotomy with transtracheal jet ventilation may be life saving. Cricothyrotomy may be tried in children older than ten years. Fiberoptic - assisted intubation is helpful in patients with injury to the upper airway. Rarely an emergency tracheostomy is indicated following failed procedures to secure the airway.

Table I. Indications for cervical spine immobilization

1. Any child sustaining multiple blunt trauma
2. Penetrating trauma to the head, neck or torso
3. Submersion or diving injuries
4. Fall from height
5. Rapid acceleration - deceleration injury
6. Altered level of consciousness
7. Complains of neck pain or evidence of neck injury after trauma
8. Neurologic abnormalities or subjective complaints of neurologic abnormalities (even if no longer present)

Table II. Indications for intubation

- GCS < 13
- Hypotensive shock
- Head trauma with raised ICP
- Respiratory failure/ Hypoventilation
- Not able to open eyes or verbalize
- Flail chest
- Severe maxillofacial trauma
- Fall in GCS >3, irrespective of initial GCS

Breathing and ventilation

Provide assisted ventilation if child is hypoventilating. Head trauma is the most common cause of respiratory insufficiency. Ventilation requires adequate function of the lungs, chest wall and diaphragm. Each component must be examined rapidly.

Inadequate ventilation is clinically identified by inadequate chest rise, decreased air entry, abnormal respiratory pattern and decreased responsiveness which is secondary to hypercarbia. Tension pneumothorax, hemothorax, flail chest, pulmonary contusion and open pneumothorax can lead to impaired ventilation. The patient's chest should be exposed to see chest excursion. Decreased chest expansion associated with decreased air entry and mediastinal shift should suggest the presence of pneumothorax or hemothorax. Percussion will help to differentiate between the two conditions. The presence of subcutaneous emphysema in the chest and neck should alert to the possibility of an underlying tension pneumothorax.

• An emergency needle thoracocentesis should be done to decompress the pleural cavity in tension pneumothorax without waiting for an X-ray. This has to be followed by the placement of an intercostal drainage tube(ICD).

- Occlusive dressing should be applied to open pneumothoax.
- Hemothorax should be treated with an ICD. Operative thoracotomy may be needed if initial drainage is >15mL/kg or chest tube output >4mL/kg/hour.
- Flail chest is rare in children. If present it is managed by positive pressure ventilation.
- End tidal carbon dioxide monitoring device should be attached to the endotracheal tube. This not only helps to identify endotracheal tube displacement but also helps to identify hypercarbia noninvasively. In patients with raised intracranial tension (ICT) it is very useful to help maintain normocarbia.

Circulation and hemorrhage control

Cardiopulmonary assessment with reference to circulation includes heart rate (HR), simultaneous palpation of central and peripheral pulses, core-peripheral temperature gap, capillary refill time (CRT) blood pressure (BP) and colour. Shock is identified by the following signs: quiet tachypnea, tachycardia, cold extremities, weak pulses, prolonged capillary refill time (CRT) and altered mental status. Signs of shock may be subtle initially in the child. An injured child who has cold skin and tachycardia is in shock until proven otherwise. In a child who also has a raised ICT due to associated head injury, the signs of shock may be masked as these children are likely to have a high BP and bradycardia. Hypotension is a late sign in children and indicates a loss of blood volume ≥30%.

Shock: can be multifactorial

- Children with polytrauma commonly develop hypovolemic shock secondary to blood loss. Hemorrhagic shock secondary to isolated intracranial bleed is rare except in very young infants. The common sites of massive blood loss are intrathoracic or intra abdominal bleeding (hepatic and splenic injuries) fracture of long bones and sometimes scalp bleed.

- Resuscitation: A vascular access either intravenous or intra osseous should be obtained quickly The latter should not be placed in a fractured limb. Two peripheral IV lines preferably with large bore needles or atleast with 20 or 22G needles should be secured in extremities that are not obviously injured. Take blood for grouping, typing and cross matching. Administer 20mL/kg of normal saline or Ringer's lactate rapidly. 2 or 3 such boluses may be required. Broselow pediatric emergency tape, a colour coded length based resuscitation tape will be very useful in critically ill children. The weight of the child for the length along with the dose of all resuscitation medications will be readily available in the tape. If the child does not respond to to 40-60 mL/kg of crystalloid, transfuse 10 mL/kg of ABO and Rh type specific cross matched packed red cells. If group and type specific blood is not available O negative blood may be given. The blood should be warmed especially if large volumes are needed or in young infants to prevent hypothermia. Fluid resuscitation and blood transfusion should be continued till signs of shock are present. Empiric platelet and fresh frozen plasma may have to be considered when more than two blood volumes have been replaced during resuscitation.[3] Any injured child who has not responded to the above regimen is likely to have internal bleeding and needs emergency surgery. Signs of intra abdominal bleed from organ rupture include abdominal tenderness, adominal distension that does not improve after gastric decompression and signs of shock. Rarely infusion of epinephrine may be needed to help bridge the time from primary resuscitation to surgery room.

- A urinary catheter should be inserted to monitor hourly urine output which is a good indicator of the adequacy

of volume resuscitation. Maintain a urinary output of 2ml/kg/hour in infants and 1mL/kg/hour in children. Do not introduce a urinary catheter if there is blood in the meatus.

- Direct pressure should be applied to all the bleeding sites. Blind application of hemostatic clamps and use of tourniquets are contraindicated except in cases of traumatic amputation associated with bleeding from a major vessel that does not stop with application of pressure.[7] Dressing should be applied to sucking wounds.
- Neurogenic shock can occur if there is trauma to the spinal cord above T4. This is characterized by vasodilatation with a normal HR as the sympathetic chain is affected. The patient may have warm extremities with bounding pulses. The extremities will become cool if neurogenic shock occurs with hypovolemia.
- Obstructive shock can occur following tension pneumothorax or cardiac tamponade. The latter is identified by Beck's triad (hypotension, muffled heart sounds, jugular venous distension) Emergent treatment of the obstruction by needle thoracocentesis or pericardiocentesis is indicated.
- Cardiogenic shock though rare may occur following myocardial contusion. Symptoms and signs include chest pain, dysrhythmias, tachycardia, a gallop rhythm and features of cardiogenic pulmonary edema. Treatment is primarily supportive.
- Low volume fluid resuscitation(LVFR): In patients with uncontrolled hemorrhagic shock where surgical intervention is required to arrest intra abdominal or intra thoracic bleeding, the use of LVFR may be indicated. Because internal hemorrhage cannot be controlled by external means, the body effectively tamponades hemorrhage especially venous injuries. Aggressive fluid resuscitation raises the CVP, disrupt clots, dilutes clotting factors and worsens hemorrhage.[1] Maintaining a low normal BP is often sufficient. Indications for emergent surgery during resuscitation:

1. Any injured child whose shock has not responded to 40-60mL/kg of crystalloid and 10ml/kg of PRBC is likely to have internal bleeding and needs emergency abdominal surgery.
2. Penetrating injuries of the head, neck and abdomen.
3. Suspicion of hollow viscus perforation or major pancreatic duct disruption.

Disability

A quick assessment of the mental status is made based on the AVPU scal (Alert, Responsive to Voice, Pain responsive, Unresponsive).Whenever possible the initial Glasgow coma scale (GCS) has to be documented. Any fall in GCS of > 3 is an indication for intubation. The pupils should be assessed for size and reaction to light. Unequal pupils indicate raised ICP with impending tentorial herniation and an urgent need to initiate measures to reduce the same. Suspected C-spine injury is a contraindication for testing doll's eye movements. Decerebrate and decorticate posturing may be due to severe hypoxia, hypotensive shock or raised ICP. It is important to interpret the neurolgic findings after correcting hypoxemia and shock. If the neurologic signs persist underlying brain injury has to be considered. GCS <8 and pupillary asymmetry are indications for neurosurgical consultation.

Emergency management of raised ICP

1. Head should be raised to 15-30 degree provided there is no hypotension.
2. Head shoud be kept in midline.
3. Intubation and ventilation to maintain normocarbia (PCO2-35-40)
4. Osmotic agents - Mannitol 0.25-0.5gm/kg in those who are not in shock or 3% saline 5ml/kg stat in those with shock should be administered as a bolus over 20-30minutes.
5. Prevent or treat secondary brain injury by treating hypoxia, hypovolemia and hypotension

Exposure

The patient shoud be completely undressed, usually by cutting off the garments for complete examination. Children are especially prone for hypothermia because of the high ratio of body surface area to body mass. Hypothermia may prolong coagulation times, affect CNS function and render the child refractory to treatment. The child should be covered with blankets. Overhead lamps and warmers may need to be used to prevent hypothermia during exposure and resuscitation. The core temperature should be measured.

The primary survey and resuscitation should be preferably complete within first 15-20 minutes. Once the primary survey is completed the child is log-rolled on to a spinal board after inspecting the back and spine for any swelling, bruises, tenderness and immobilized.

Secondary survey is then undertaken for definitive evaluation of the injured child. It comprises of the "SAMPLE" (Signs and symptoms, Allergies, Medications, Post medical history, Last meal, Events) history and a head to toe physical examination including a reassessment of the vital signs. If at anytime during the secondary survey the child deteriorates the primary survey should be repeated and life saving measures initiated. Examination indicated radiographic evaluations and laboratory studies are also included in the secondary survey.

History

A focused history should include the mechanism of injury as the patient's condition is greatly influenced by the mechanism of injury. "SAMPLE" is a useful pneumonic and stands for symptoms, allergies, medications currently used, past illnesses, last meal and events related to the injury.

Head to toe examination

Is essential to identify any injuries missed during the primary survey especially any life-threatening injuries such as tension pneumothorax, massive hemothorax and gastric dilatation.

Examination of the head: Includes palpation of the scalp for any lacerations, bruises and fractures. Reassess pupils. Look for hemorrhages of the conjunctiva and fundus. The latter may suggest inflicted injury especially in an infant. Check for visual acuity if child is conscious. Cerebrospinal fluid rhinorrhea, otorrhea, blood in the tympanic membrane, Racoon's eyes and Battle's sign suggest a basilar skull fracture.

The neck is examined for tenderness of the cervical spine, swelling, torticollis or spasm suggesting cervical spine fracture. Tracheal deviation, subcutaneous emphysema and laryngeal fractures may be discovered on detailed examination. Carotid arteries should be palpated and auscultated for bruit.

Examination of the chest: Inspect for wounds, bruising, deformity, respiratory effort, paradoxical motion as in flail chest, asymmetrical chest movement in pneumothorax or hemothorax. If a sucking chest wound is present, apply a sterile occlusive dressing. Palpate for any swelling, tenderness or crepitus. Decreased breath sounds, hyper resonance and shock may be the only indication for a tension pneumothorax. Distant heart sounds with jugular venous distension and hypotension (Beck's triad) may suggest cardiac tamponade. Impaled objects protruding from the chest should be left in place until definitive surgery. Rib fractures are uncommon in children. However if present it indicates severity of the injured force. The pliable chest wall increases the frequency of pulmonary contusions and pulmonary hemorrhage without rib fractures. 1st and 2nd rib fractures associated with widened mediastinum in chest radiogram is suggestive of underlying vascular injury.

Examination of the abdomen: The aim is to identify if a visceral injury exists. Most conscious children will be frightened, hence gentle examination of the abdomen should be done after gaining confidence of the child. The crying young infant will swallow air which also leads to abdominal distension.

Introducing an orogastric tube to relieve distension is part of the resuscitation. Suspect visceral injury in the presence of abdominal wall contusion, distension, abdomen or shoulder pain, guarding, rebound tenderness, signs of peritonitis, hematuria or shock. An abdomen that remains distended after gastric decompression suggests intra abdominal bleed or a disrupted hollow viscus. Elevations in serum transminases, or amylase and lipase suggest injury to the liver and pancreas. Urinalysis should be performed in patients with abdominal injury. Gross or microscopic hematuria suggests renal trauma.

Skeletal examination: Palpate all the bones for deformity, discontinuity and contusion. Pressure should be applied to the pubis and anterior superior iliac spine to assess for the presence of pelvic instability. Look for pallor, pulselessness, paresthesia and paralysis which indicate neurovascular trauma. Sensation should be assessed in all limbs. Severe angulations of the extremities should be straightened and immobilized. Apply splints and traction where indicated. Cover open fractures and wounds with sterile dressings. Irrigate wounds and debride devitalized tissues. Soft tissue injuries should be noted. The back should be completely examined.

The spinal cord and vertebral column: Assess motor response and pain response. Look for features of quadriplegia, paraplegia and nerve root injury. Palpate the vertebrae for swelling, tenderness and deformity.

Perineum, rectum: Inspect the perineum for lacerations, hematoma or active bleeding. Blood in the urethral meatus indicates pelvic fracture. A rectal examination should be performed to assess the sphincter tone and rectal integrity. Genitourinary injuries should be suspected in any penetrating abdominal or pelvic trauma and in all blunt abdominal or pelvic trauma associated with hematuria. Lower urinary tract injuries (bladder and urethra) are associated with pelvic fractures.

Imaging

Radiological examinations are part of the secondary survey. However an unstable patient should never be shifted to the radiology department. Traditionally x-ray of the cervical spine-lateral view, chest and pelvis are taken in all polytrauma patients. Since a normal lateral cervical spine x-ray does not rule out SCIWORA, a MRI of the spine may be needed to clear the spine. Skeletal x-rays are taken based on the clinical suspicion of a fracture. CT of the head is taken if the patient has altered level of consciousness. In a seriously injured child who has an endotracheal tube in place, CT of the C1 and C2 spine should also be taken. CT of the abdomen should be obtained whenever signs of intra abdominal injury are present and the patient is hemodynamically stable. Most CT abdomen should be done with IV contrast only as oral contrast will increase the risk of aspiration.[1] In general in patients with severe multiple trauma in whom a complete examination is not possible routine CT of the head, abdomen, thorax and pelvis may be beneficial.[3] Focused assessment by sonography in trauma(FAST) may be useful in detecting intra-abdominal blood where CT can not be obtained. Echocardiography is useful in the evaluation of thoracic injury as it may reveal anatomic or functional cardiovascular injury or injury adjacent to cardiovascular structures. Angiography may be indicated if vascular injuries are suspected.

Definitive care

If definitive care can not be given at the local hospital, the patient should be transferred to a hospital that has the resources and capabilities to care for the patient, preferably a trauma center. During transport child should receive the same care as in the referring hospital. Transport is arranged only after proper communication by the referring physician to the physician in the referral hospital.

Documentation

It is very important to document all findings, events and procedures accurately. Documentation of time for all events is very important. Chronologic reporting with flow sheets helps to quickly assess changes in the patient's condition. Good documentation helps to protect the physician from medico-legal problems.

Counseling the parents

It is an important component in trauma resuscitation. If possible assign one person to deal with the parents during resuscitation of the child. The parent's doubts should be cleared and procedures explained clearly. Permit parents at the child's bedside once the child is stabilised. The conscious trauma victim especially an older child should also be counseled.

Points to Remember

- ***The most common cause of preventable death in a trauma victim is not securing the airway.***
- ***Opening the airway with jaw thrust and simultaneous inline cervical stabilization are the first steps in the management of a poly trauma victim***
- ***Primary survey is aimed at recognizing life threatening injuries and immediate resuscitation of the same.***
- ***Secondary survey comprises of a history and head to toe examination to detect all injuries.***
- ***Emergency surgery is often needed in a child in whom hypotension is persisting despite 40-60mL/kg of crystalloids and PRBC transfusion.***
- ***The initial golden hour management reduces mortality.***

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PROTON PUMP INHIBITORS IN PEDIATRIC PRACTICE

**** Naresh P Shanmugam***

Abstract: *Proton pump inhibitors are widely used in pediatric practice for various acid related disorders. Esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole are five PPIs belonging to a class of irreversible inhibitors, currently available in market. This article gives a brief overview of difference between various proton pump inhibitors, uses and complications associated with it. Pediatric drug dosages and safety data's on PPIs were extrapolated from adult data and there are only few pediatric studies to support the data. Over all they are safe to use at prescribed doses for short term. Long-term safety data is not available in children.*

Keywords: *Proton pump inhibitors, Children, Indications, Dosage.*

Proton pump inhibitors (PPIs) are group of drugs, which has a common benzimidazole/ pyridine structure. Proton pump inhibitors block acid at the final common pathway of acid secretion-that is at the proton pump, and thereby offer the most potent suppression of gastric acid. The concept of PPIs to control acid secretion was proposed by Dr. George Sachs et al. in 1976. It took more than a decade for the first PPI omeprazole to be introduced in market. Omeprazole was first approved in Sweden in 1988 for treatment of duodenal ulcer. By the year 2000, omeprazole have been prescribed, equivalent to 23 million treatment years. Due to its effectiveness and long duration of action it over took H2 Blockers in pediatric practice. Apart from omeprazole and lansoprazole, the pharmacokinetics is less known and the values are derived from adult studies.

There are two classes of PPIs, covalent and competitive inhibitors. Those in the covalent class inhibit the pump by irreversibly binding H+/ K+ATPase enzyme and inhibits hydrogen ion secretion from the parietal cells. The irreversibility of the covalent bond results in inhibition of acid secretion until more enzyme is synthesized. Drugs in the competitive class of PPI bind on the extracellular surface of the proton pump and cause reversible inhibition. Competitive inhibitors were associated with undesirable side effects and so are not available in market.

* Department of Pediatric Gastroenterology, Hepatology and Transplantation, Global Hospitals and Health City, Chennai.

Pharmacodynamics

In the class of covalent inhibitors, there are five drugs available in market (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole). These drugs have different substitution in their pyridine and/or benzimidazole group. All these PPIs are prodrugs and designated to be released in alkaline duodenum, where it would be absorbed. Through blood the prodrug diffuses into parietal cells of gastric mucosa, where it is activated to proton-catalysed formation of tetracyclic sulfonamide, which cannot diffuse back across membrane. The active drug binds covalently with sulfhydryl groups of cysteines in H+/K+ATPase enzyme and permanently disables them. Acid secretion resumes only after new pumps are synthesized, providing a prolonged acid suppression (24-48 hrs) despite shorter plasma half-life's (0.5 to 2hr).[1]

Indication for PPI use in children

PPIs could be used in any condition that would benefit from suppression of gastric acid secretions. Drug dosage in pediatric practice is outlined in Table I. Few of the indications of PPIs in pediatric practice is discussed below.

i. Gastroesophageal reflux and esophagitis

Gastroesophageal reflux is a common indication for initiation of PPI treatment. In a systematic review, it was found that PPIs were not effective in reducing GERD symptoms in infants.[3] All the five agents (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) have been demonstrated to control GERD symptoms in children and adolescents and heal esophagitis when used at prescription doses, with no added advantage amongst them.[4] A 2001 meta-analysis compares the effectiveness of all five PPIs in the healing of reflux esophagitis and found

Table.I. Proton pump inhibitor dosage in children[2]#

	FDA recommendation	Drug dosage	
Omeprazole*	>1 year	0.7 to 3.5 mg/kg/day Max 80 mg	Once a day or two divided doses
Esomeprazole*	>1 year	10 mg <20 kg, 20 mg> 20 kg	Once a day
Lansoprazole*	>1 year	0.5 to 1 mg/kg 15 mg max<30 kg 15 to 30 mg > 30kg	Once a day
Pantoprazole	>5 yrs	20 mg for 15 to 40 kg 40 mg for > 40kg	Once a day
Rabeprazole	>12 yrs	20 mg	Once a day

* Could be given for less than one year by specialist recommendation

From drug monographs

no advantage of one over the other.[5] The efficacy of the PPIs in preventing esophagitis relapse is similar for all drugs. Though PPIs help in decreasing asthma episodes associated with GERD, use in poorly controlled asthma with no evidence of GERD neither improved symptoms nor lung function but was associated with increased adverse events.[6]

ii. Gastrointestinal ulcer healing and rebleeding

In studies comparing PPIs for the treatment of duodenal ulcers, all the drugs had similar healing rates but rabeprazole was shown to have quick symptomatic relief.[7] A Cochrane meta-analysis showed that treatment with PPIs consistently reduced the rate of rebleeding after an episode of ulcer bleeding and also reduced the requirement for surgical treatment. No distinction among PPIs was made.

iii. Helicobacter pylori treatment

In Helicobacter pylori eradication regimen (triple therapy) cure rates among omeprazole, lansoprazole and pantoprazole were similar and no added advantage of one over other.[8]

Adverse effects of PPIs

Suppression of gastric acid secretion is associated with positive feedback to increase gastrin secretion. This result in parietal cell hyperplasia and gastric polyps, but so far malignant changes haven't been reported. In a study done by Tolia et al on long term safety of PPIs in 42 children has shown that, treatment with PPIs for an average of 46 months was associated with high gastrin levels, parietal cell hyperplasia, gastric polyps, constipation and diarrhoea. These changes were not associated with type or duration of treatment.[9] Side effects associated with PPI usage are outlined in Table II.

Table.II. Adverse effects of proton pump inhibitors

- High gastrin levels
- Parietal cell hyperplasia
- Gastric polyps
- Atropic gastritis associated with H.Pylori
- Hepatitis/ transaminitis
- Osteoporosis
- Hypomagnesemia
- Increased risk of Clostridium difficile-associated disease
- Vitamin B12 deficiency

Conclusion

The Oregon Health Resources Subcommittee Report[10] on PPIs suggested that, there is no evidence to demonstrate a clinical difference in efficacy to justify selection of any

PPI as clinically superior to the other drugs in the class. This includes consideration of comparative effectiveness and incidence and nature of adverse events between omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. There are no clinically demonstrable differences amongst the PPIs whether treatment is for GERD, peptic ulcer, non-steroidal ulcer, duodenal ulcer, or eradication of Helicobacter Pylori and no evidence to support differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities Long term PPIs are associated with side effects and should be used only after appropriate investigation by specialist.

Points to Remember

- ***PPIs are more effective than H2 blockers***
- ***There is no advantage of one PPI over other***
- ***Long term safety of PPI in children is not known***
- ***Pediatricians can use short term PPIs, but long term usage needs thorough investigation before treatment initiation by specialist.***

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CLIPPINGS

Partial exchange transfusion to prevent neurodevelopmental disability in infants with polycythemia

Hyperviscosity of blood results in increased resistance to blood flow and decreased oxygen delivery. In the neonate, hyperviscosity can cause abnormalities of central nervous system function, hypoglycemia, decreased renal function, cardiorespiratory distress, and coagulation disorders. Hyperviscosity has been reported to be associated with long-term motor and cognitive neurodevelopmental disorders. Blood viscosity exponentially increases when an infant has polycythemia (hematocrit ≥ 65%). Partial exchange transfusion (PET) is traditionally used as the method to lower the hematocrit and treat hyperviscosity.

There are no proven clinically significant short or long-term benefits of PET in polycythemic newborn infants who are clinically well or who have minor symptoms related to hyperviscosity. PET may lead to an increase in the risk of NEC. The data regarding developmental follow-up are extremely imprecise due to the large number of surviving infants who were not assessed and, therefore, the true risks and benefits of PET are unclear.

Eren Özek 2 , Roger Soll 1,* , Michael S Schimmel 3 Editorial Group: Published Online: 17 FEB 2010.

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SAFE TRANSFUSION OF BLOOD PRODUCTS – WHAT A PEDIATRICIAN SHOULD KNOW

**** Revathi Raj***

Abstract: *Blood transfusion saves lives. However, transfusion should be prescribed only when the benefit of transfusion clearly outweighs the risks in each and every child we treat. Component therapy is the way forward in modern transfusion medicine. Fresh whole blood should neither be stocked nor dispensed as every unit can be optimally utilised to save three lives with component therapy. The knowledge of how to use packed red cells to optimise hemoglobin, platelets to treat thrombocytopenia and fresh frozen plasma to treat deficiency of clotting factors resulting in bleeding is required of every physician. The practical aspect of how to make transfusion safe for our patients is discussed in this article.*

Keywords: *Component therapy, packed red cells, platelets, apheresis, fresh frozen plasma, cryoprecipitate*

The process of blood donation, component separation and issue of blood products has been standardised worldwide. Donated blood from healthy voluntary donors is screened for five mandatory diseases in our country, namely HIV, hepatitis B, C, Syphilis and malaria. The unit is then divided into its components by a process of centrifugation and stored in their respective storage area for issue at the request of a clinician (Fig.1).

Packed red blood cells

Indications

There is no strict 'level' at which red cells should be transfused. If there is anaemia with co-morbid conditions such as pneumonia or malaria or prematurity transfusion is indicated. Red cells should be cross matched for compatibility with the recipient. In infants less than 3 months, cross matching can be done with maternal sample. In an emergency, O negative packed red cells can be used without crossmatching.

Planning transfusion

- Optimal volume of red cells (packed cells) = desired rise in Hb x weight (kg) x 3 or 20 ml / kg of packed red cells
- Transfusion rate: 2-5ml/kg/hr
- Severe chronic anaemia, transfuse in 2-3 aliquots of 5ml/kg packed red cells
- Transfusion must be completed within 4 hours of the blood leaving the blood bank
- Bedside handling of packed red cells must be strictly avoided and the required volume must be aliquoted in the blood bank using strict aseptic procedure and a sterile docking device

Platelets

Indications

- Children with aplastic anemia or leukemia, platelets are to transfused

  If $<10 \times 10^9$/L in non-bleeding stable patients

  If $<20 \times 10^9$/L in patient with other abnormalities like fever
- DIC to maintain platelets $> 20 \times 10^9$/L
- Massive blood transfusion to maintain platelets $> 50 \times 10^9$/L
- Cardiopulmonary bypass surgery as platelet function defects and thrombocytopenia often occur and may require platelet transfusion
- Surgery prophylaxis keep $> 50 \times 10^9$/L for LP, epidural anaesthesia, insertion of central venous lines transbronchial biopsy, liver biopsy, renal biopsy and laparotomy.
- Keep $> 100 \times 10^9$/L for neuro and ophthalmic surgery
- Platelet function disorders may require platelets only for bleeding emergencies even with a normal platelet count

* Consultant Pediatric Haematologist
Apollo Hospitals,
Chennai.

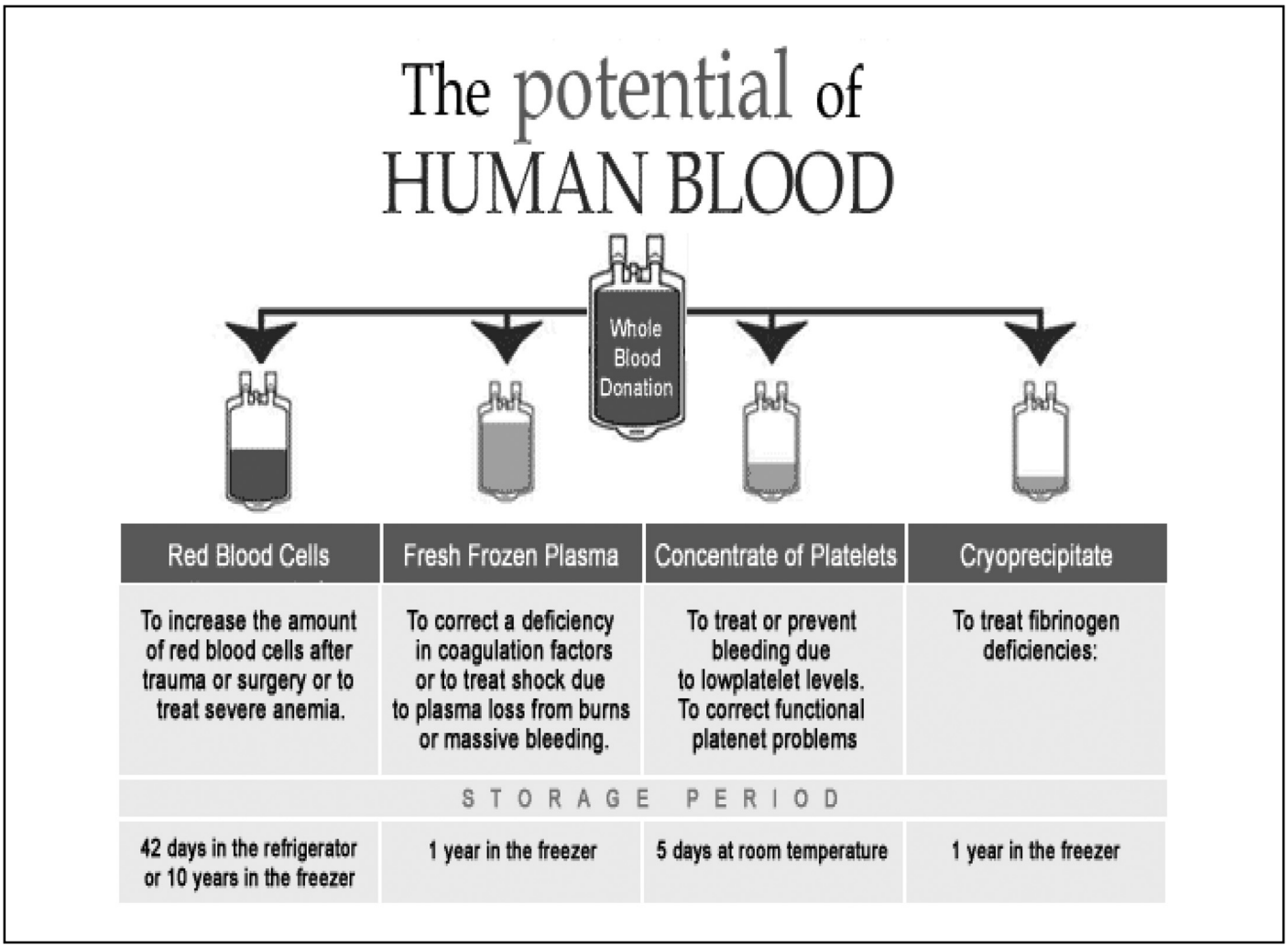

Fig.1. Components of blood and storage period

- Immune thrombocytopenia only when there is major gastrointestinal or central nervous system bleed.

Planning transfusion

- Neonates / infants <10kg, one unit for every 10 kg or 10ml/kg of group specific platelets.
- Platelet transfusion must be completed within half an hour of issue from the blood bank.

Apheresis platelets can be used in children with refractory bleeds. One apheresis or single donor platelet (SDP) is equivalent to 6 units of random platelets.

Fresh Frozen Plasma (FFP)

Indications

- Bleeding among patients with PT > 17 sec (for newborns > 19 sec)
- Preparation for bedside invasive procedure if PT > 17 sec (for newborns > 19 sec)
- As part of the emergency management of warfarin reversal.
- Inherited clotting factor deficiencies with acute bleeding.

Planning transfusion

- Fresh frozen plasma should be dosed based on patient weight with the usual dose being 10 ml/kg body weight
- The frequency of transfusion depends on the clinical condition of the child and the half life of the clotting factor being replaced
- FFP infusion must be completed within 1 hour of issue from the blood bank

Cryoprecipitate

Indication

- Bleeding in the setting of fibrinogen < 100 mg/dL, von Willebrand's disease, hemophilia A and factor XIII deficiency.

Planning transfusion

- Cryoprecipitate should be dosed based on patient weight with the usual dose being 5 ml/kg body weight.
- The frequency of transfusion depends on the clinical condition of the child and the half life of the clotting factor being replaced.
- Cryoprecipitate infusion must be completed within 1 hour of issue from the blood bank.

Leucodepletion

Leucocytes present in cellular blood components (red blood cells and platelets) are responsible for three transfusion complications. (i) Febrile non-hemolytic reactions, (ii) Sensitization to HLA antigens and (iii) Transmission of CMV infection.

Leucoreduction is routinely accomplished by filtration with high performance filters which achieve a two to three logarithm reduction in leucocytes. Apheresis platelets are collected by a method which renders them leucoreduced. Filters are different for red cells and platelets and can be used only once. Bedside filters used during transfusion are now being replaced by filtration in the blood bank before issue of the product.

Indications

- Patients who have experienced febrile, non-hemolytic transfusion reactions.
- Patients who will require long-term transfusion support, particularly long-term platelet support.
- Transplant recipients or candidates.
- Patients requiring CMV-reduced risk transfusions.

Irradiation

Exposure of blood products to 25 GY of radiation kills lymphocytes. This prevents transfusion associated graft versus host disease.

Indications

- Bone marrow transplant patients
- Hodgkin's therapy
- Fludarabine therapy
- Intrauterine transfusion
- Transfusion from close relatives

Premedication for blood transfusion

There is NO indication for routine use of premedication for blood product transfusion.Oral paracetamol and intravenous chlorpheniramine can be used in multiply transfused patients. Hydrocortisone needs to be used only if there is an urticarial reaction or a history of a significant allergic reaction during previous transfusions.

Transfusion reactions

These can be major reactions or minor reactions.

Minor reactions are fever, chills, rigors and urticaria. Steps to be taken for minor transfusion reactions are

- Stop the transfusion and assess the patient
- Use paracetamol 15 mg / kg oral
- Inj. pheniramine maleate 1mg/kg
- Inj. Hydrocortisone 5 mg/kg IV
- Commence transfusion after 15 to 30 minutes.
- Observe patient for 1 hour after transfusion before discharge
- Advice to return in case of fever

Major transfusion reaction in case of fever > 101^{O}F, tachycardia, a fall in blood pressure from baseline, anxiety, flushing, vomiting or muscle cramps. Steps to be taken for major transfusion reactions are

- Stop the transfusion immediately
- Check the patient and bag blood groups
- Medications as per minor reaction
- Resuscitate with normal saline to maintain blood pressure and renal perfusion

This reaction is usually due to wrong blood given to the wrong patient and major ABO incompatibility. The other causes are allergic reaction, transfusion related acute lung injury and bacterial contamination of the unit.

Transfusion must be performed by trained personnel in a safe environment. We need to encourage regular voluntary donors to help save little lives. Urgent improvement in infrastructure is required for blood banks across our country to move towards component therapy and to make blood transfusion safe for all our patients.

Points to Remember

- ***PRBC transfusion should be completed within four hours of blood leaving the blood bank.***
- ***Platelet transfusion should be completed within half an hour and FFP within one hour of issue from the blood bank.***
- ***Leucodepleted transfusion in indicated in transplant recipients or candidates waiting for transplant and in those who need long term transfusion support.***
- ***There is no need for premedication prior to blood product transfusion, as a routine.***

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CLIPPINGS

Kinesthetic stimulation versus methylxanthine for apnea in preterm infants

Apnea of prematurity may lead to hypoxemia and bradycardia requiring resuscitative measures being instituted. Many treatments have been used in infants with apnea of prematurity including methylxanthines. Physical stimulation is often used to restart breathing and it is possible that repeated stimulation such as with an oscillating mattress or other kinesthetic stimulation, might also be used to treat infants with apnea and prevent its consequences.

To determine if kinesthetic stimulation is more effective than a methylxanthine in preventing clinically important apnea in preterm infants with apnea,the standard search strategy of the Cochrane Neonatal Review Group was used.

All trials using random or quasi-random patient allocation in which kinesthetic stimulation was compared to methylxanthine therapy for apnea of prematurity were eligible.

The results of this review should be treated with caution. Theophylline has been shown in one small study to be superior to kinesthetic stimulation at treating clinically important apnea of prematurity. There are currently no clear research questions regarding the comparison of methylxanthines and kinesthetic stimulation to treat apnea of prematurity.

David A Osborn[1,*], David J Henderson-Smart[2,] Editorial Group: Cochrane Neonatal Group Published Online: 20 JAN 2010, DOI: 10.1002/14651858.CD000502.

Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants

Necrotizing enterocolitis (NEC) is the most common gastrointestinal problem of preterm neonates. There have been reports published suggesting that the use of enteral antibiotics may be effective as prophylaxis. This systematic review was undertaken to clarify the issue.

All randomized or quasi-randomized controlled trials where enteral antibiotics were used as prophylaxis against NEC in LBW (< 2500 g) and/or preterm (< 37 weeks gestation) infants.

Evidence suggests that oral antibiotics reduce the incidence of NEC in low birth weight infants. However concerns about adverse outcomes persist, particularly related to the development of resistant bacteria. To address this question further, a large trial would be required with a sample size sufficient to examine all the important benefits and harms. Adverse outcomes associated with infection should be evaluated, and microbiological studies looking for the development of resistant bacteria should be undertaken

Richard Graham Bury[2], David Tudehope[1,*] Editorial Group: Cochrane Neonatal Group, Published Online: 21 JAN 2009. DOI: 10.1002/14651858.CD000405.

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ACUTE OTITIS MEDIA

**** Balachandran K***

Abstract: *Acute otitis media (AOM) in children is the most common condition every pediatrician and ENT Surgeon come across in day to day practice. The age group ranges from less then 1 year to 5 years. The attending physician should be aware when to start antibiotic and when to refer the child to ENT surgeon for further management, especially for surgical intervention if required.*

Keywords: *Acute otitis media, Antibiotics, Children.*

The middle ear cleft consists of the eustachian tube (ET), tympanic cavity, mastoid antrum and air cells. Acute otitis media (AOM) is usually a complication of upper respiratory tract infection (URI). It is confined to mucoperiosteal lining of the middle ear cavity. Spread of infection beyond this anatomical site results in complications like mastoiditis, petrositis, meningitis, labyrinthitis, etc. The symptoms vary according to the type of infecting organism, anatomy of the ear and extent of infection.

AOM can arise as a result of infection from nasopharyngeal or milk inhalation through eustachian tube, blood borne infection, from external canal through previously perforated tympanic membrane (TM) or by baro trauma.[1-4]

Age incidence: Peak incidence is between 5 to 7 years and 50% seen under 2 years of age.

Sex incidence: 60 to 65% occurs in males and no reason for this apparent inequality has been identified.

Socio economic status: Highest in low income group because of overcrowding and undernutrition. Urban children are more affected than the rural.

Climate: Higher incidence has been observed in the winter.

Etiology

Nasopharyngeal masses: Adenoids, nasal polyps, teratoma, angiofibroma of palate, lymphoma,etc produce obstruction of eustachian tube resulting in AOM.

Respiratory disease: Chronic rhinitis, sinusitis, bronchitis and pneumonia can produce AOM due to infected sputum propelled into ET.

Allergy: As an etiological factor in AOM is debatable. Allergic edema of ET can produce obstruction resulting in AOM. However many atopic children have no ear problem. The population of adenoid mast cells of patients with otitis media with effusion (OME) was significantly greater than in children without OME.

Pre-existing middle ear effusion: May act as a culture media for the invading pyogenic cocci.

Immuno deficiency syndrome: When recurrences are very frequent, hypogammaglobulinemia has to be ruled out.

Chronic systemic disorders: Diabetes, leukemias, anemia, cystic fibrosis and nephritis.

Primary ciliary dyskinesia: Rarely can produce recurrent otitis media (OM).

Cleft palate: Can produce recurrent OM due to malfunction of ET

Pathology

While AOM is considered mainly a bacterial disease, viruses undoubtedly play a role in many cases paving a way for the bacteria to invade

Most common organisms are Streptococcus pneumoniae and Hemophilus influenzae. Next common are group A hemolytic streptococcus, Staphylococcus aureus and Moraxella catarrhalis, gram negative bacilli like Pseudomonas aeroginosa, various Proteus species and Klebsiella pneumoniae.

These organisms can produce mucosal edema with increased secretion followed by hyperemia, white cell infiltration, pus formation, destruction of cilia in the lower part of tympanic cavity and ET, preventing drainage and leading to AOM.

Spread of infection

AOM can spread outside middle ear cavity into the cranium by retrograde thrombophlebitis, bone necrosis, congenital dehiscence or fracture line resulting in extradural,

* Professor and HOD (Retd.)
Dept. of ENT
Govt. Dharmapuri Medical College and Hospital,
Dharmapuri.

subdural brain abscess, lateral sinus thrombosis and otitic hydrocephalus. It can also lead to suppurative labyrinthitis, facial palsy, various types of neck abscess and petrositis.

Clinical features

Symptoms

Nature of symptoms depends on the following factors (1) virulence of the organism, (2) host defence, as well as (3) effectiveness and compliance of treatment.

Symptoms vary from minor ear pain to a fulminating febrile illness with complications. The most common symptoms are pain, especially on pulling of ear, irritability and restlessness, avoidence of food, fever, etc. Also history of preceding URI may be present. Deafness, discharge from affected ear and some times giddiness can be present.

Signs

Gentle examination must be done with the child resting on the mother's lap.

Ear: Tympanic membrane (TM) may be congested, bulge posteriorly or perforated. Tuning fork test may identify conductive deafness. Aural exam may rarely show granulation tissue.

Nose: Shows inflammation of the mucosa and discharge may be present. Post nasal discharge may be noticed in case of co-existing sinusitis.

General signs may be fever, tenderness over the mastoid region. Neck stiffness and nystagmus are uncommon but when present indicates intracranial extension.

Investigations

Ear swab: If otorrhea is present gram stain and culture and sensitivity have to done. If no discharge, throat and nasal swab can be taken.

Hemogram usually shows increased leukocyte count when immunodeficiency is suspected immunogloolin assay, has to be done.

Urine examination and blood sugar in recurrent otitis media are to be done to rule out diabetes.

Pure tone audiometry, tympanometry can be done in older children.

Mastoid Xray: To diagnose mastoiditis

Treatment

Medical

Adequate humidity, nourishment and analgesics are the initial steps in management.

Role of antibiotics: In the first 24 to 48 hours, no antibiotics are needed. If symptoms persist antibiotics should be started and amoxicillin is still the drug of choice.

Surgical management

Myringotomy: In a symptomatic child with excruciating pain and if TM is bulging, myringotomy can be done.

Adenoidectomy: In case of recurrent otitis this can be considered to remove source of sepsis. This procedure does not lower immunity, it removes mast cells present in the adenoid mass, there by less attacks are encountered in children.

Sinusitis if present has to be treated and cleft palate if present has to be corrected.

If the middle ear effusion persists for more than three months, tympanostomy tube along with adenoidectomy is preferred. Sequelae of unresolved effusion can result in hearing loss leading to behavior disorders and may have impact on speech, language and reading skills.

Points to Remember

- ***AOM is an important disease of children.***
- ***Medical treatment is the first line of management.***
- ***In cases of recurrent episodes, physician should think of treating the pre disposing factors and there by the sequelae of AOM can be prevented.***

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LIMPING CHILD

**** Sankar R***
***** Sridhar M***

Abstract: *Deviations from a normal age-appropriate gait pattern can be caused by a wide variety of conditions. A limp is one of the commonest reasons for a child to visit a doctor. A detailed understanding about this condition is necessary since this symptom could be the clue to a serious underlying diagnosis. Careful assessment from head to toe with pertinent history and investigations is necessary to diagnose the underlying condition. In this article we have tried to explain an age based assessment and management of a limping child.*

Keywords: *Limping, Child, Septic, Hip.*

It is difficult to assess the incidence of limping child in our country. In the west, Fischer et al., noted an incidence of 1.8 per 1000 children visiting an emergency department for an acute atraumatic limp.[1] Limp is an abnormal gait which can be caused by pain, muscular dysfunction or deformity. The presentation can be painful or painless. Painless limp does not require urgent evaluation, whereas, painful limp should be treated as an emergency. It is one of the commonest disorders in pediatric orthopedics which triggers significant interest among general pediatricians. There is a myriad of causes for this symptom and that can include non- skeletal reasons as well. As it is the norm in medical profession a thorough history and careful head to toe examination would be necessary to sort out the cause of this condition. A diagnosis can be arrived at with appropriate laboratory investigations following history and examination on most occasions. If serious conditions requiring quick intervention are ruled out and if the diagnosis is still in doubt, a period of observation might be necessary before reviewing the situation.

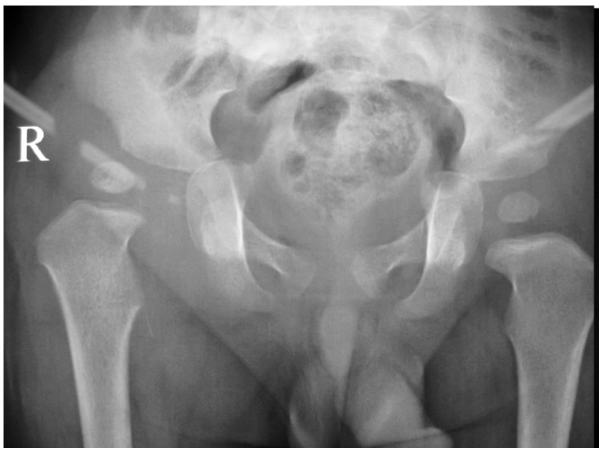
Clinical history: Probably the most important tool to achieve a diagnosis is the clinical history and should include history of trauma, duration of symptoms, symptoms suggestive of infection and past history of similar happenings. History of bleeding or clotting problems in the patient or family, history of weight loss, associated symptoms to rule out chronic infections like tuberculosis, malignancy and history suggestive of auto immune conditions like multiple joint swellings, gastrointestinal symptoms, skin rashes, mouth ulcers, etc, should also be sought. Malignant bone tumors can present with intermittent pain at rest and should be considered in children with limp.[2] Night pain, especially pain that wakes a child from sleep, is a worrisome indicator of a malignant process and steps should be taken toward rapid diagnosis. Fortunately in children who are limping, the incidence of serious conditions are rare and frequently are a result of self limiting viral infections presenting as a synovitis,[1] but the possibility of a co-existing significant condition should always be entertained. Usually a child whose limp shows signs of improvement may safely be observed as long as there are no constitutional symptoms.[3] Thorough history and examination will, rule out disorders which are common, does not need investigations and can be managed with simple measures. They include thorn prick or corn foot, inguinal adenitis, local trauma, intramuscular injection or muscle pain. Muscle pain can occur secondary to systemic problems like dengue or viral myositis, leptospirosis or unaccustomed exertion.

Differential diagnosis: It is easier to look at the causes based on assigned age group and for that purpose we can divide the pediatric age group as toddler (1-3 years), child (4-10 years), adolescent (11-16 years) (Table I). The common causes for the limping toddler are transient synovitis, septic arthritis (Fig. 1) and osteomyelitis and toddlers fracture (Fig. 2a&b).

In a limping child the commonly seen conditions are transient synovitis and Perthes disease (Fig. 3). In a limping adolescent slipped capital femoral epiphysis (Fig. 4), hip dysplasia and idiopathic chondrolysis of hip are the common conditions to rule out. Neoplasms, blood disorders like sickle cell anemia and infections can also present in this age group with a limp and should be actively ruled out.

Investigations and management: The diagnostic challenge is to distinguish between disease processes that

* Consultant Pediatric Orthopedician,
** Consultant Pediatrician,
Apollo Children's Hospitals,
Chennai.



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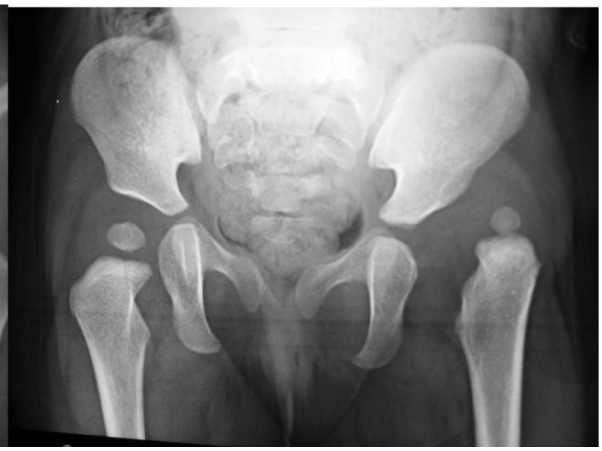

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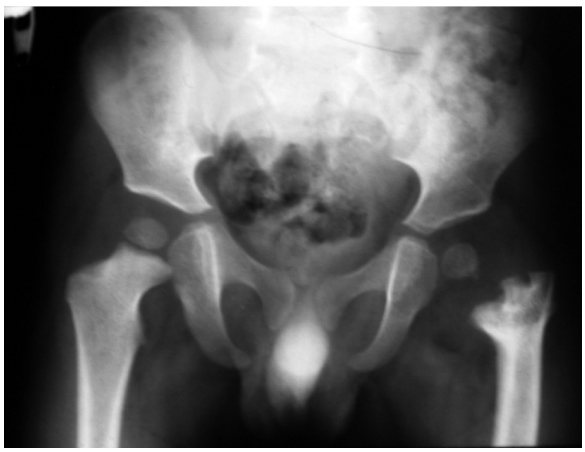

(1c)

Fig.1. Septic arthritis right hip (a) resulting in subluxation of joint. Note acetabulum is well formed. (In Developmental Dysplasia of hip(b), acetabulum will be shallow). Fig 1c shows late treatment of left septic hip resulting in destruction of the joint.

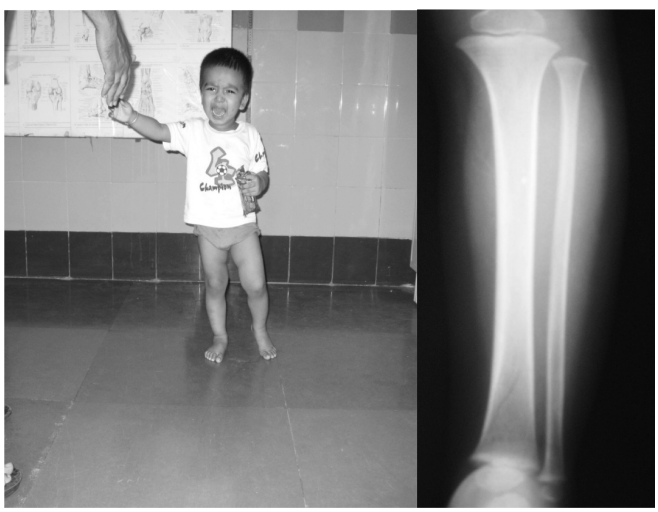

Fig.2a&b. Child with history of fall, has difficulty in weight bearing on left leg. X ray shows evidence of spiral fracture tibia. (Toddler's fracture)

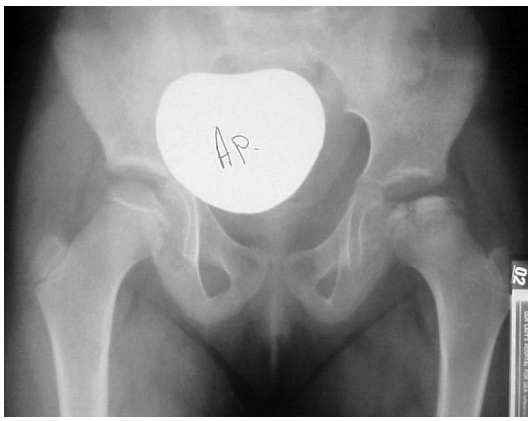

Fig.3. Left Perthes disease with fragmentation of femoral head

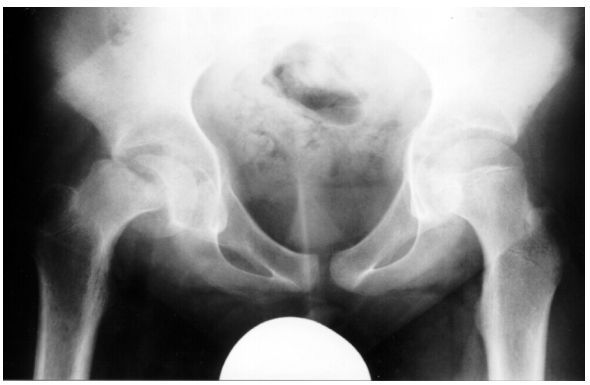

Fig.4. Right slipped capital femoral ephiphysis showing severe displacement of femoral head

Table I. Causes of limping child

	Toddler	Child	Adolecent
Causes of limp	1. Transient synovitis 2. Septic arthritis 3. Osteomyelitis 4. Toddler's fracutre 5. Inflammatory disorders (lyme disease, JRA, Rheumatic fever) 6. Neoplasms	1. Transient synovitis 2. Perthe's disease 3. Discoid lateral meniscus 4. Idiopathic tight Achilles tendon 5. Trauma	1. Slipped capital femoral epiphysis 2. Overuse syndromes (Osgood-Schlatter disease) 3. Hip dysplasia 4. Idiopathic chondrolysis of hip 5. Osteochondritis dissecans 6. Tarsal coalitions

are benign and self limiting (such as transient synovitis), acute or life threatening (such as septic arthritis or acute leukemia), or chronic and disabling (such as Perthes disease). In most cases the causes are benign and self limiting and around two thirds of patients can be managed in the emergency department.

Let us discuss some of the common causes of a limping toddler. A septic arthritis is by far the commonest condition requiring immediate intervention. Though any of the joints can be affected, the hip joint is the most common joint involved. A suspicion of infection should be followed by routine blood investigations including ESR, CRP and blood culture. Imaging should begin with standard radiograph of the area concerned.[4]

An ultrasound of the hip would usually show increased joint space and fluid, though this cannot be used to distinguish between sterile, purulent or hemorrhagic fluid accumulations.[5] In the absence of clear cut bleeding diathesis, the cornerstone of treatment is surgical drainage and irrigation of the hip. The aspirated fluid should be sent for microscopy, culture and sensitivity. Empirical antibiotic should be commenced after aspiration and should be continued till constitutional symptoms improve. Missed or late diagnosis can lead to severe and lifelong sequelae (Fig.1c).[6] Wiener et al showed synovial fluid from septic joints has higher concentration of lactate compared to non septic arthritis.[7] Other diagnostic clues from the aspirate would be WBC more than 80,000/ml with more than 75% polymorphs**,** Culture may be negative for bacterial growths in 70% of patients. According to Kocher et al, a child with a painful hip suspected to have a septic arthritis should have 1) non-weight bearing on the affected side, 2) fever, 3) ESR more than 40mm/hr, 4) WBC more than 12000. Presence of all 4 criteria will give a 99% chance of a positive diagnosis.[8]

There are no strict guidelines in diagnosis of osteomyelitis but unexplained bone pain with fever means osteomyelitis until proven otherwise. Infection markers are most often raised and a blood culture must be done to prove infection. If clinical condition does not improve after 36 hours, surgical debridement should be considered. Initially parenteral antibiotic is preferred followed by oral antibiotic once there is a clinical and laboratory improvement. Transient synovitis is a diagnosis of exclusion and a joint aspirate will usually show 5000-15000 cells/ml with less than 25% polymorphs. The treatment is NSAID and restricted activity.

Psoas abscess: High index of suspicion is needed to diagnose this condition. This should be considered as a differential diagnosis in any child presenting with fever, painful hip, groin pain, abdominal pain or painful limp or as swelling in the inguinal region. It may occur secondary to septic abdominal focus either in the kidney, appendix or lymphnode. In sub acute presentation tuberculous spondylitis should be considered. CT an MRI are useful in diagnosing psoas abscess.

Discitis, vertebral osteomyelitis: Here fever, back pain and local spinal tenderness may be present. X ray and MRI spine are useful diagnosing this condition.

In toddlers, fracture patients refuse to bear weight and the history frequently is unremarkable for any particular traumatic event (Fig. 2 a&b). Even though initial radiograph of the affected leg may be normal, follow-up radiograph will show evidence of periosteal reaction suggestive of fracture. This can usually be treated with plaster cast for 3 weeks.

Painless or non antalgic limp is usually due to neuromuscular problems like cerebral palsy, poliomyelitis

sequelae, primary neuropathy or primary orthopedic problems. These conditions are usually chronic in nature. Always check for leg length discrepancy in any child presenting with painless limp.

Developmental dysplasia of hip and neuromuscular disorders presents with abnormal gait from the time child starts walking. Developmental dysplasia of hip can be unilateral or bilateral and should be treated early to obtain a good outcome. In neuromuscular disorders there are other features in history explaining the brain injury. Inflammatory disorders usually present with mild painful limp with a history of pain presenting for more than 4-6 weeks. Medical management results in good control of inflammation. In severe cases, intra-articular steroid injections can be used to treat them.

Hematological malignancies often present as a limp and in acute lymphoblastic leukemia 20% of patients present with musculoskeletal complaints and upto 12% only has limp at presentation. A blood picture and count with a bone marrow would confirm the diagnosis. Solid tumors presenting as a limp can be benign, malignant or secondary tumors.

In a limping child apart from transient synovitis, Perthes disease needs to be ruled out. The limp is often painless and intermittent, usually in the groin, inner thigh or in the knee. There would be limitation and pain on internal rotation, and limitation of abduction particularly in flexion. A child will walk with externally rotated limp. An X-ray of the hip joint would confirm the suspicion and treatment is based on the stage of the disease. Aim of the treatment is containment of the hip. Physiotherapy will help to retain the range of movements.

In a limping adolescent, slipped capital femoral epiphysis is by far the commonest cause of limp and should be looked for with an X-ray. Usually the child will be either obese or tall and slim. They may present with a referred pain in the inner side of the thigh or knee. Sometimes this may be associated with endocrine disorders like increased growth hormone or decreased sex hormone levels. They can be bilateral in endocrinopathies. Children treated early will have a better prognosis.

Adolescents during growth spurts can present with pain around the knee due to Osgood-Schlatters disease or Sinding-Larsen disease. These are benign conditions due to osteochondritis and can be managed conservatively with good outcome.

The role of the general pediatrician is paramount because in the absence of a clear cut trauma, patients usually present as the first port of call to them. Knowledge of the conditions causing the limp is essential to decide whether the patient requires immediate intervention or further observation.

Points to Remember

- ***Limping is one of the commonest causes for a child to visit an orthopedician.***
- ***Painful limp must be treated as an emergency.***
- ***Surgery is curative in septic arthritis and osteomyelitis if diagnosed early.***
- ***The hip is the most common site of pathology, and pain is often referred to the knee.***
- ***A delay in the diagnosis of a slipped upper femoral epiphysis may worsen the outcome.***

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INHALATION THERAPY - PRACTICAL ISSUES

**** Gowrishankar NC***

Abstract: *Inhalation therapy is given in many respiratory disorders in children. This article deals only with issues related to inhaled medications in children with asthma. Even though most of the literature dealing with long term management of asthma tells about the need for inhaled medications to be given properly, there are many issues which occur while using. This article gives an insight of the problems and steps to overcome them in inhalation therapy.*

Keywords: *Inhaled medications, Practical issues, Asthma management, Children.*

Drug delivery through the respiratory system is more complex. The advantages of giving medications by aerosol is that the drug is delivered to the site of action directly which leads to higher local concentration leading onto faster onset of action with minimal side effects. But not all inhalation devices are appropriate in the pediatric age group as a) devices perform in different ways, b) inhalation techniques need mastering, c) different age groups have different psychomotor skills and to achieve same therapeutic effect different doses may be required and d) because of the heterogeneity of patients no single inhaler will satisfy the needs of all. There are three major misconceptions regarding the use of inhalers in children (i) nebulizer is more effective than a pressurised metered dose inhaler with spacer in treating acute asthma in children (ii) using an inhaler correctly is easy and (iii) correct use of the inhaler, once taught, persists over time. Important drug delivery issues specific to children include compliance, lower tidal volumes and inspiratory flows, determination of appropriate dosages and minimization of adverse local and systemic effects.[1]

Inhaled steroids and long acting β_2 agonists (LABA) are the main stay of treatment in any child with persistent asthma. Inhaled short acting β_2 agonists are the main stay of therapy for acute asthma while inhaled corticosteroids are the cornerstone for long term management of asthma. Effective inhalation therapy using pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) is the cornerstone of asthma management.[2] Contrary to general opinion, using an inhaler correctly is difficult for children. Many children with asthma use their inhaler devices incorrectly, even after instruction for correct use of the inhaler. Also, correct inhalation technique deteriorates over time. Even older children who understand the nuances of inhaler preferably need a holding chamber with valve for proper delivery of the medication used. Most of the time the pediatric physician writes the prescription for inhaled medicines but fails to demonstrate and teach the proper inhalation technique citing lack of time in a busy practice. It has been found that the time taken to teach the inhalation technique is not more than 2.5 minutes.[3]

Inhaler systems differ in their construction, aerosol cloud generation, optimal inhalation technique and ease of use. Errors in inhalation therapy may be device dependent or device independent. The main device dependent problem is improper preparation of the inhaler. Device independent errors include lack of exhalation before inhalation, inadequate inspiratory flow and inhalation through the nose. It should be the duty of every pediatrician to teach the correct technique of inhalation for every child who has been given a prescription for inhaled medicines.

Inhaled medicines can be given by pressurized metered dose inhalers, dry powder inhalers or nebulisers. The principle in each of these differ to some extent but the basic fact is that medicine goes in the form of aerosol particle into the respiratory tract and exerts its action locally in the airways.

Pressurized metered dose inhalers (MDI)

Pressurized metered dose inhalers (pMDIs) are now the device of choice in infants and children under 5 years old, when used in combination with an appropriate valved holding chamber or spacer.[4] It contains drug in crystallized or solution form with propellant and surfactant. Metered dose inhalers are the most commonly used devices for generation of aerosol. The pressurised metered dose inhaler (pMDI) is still the most frequently prescribed device

* Pediatric Pulmonologist and Bronchoscopist,
Mehta Children's Hospital,
Chennai.

worldwide.[3] They consist of a micronised form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the other constituents. When the device is actuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolisation of the drug. As it travels through the air, the aerosol warms up leading to evaporation of the propellant that reduces the particle size to the desirable range.[5] All the MDIs nowadays use only hydrofluoroalkane (HFA) as propellant which gives an aerosol with a mean plume temperature of about 57^{O}F. Hence there is no cold Freon effect which occurs with CFC based inhalers. The particle size produced by HFA based MDIs is finer, softer and is generated at slower speeds and hence there is improved delivery of the aerosol to the peripheral airways.

On actuation of MDI, the aerosol particle is delivered at a high velocity which makes the inhalation of the medication difficult for patients with asthma. This can be overcome by the use of a holding chamber (spacers). These holding chambers eliminate the need for coordination, allow more complete evaporation of the propellant and deposition of these in the holding chamber and ensure aerosol particles have a slower velocity, smaller particle size when they reach the patient. Further it reduces the oropharyngeal deposition to a significant extent. There is always a debate as to which is superior - a large volume or smaller volume holding chamber. The first point is whenever an inhaler is prescribed in children the prescription should always have a holding chamber also with it. It is ideal to choose a holding chamber which provides 10 -13 cm between pMDI nozzle and mouth. If a smaller volume holding chamber is used two tidal breaths and for a larger volume holding chamber three tidal breaths are enough to take in the inhaled medicines. Taking more tidal breaths does not increase the deposition of the inhaled medicine in the lungs.

Valved holding chamber permits the aerosol particle to be removed during inhalation and it is advisable to use a valved holding chamber rather than a non valved one. Plastic holding chambers have electrostatic charges in the chamber and attract aerosol particles reducing the drug delivery to distal airways. In plastic holding chambers cleaned with water, electrostatic charge are present in the holding chambers after cleaning which attracts aerosol particles thus decreasing the drug deposition in the first 10 to 20 actuations. It is advisable to wash with dilute solution of dish washing detergent, without subsequent rinsing to decrease the static charge so as to improve drug delivery. Holding chambers with polyamide material is available which overcomes the problem of electrostatic charges. The nil static charge holding chamber made of polyamide material needs to be cleaned monthly with tap water and allowed to dry by air before it is used. Powder residue deposited inside the holding chamber is not harmful but it needs to be cleaned.

Even when a holding chamber is used the technique to take the medication after actuation is either a deep inhalation and holding breath for few seconds or take three to five normal tidal breaths after actuation. Breath holding increases the penetration as well as the number of particles deposited in the lungs and hence is superior.[5,6] It is not possible to follow the same technique who are less than four to five years. Tidal breathing is the only option for the children below that age group.[6] Hence either technique can be advised based on the age of the child.

Before using a new MDI it has to be primed. Priming is nothing but discharging four or five doses before starting to use the inhaler. This is to ensure accurate and adequate mixing of the propellant and medication. Inhalers have adequate extra doses for priming. Also priming is needed if inhaler is dropped or if it is not used for a period of time. Many a times care takers find it difficult to find out if the canister is half empty or completely run out of the medicine. Some propellant remains in the cannister after all the medication has been used. Hence it is not possible to find out if MDI is empty by shaking it. Also the technique of dropping canister in a pan of water to see how it floats is unreliable and no longer recommended. Patient or care taker has to maintain a log on the number of actuations and dispose the canister after designated number of actuations has been reached though in practice, most do not maintain a log of doses used. MDIs are now being manufactured with integrated dose counters and hence this problem can be overcome.

Dry powder inhalers (DPI)

Dry powder inhalers (DPIs) have several advantages over MDIs. They are breath-activated, easy and convenient to use and environmentally friendly.[6] The basic mechanism in DPI is that the child has to generate adequate air flow velocity to take aerosol into the respiratory tract. For the child to generate the aerosol an inspiratory flow of atleast 60 L/min is needed. If the child is unable to generate this flow then the amount of aerosol reaching the distal airways is reduced. This is in contrast to the MDI wherein on actuation aerosol comes out at a known velocity and the patient has to breathe in the aerosol. Because there is no other interface between the patient's mouth and the DPI device, a significant amount of inhaled drug is deposited in

the mouth which can get absorbed and lead onto adverse effects like oral thrush, dysphonia when inhaled corticosteroid is given through DPI. This can be easily avoided if the child just rinses or gargles the mouth after using DPI. In older DPIs a new rotacap has to be inserted for each usage. The newer DPIs have cartridges with multiple doses obviating the need for carrying the rotacaps separately. Also because the dose counter is inbuilt in the newer DPIs the number of doses used or still remaining can be easily known. The introduction of multiple dose DPIs improved the image of the dry powder systems in the eyes of both the clinician and the patient.[7] Unlike MDI the newer DPIs does not need cleaning with water. A potential disadvantage of DPI systems is that patients need to generate inspiratory flow rates of at least 30 L/min to obtain optimal drug delivery. DPIs should not be used for acute care settings(acute asthma) as the child may not be able to generate the required inspiratory flow to take the aerosol into the distal airways. DPI delivers 5- 10% of drugs to distal airways but the main advantage is that the aerosol particle size is larger compared to that delivered by MDI. The advantage of delivery of a larger size particle to distal airway is that the drug delivery is improved as one particle with mass median diameter (MMAD) of 4 micron contain 16 times more drug than a particle with a MMAD of 1micron. In reality, DPIs are more cost-effective as they deposit more drug in the lungs, may improve compliance and result in more effective asthma control.[8] As dry powder inhalers (DPIs) are driven by the peak inspiratory flow of the patient they are usually not appropriate for children under 5 or 6 years of age.

Nebulisers

Nebulizers continue to play a role in the treatment of acute asthma where high doses of bronchodilator are required.[3] Nebulisers are reserved for use in acute care settings (acute asthma) only in hospitals or clinics. It is advisable to use oxygen at the rate of 8-10 L/ min to drive the nebulised medications. This will prevent hypoxia due to ventilation perfusion mismatch during nebulisation with short acting $\hat{a}_2$ agonists. It is advisable not to recommend nebulisers for home care use. Always in nebulisation the diluent used should be normal saline. Distilled water, water for injection or any other IV fluid should not be used as diluents. The nebulisation should be completed within a maximum of 5-8 minutes. The total volume in the nebulizer chamber should not exceed 5 ml. Salbutamol nebulizer solution can be mixed with nebulising solution of ipratropium bromide but should never be mixed with budesonide. Respules of salbutamol will contain 1 mg/ ml whereas nebulizer solutions will have 5 mg/ml. Hence it is always necessary to give the correct dosage of salbutamol when giving nebulisation. Ultrasonic nebulisers give aerosol of uniform particle size but is a costly machine to buy and maintain while jet nebulisers are less costly but give aerosol of varying particle size. Conventional jet nebulizers are highly inefficient, as much of the aerosol is wasted during exhalation.[9] If anyone has access to central oxygen supply as in hospitals or has oxygen cylinders in their office practice the nebulizer chamber can be connected to the oxygen tubing and aerosol can be generated if oxygen flow is maintained between 6-8 L/min.

In order to have maximum benefit with inhalation therapy it is necessary not to allow children especially adolescents to take inhaled medicines without supervision of caretakers, never to use MDI without spacer, changing over to MDI from DPI if medium or high doses of inhaled steroids are needed and not to give prescription to buy nebulizer for use at home. Inhalation instructions should be given repeatedly to achieve and maintain correct inhalation technique in asthmatic children and if the patient makes multiple errors, it is advisable to focus on improving one or two key steps at a time.[10]

Points to Remember

- ***Inhalation therapy is a complex treatment.***
- ***Best way to optimize inhalation technique - accurate, repeated healthcare training on how to use.***
- ***Once a patient is familiar and stabilised on one type of inhaler, they should not be switched over to new devices without their involvement.***
- ***Repeated assessment of the inhalation technique during follow up is the key to success in inhalation therapy.***
- ***Longer the residence time of aerosol in peripheral airways greater the deposition.***
- ***Breath holding increases the residence time and enhances the aerosol deposition.***

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Phone: 044-28190032,42052900,
E-mail: ijpp_iap@rediffmail.com

GENERAL ARTICLES

CHIKUNGUNYA FEVER IN INFANTS AND CHILDREN

**** Kishore Baindur***
***** Narasimhappa G M***

Abstract: *Chikungunya is an arboviral disease transmitted by the bite of the Aedes mosquitoes. It is specifically a tropical disease, with varied clinical manifestations ranging from asymptomatic infection to severe incapacitating disease. Common clinical manifestations include sudden onset high grade fever, rash, arthropathy, conjunctivitis. Unlike adults, children present with distinct clinical manifestations. Atypical features include sensory changes, retro bulbar neuritis and acute flaccid paralysis. Treatment is symptomatic. Chikungunya is a re-emerging disease in the Indian sub-continent and may be attributable to viral mutation, increased globalization, introduction of the virus into a susceptible population.*

Keywords: *Arbovirus, Chikungunya, Aedes mosquito, Arthralgia, Re-emerging infections.*

Chikungunya fever is an acute febrile illness caused by arthropod borne Chikungunya virus belonging to the family Togaviridae and genus Alphaviridae. It is primarily transmitted to humans by the bite of the Aedes mosquitoes. In 2005-2006 Chikungunya epidemics that occurred in India and other Indian Ocean countries affected millions, with devastating social and economic consequences. The Indian epidemic of 2006 was an eye opener for Indian health authorities and was the first epidemic in almost 32 years and affected more than 16 states and union territories.[1,2]

Epidemiology, outbreaks and re-emergence

Global scenario: Chikungunya was first reported from Tanzania in 1952. After that, epidemics have been documented in many countries like Africa, Asia and other parts of the world. Most of the South East Asian countries have documented chikungunya outbreaks. In between outbreaks the virus was silent for many years to decades. This disease variability was thought to be because of factors like epizootic cycle of virus, differential susceptibility of virus to human, animal and insect hosts, environmental conditions favouring breeding and vector density.[1,2,3]

India: In India, chikungunya was first reported in Calcutta (1963), Chennai (then Madras), Pondicherry (1964), and Andhrapradesh (1965) and subsequently in Barsi district of Maharashtra in 1973. After this, except for few occasional case reports there were no epidemics for 32 years. By the end of 2005 there was an outbreak with re-emergence of Chikungunya virus. The 2006 epidemic affected more than 1.4 million, these official figures lack accuracy; actual cases would have been 5 times the figures originally reported. According to the latest status report from ministry of health and family welfare, Govt of India, 47999 suspected cases have been reported in the country as on 31-12-2010 with West Bengal having highest (20503) where as 73,288 cases were reported in 2009 overall with Karnataka having highest (41230).[4,5]

The agent, host and environment interaction

Chikungunya virus, an Arbovirus belonging to the genus Alphavirus(Togaviridae family)has a single stranded RNA genome, a 60-70nm diameter capsid and a phospholipid envelope. The Alphavirus group comprises of 28 viruses six of which cause human joint disorders. All previous Indian outbreaks were caused by Asian genotypes where as 2006 epidemic is by the Central/East African genotype of the virus.[6]

The Chikungunya Virus is transmitted by the vectors Aedes genus of mosquitoes, A.aegypti and A. albopictus. A wider range of Aedes species (including A.furcifer, A.fulgens, A.vittatus, A.vigilax) transmit the virus in Africa which also maintain sylvatic cycle. The Culex and the Anopheles species of mosquitoes also transmit the virus rarely. A.albopictus is widely distributed worldwide, adapts to rural and urban areas. They are aggressive zoophilic and anthropophilic organisms. They are diurnal and hence nets are not effective against them.[6]

* Senior Consultant and HOD

** DNB Faculty, Dept of Pediatrics, St.Martha's Hospital, Bangalore.

In India, the major vector of the Chikungunya virus is the A.aegypti which breeds in stored fresh water. Chikungunya is maintained in human populations by the human-mosquito-human cycle in Asia, where as a sylvatic cycle maintains the virus in Africa (involving non human primates and forest Aedes mosquitoes). The vector potential of Culex and Anopheles requires further investigation.[6,7]

Human beings are the main reservoirs (host) during epidemics. At other times, reservoirs include the vervett monkeys, baboons, lemurs, rodents and birds. Factors which result in the hosts acquiring infection include high susceptibility, an immunologically naïve population and travel which enable movement of the virus. As the mosquito breeds in stagnant water, other factors like poor infrastructure and sanitation may also contribute to the spread of Chikungunya Virus.[1,6,7]

Pathogenesis of chikungunya fever

There is paucity of literature on molecular pathogenesis of Chikungunya virus. Defective cell mediated immunity where CD8+ T-Lymphocytes are inactive or absent is implicated in the etiology of chronic disease and viral persistence. Excessive secretion of toxic chemokines or apoptosis is thought to be the cause of cell/tissue destruction and associated symptoms. An antibody dependent enhancement (ADE) mechanism similar to that caused by dengue virus is also suggested. Cell tropism of Chikungunya Virus in the murine brain, susceptibility of adherent cells like epithelial and endothelial, primary fibroblasts and macrophages to CHIKV whose replication induces cytopathic effect and apoptosis. Presence of viral antigen in muscle progenitor cells (muscle satellite cells) in a muscle biopsy of a patient with clinical relapse suggests possibility of persistence Chikungunya viremia.[2,8]

Clinical manifestations

Clinical features are varied, ranging from asymptomatic illness to severe disease. Clinical features in infants and children are very distinct from those seen in adults. Extreme age groups are at maximum risk for severe manifestations of Chikungunya virus disease.[9,10,11]

After an incubation period of 3-5 days : (range 2-12 days), CHIKV presents with abrupt onset of high grade fever without prodromal features with rash and arthralgia.

Fever is the major symptom followed by other features. In majority of the cases, fever is sudden in onset peaking upto 105°F. There may be many or single spikes followed by rapid or slow return of fever to baseline. In some patients biphasic pattern is also documented. Fever typically lasts for about 3-5 days.

Rash develops at the end of febrile phase and subsides without any sequelae after 3-4 days. Typical rash will be diffuse maculopapular or morbilliform eruption, seen over arms, back and shoulders and sometimes all over the body. Pigmentary changes of skin and face in the form of brown to black pigmentation, freckle like macules, slate greasy pigmentation of face, pinna of ears and extremities are also reported in some studies. Genital and intertriginous ulcers are also seen in some patients. Vesiculobullous eruptions, epidermolysis bullosa has been seen in infants.[12]

Arthritis and arthralgia are uncommon in children unlike in adults, in whom it can be severe and can cause morbidity with incapacitating pains lasting for months. It affects mainly the small and peripheral joints. Residual arthralgia is uncommon in children.

Bleeding manifestations like bleeding gums, epistaxis, hemetemesis and melena are also seen less frequently unlike in dengue fever where it is seen in majority of patients (up to 85%).

Commonly CNS manifestations like severe encephalitis, seizures, GBS are seen in alpha virus infections but less commonly seen with Chikungunya Virus. Febrile seizures may occur in infants and younger children. Other manifestations like focal seizures, altered sensorium, blindness, acute flaccid paralysis are reported with less frequency.[13]

Other frequent manifestations like lymphadenopathy, conjunctivitis, swelling of eye lids, pharyngitis, headache, myalgia and watery stools are seen in infants and children.

Neonates: Studies at Reunion islands have shown that mothers affected during perinatal period can affect the newborns. The mean duration of time between onset of disease in the mother and baby is 5 days. The most common symptoms are fever, rash and edema of extremities. Other complications like seizures, bleeding manifestations and circulatory collapse are also seen. Cardiac abnormalities on echocardiography and MRI abnormalities of brain are also seen.[14,15]

Case definition (WHO Guidelines)[16]

Though case diagnosis can only be made by laboratory means, chikungunya should be suspected when epidemic occurs with the characteristic triad of fever, rash and joint manifestations.

Clinical criteria: Acute onset of fever >38.5°C and severe arthralgia/ arthritis not explained by other medical conditions

Epidemiological criteria: Residing or having visited

epidemic areas, having reported transmission within 15 days prior to the onset of symptoms

Laboratory criteria: At least one of the following tests in the acute phase:

a) Virus isolation

b) Presence of viral RNA by RT-PCR

c) Presence of virus specific IgM antibodies in single serum sample collected in acute or convalescent stage

d) Four-fold increase in IgG values in samples collected at least three weeks apart

Cases can be categorized as

Possible case: A patient meeting clinical criteria

Probable case: A patient meeting both the clinical and epidemiological criteria

Confirmed case: A patient meeting the lab criteria, irrespective of the clinical presentation

Differential diagnosis

Dengue and Chikungunya virus share a common vector (aedes) and also the same clinical features. The presence of skin rash leads to a diagnostic dilemma but both dengue and Chikungunya virus can co-exist sometimes. Unlike dengue fever, Chikungunya virus rarely presents with circulatory collapse. Other differentials are infections with other alpha virus that can present with fever and arthritis syndrome. Other common differentials to be excluded are hepatitis, acute rheumatic fever, rickettsiosis and relapsing fevers.[9,10]

Diagnosis

The clinical diagnosis of Chikungunya virus infection is confirmed by different laboratory methods, including a) isolation of the virus in cell culture from plasma or serum b) detection of the viral RNA by Reverse transcriptase polymerase chain reaction (RT-PCR), Real time Accelerated reverse transcription loop mediatd isothermal amplication (RT LAMP) in serum and c) detection of the Chikungunya virus-specific serologic antibodies (IgM and/or IgG antibody).[1,2]

Virus isolation is done by inoculation of the biological sample from mosquitoes and mammals into cell cultures or suckling mice. Molecular tests detect the viral RNA only during the viremic phase in patients, which generally lasts from days 0- 6 after the clinical onset.

Chikungunya virus specific IgM and IgG antibodies are detectable in plasma and serum samples from infected and convalescent patients by inhibition of the hemagglutination, complement fixation, immunofluorescence (IF) and immunoenzymatic assays (ELISA). The IgM specific response against Chikungunya virus is detectable starting from 2-6 days after the onset of symptoms by ELISA and IF, and lasts for several weeks to months. The IgG antibodies are detectable in sera from convalescent stage patients and usually persist for several years as shown in Fig.1. All these serological methods are highly sensitive but lack moderate specificity because of antigenic cross-reactivity between Chikungunya virus and other arboviruses such as Dengue virus, O'nyong-nyong virus and others. Confirmation is done by performing a plaque reduction neutralization test (PRNT) in vitro.[17,18]

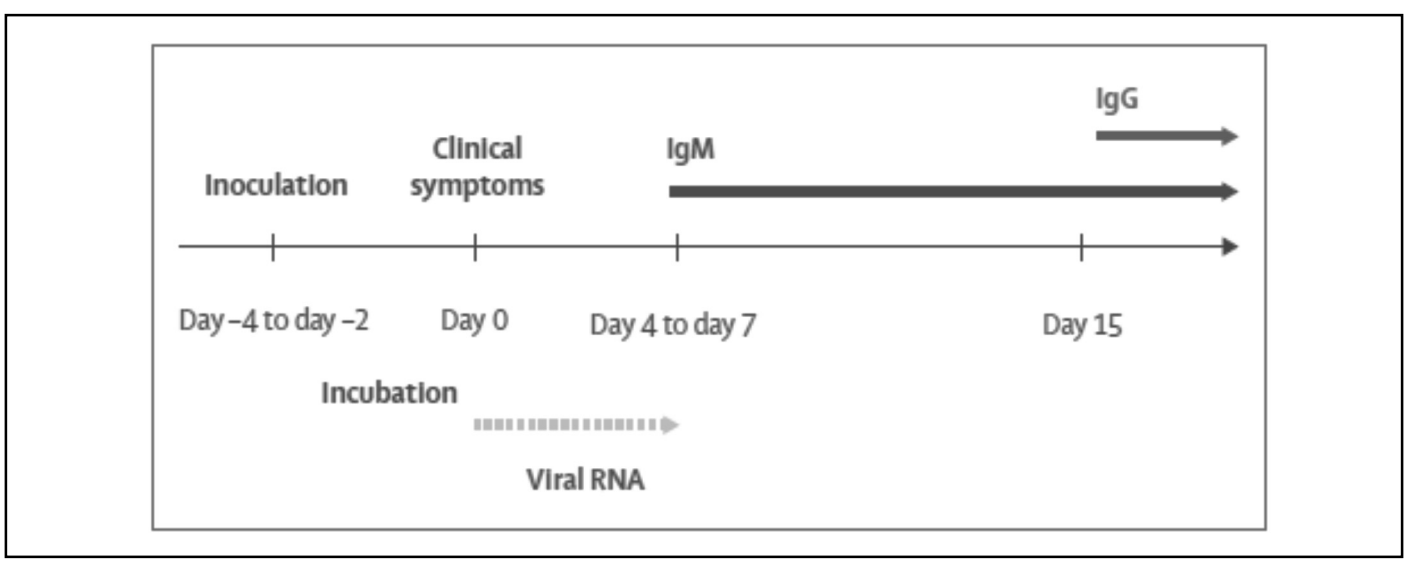

Fig.1. Immunological reponse to chikungunya virus infection[1]

Immunity and vaccination

Chikungunya virus infection elicits long-lasting protective immunity. Experiments in animal models have shown cross-protection among chikungunya virus and other alphaviruses.A live-attenuated strain of CHIKV was obtained from an old strain of Asian origin (Bangkok, 1962) and cultured on MRC5 (human fetal fibroblast cell line) human fibroblasts. Preclinical studies and Phase II trials were conducted on 200 healthy US Army volunteers. Very satisfactory seroconversion rates (98% on day 28) and neutralizing antibody titers were obtained, persisting in 85% of cases at 1 year. Further development was stopped due to new priorities in the US Army and perhaps also due to the problem of potential interference arising from sequential administration of vaccines specific for different alpha viruses. More recently, three new recombinant versions of CHIKV vaccines were reported and successfully tested on mouse or macaque animal models.[2,19]

Treatment and drug trials

There is currently no effective antiviral treatment for chikungunya. Treatment is therefore purely symptomatic and is based on non-salicylate analgesics and non-steroidal anti-inflammatory drugs. Synergistic efficacy was reported between interferon-α and ribavirin on chikungunya virus in vitro in some studies. A trial of chloroquine has shown some equivocal results in patients with arthralgia.[9]

Prevention

At present the only way of preventing CHIKV is effective individual protection against mosquito bites and vector control. Control of both adult and larval mosquito populations uses the same model as for dengue and has been relatively effective in many countries and settings. Mosquito control is the best available method for preventing chikungunya. Breeding sites must be removed, destroyed, frequently emptied and cleaned or treated with insecticides. Control of A aegypti has rarely been achieved and never sustained. Recent data show the different degrees of insecticide resistance in A albopictus and A aegypti. However, vector control is an endless, costly and labour-intensive measure and is not always well accepted by local populations, whose cooperation is crucial. Bed nets should be used in hospitals and day-care facilities. Surveillance is also important for early idendification of outbreaks.[5]

Points to Remember

- ***Unlike adults who present with abrupt onset high grade fever, rash and arthralgia, in children many atypical features are noted (neurological and dermatological).***
- ***Recent epidemics have reported mother to child transmission of Chikungunya virus infection affecting neonates with severe disease. Neonates can present with erythroderma, hyperalgesia, fever with rash, apnea, seizures, some requiring ventilation also.***
- ***A safe and efficient recombinant vaccine is under trial and is protective in mouse models and primates.***

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CLIPPINGS

Pre-discharge "car seat challenge" for preventing morbidity and mortality in preterm infants

Physiological monitoring studies indicate that some preterm infants experience episodes of oxygen desaturation, apnoea, or bradycardia when seated in standard car safety seats. The American Academy of Pediatrics recommends that all preterm infants should be assessed for cardiorespiratory stability in their car seat prior to discharge - the "car seat challenge". We aimed to assess the evidence to support this practice, specifically to determine whether the use of the car seat challenge prevents morbidity and mortality in preterm infants.

Randomised or quasi-randomised controlled trials that compared pre-discharge cardiorespiratory monitoring in a car seat versus no monitoring in preterm infants in the week prior to planned discharge from hospital.

It is unclear whether undertaking a pre-discharge car seat challenge is beneficial or harmful to preterm infants. Further studies are needed to determine whether the car seat challenge accurately predicts the risk of clinically significant adverse events in preterm infants travelling in car seats. If this is shown to be the case then a large randomised controlled trial is needed to provide an unbiased assessment of its utility in pre-discharge assessment.

Elizabeth Pilley[2], William McGuire[1,*] Editorial Group: Cochrane Neonatal Group. Published Online: 21 JAN 2009. 4 NOV 2005. DOI: 10.1002/14651858.CD005386.pub2.

Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants

Not enough evidence to support administering antibiotics through a feeding tube for low birth weight and new born babies to prevent necrotizing enterocolitis. Necrotizing enterocolitis (NEC) is a serious disease that affects the bowel in the first few weeks of life. The cause is unknown but milk feeding and bacteria may contribute. NEC is more common in preterm babies, possibly because of reduced immunity. Oral antibiotics have been used to prevent NEC but there are concerns about the possible adverse effects of oral antibiotics such as resistance to bacteria. The review of trials found there was not enough evidence to support the use of antibiotics to prevent NEC in preterm and low birth weight babies. More research is needed.

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Auriti C, Fiscarelli E, Ronchetti MP, Argentieri M, Marrocco G etal. Procalcitonin in detecting neonatal nosocomial sepsis. Arch Dis Child Fetal Neonatal Ed., Sep 2012

The accuracy of procalcitonin (PCT) as a diagnostic marker of nosocomial sepsis (NS) and the most accurate cut-off to distinguish infected from uninfected neonates was done in Six Neonatal Intensive Care Units .The study concluded that in VLBW neonates, a serum PCT value >2.4 ng/ml prompts early empirical antibiotic therapy, while in normal-birth-weight infants, a PCT value d"2.4 ng/ml carries a low risk of missing an NS.

GENERAL ARTICLES

WHEN NOT TO RESUSCITATE OR TO STOP RESUSCITATING A NEWBORN / CHILD?

**** Mahesh Baldwa***
***** Namita Baldwa***
****** Amit Padvi***

Abstract: *Death, which has to be peaceful, has become painful and artificial one, away from the family surrounded by the paraphernalia of modern Intensive Care Unit (ICU). Legally, active euthanasia is a crime and passive euthanasia is considered as conditionally permitted. Prolonged and futile life support leads to economic strain. As per Supreme Court (SC) guidelines in Aruna Shanbaug case, institutions can draw protocols/guidelines, for not starting and stopping/ withholding resuscitation. We suggest admitting all "End-Of-Life-Situation" (EOLS) patients in specially designated "EOLS-ICU" for increasing the efficiency of regular ICU. Advantage of this is that parents/ relatives will allow pediatricians to administer passive euthanasia protocol ethically, legally and psychologically in EOLS-ICU, since other patients in EOLS-ICU, are also in similar situation.*

Keywords: *Euthanasia, Resuscitation, Newborn/child, ICU*

Motive of pediatricians is to support potential chance of living. Even though occurrence of death is day to day affair in ICU, there is no doubt intensive care unit (ICU) saves lives of many newborns and children. In some critically ill, the life-support interventions do not help to mitigate the suffering, but increase the agony and burden of prolonged dying process and costs. Pediatrician's attempt at withholding/withdrawing or attenuating aggressive treatment may cause acceleration/hastening of death and in not initiating resuscitation in a newborn may have caused a lost chance at making a child to survive. Worse is that the child may not die but survive with anoxic damage. Legally, all these may fall either in the domain of euthanasia or negligence. Therefore pediatricians need to evolve legally safe and effective strategies, circumstances to guide their course of action to avoid litigation.

Frustration of nurturing defective/ damaged newborn/child

"Will the baby will be affected if he/she is resuscitated and survives?" is the question often raised by parents/ relatives. So, often the concern of parents/relatives may not be whether resuscitation will be successful or not but, if it is successful, whether the infant will be severely handicapped. More and more parents/relatives are becoming intolerant to putting up with defective baby because of the norm of nurturing one or two children at the most. This norm frustrates parents/relatives from nurturing and spending on an affected newborn/child.

Parents/relative's autonomy for initiation, continuation of resuscitation

Pediatricians should inform benefits and burdens of resuscitation and avoid influencing parents/relatives by imposing their own wish. Documented consent of parents/ relatives is mandatory for initiation, continuing resuscitation and further medical management. Pediatricians should avoid invading parental authority and when in doubt obtain court order, since legally it is the practice of euthanasia.

Pediatricians to promote parents/ relatives to take their own decisions regarding 'resuscitation'

Parents/relatives, while discussing about 'resuscitation' of unsalvageable defective newborn/child leave the decision to be taken according to pediatrician's discretion saying that pediatricians 'know the best interest of baby'.

Two scenarios may emerge. (i) Pediatrician decides not initiating resuscitation. Such un-resuscitated newborn/ child may not die and survive with more than expected anoxic brain damage along with underlying defects. Newborn/child living with this handicap may have worst

* Senior Pediatrician and Medicolegal Advisor
Formerly Assistant Professor of Pediatrics

** Fellowship in Pediatric Anesthesia
Assistant Professor of Anesthesiology,
T.N. Medical College and Nair Hospital, Mumbai

*** Fellowship in Pediatric Anesthesia
Assistant Professor of Anesthesiology,
G.S. Medical College and KEM Hospital, Mumbai

outcome due to the consequences of hypoxic/ischemic encephalopathy, irreversible coma and multisystem organ injury, later permanent vegetative state (PVS). No advanced care at a later stage can substitute for effective resuscitation at birth and repair the damage due to delayed or incorrect procedures. In case of dispute, pediatrician may be charged of negligence/practicing euthanasia. (ii) On the other hand, pediatrician may decide to resuscitate. This leaves one with short term benefit of making newborn/child to survive and also a compulsion to rehabilitate for defects, with ongoing expenses.[1]

Therefore, lessons to learn is not to induce parents with your ideas unless it is a lifesaving dire emergency. But, if you do invade parental authority and don't initiate or withhold/withdraw life support then be prepared to legally defend yourself in court under IPC, Sections 76 (legal mistake of fact), S.81(non intentional harm done to avert bigger danger), and S.88 (good faith) and even by latest supreme court judgement of Aruna Shanbaug.

If pediatrician is forced to do the onerous job of deciding about 'resuscitation' strategy the outcome is either the newborn/child dies or lives with handicaps. In rare case parents/relatives emotions running amok to blame pediatricians for (i) morbidity (IPC337-338) and (ii) mortality (IPC304A) by complaining to police or consumer courts (Section 12). Though not common, most scaring is mob violence. Therefore pediatrician should undertake to make (i) good doctor patient relationship, (ii) good communication (iii)transparent documentation of medical notes about medical care (iv) monitoring infrastructure, and (v) obtain written informed consent to show documented diligence, prudence and caution taken in treating newborn/child to save one from unreasonable legal troubles.

Legal facts and circumstances say it is euthanasia/negligence?

As long as there is potential for life leading to survival, pediatricians shall strive hard to explore the possibility of making them survive. Sometimes burden of damage outweigh benefits. Continuing survival is futile because of poor quality of life later or the effort may be just a prolongation of dying process. Under these facts and circumstances, decision of withholding/withdrawing or attenuating aggressive treatment may cause acceleration of death of such newborn/child, which legally falls in the domain of euthanasia/negligence and that is the reason pediatricians need to evolve legally safe and effective strategies to guide their conduct. Sometimes the newborn is known to have short survival in spite of resuscitation and once resuscitation is started, it may be difficult to stop. Therefore decisions like not to resuscitate a new born becomes crucial and important from point of view of legality involved in alleged passive euthanasia/negligence.

Euthanasia: existing legal framework and 2011 SC judgement

1. Article 21 of the Constitution of India guarantees 'Protection of life ... The right to die with dignity and to refuse treatment, withhold or withdraw life support comes in conflict and derogation of Article 21.[2]
2. Euthanasia (from Greek: eu:"good" thanatos: death), mercy death. Physician assisted suicide is abetment of suicide, equated with active euthanasia, which is criminal offence under section 306 Indian Penal Code [IPC]). Active Euthanasia (physician assisted suicide) in very specific cases, under very specific circumstances is legal only in Netherlands, Belgium and three states of USA viz; Oregon, Washington and Montana.[3]
3. Bench of the SC with two judges in the case of P. Rathinam[4] held section 309 of IPC[5] as violation of the individual's fundamental rights under Constitution of India. This was overruled in Gian Kaur case[6], by larger Bench of SC, which said refusal of any modality of treatment including life support is not an act of suicide or an attempt at suicide. Therefore passive euthanasia is no longer a crime.
4. Ethics, 2002, rule 6.7[7] says practicing euthanasia shall constitute unethical conduct. However on specific occasion, the question of withdrawing supporting devices to sustain cardio-pulmonary function even after brain death shall be decided by team of doctors. Violation of ethics 2002 can lead to suspension of license under rule 8.3 which permits euthanasia for brain stem dead as envisaged under S.3[6] of "Heart of the Alliance" (HOTA) 1994.[8]
5. The following is the recent(2011) SC judgment on passive euthanasia in Aruna Shanbaug.

In India, active euthanasia is illegal and a crime under section 302 or at least section 304 IPC. Physicians assisted suicide is a crime under section 306 IPC. Passive euthanasia is legal even without legislation, provided certain conditions and safeguards are maintained.

Pediatricians' effort and energy is extended to preserve life. Nevertheless, circumstances sometimes arise based on medical facts, wherein the best course may be to withhold/withdraw life-sustaining medical treatment such as mechanical ventilation or artificial nutrition, hydration and surgical procedures, based on poor prognosis.

Legal to withhold/withdraw life support therapy where futile outcome expected.

Level of care for newborn/child is progressively improved as years passed by and it has become a reality for very low birth weight, asphyxiated and newborn/child with gross defects. Until some years back, many of these newborns/children inevitably died because of lack of adequate care. Now pediatricians can prolong their life, but with handicaps in many cases. A debate has cropped around the globe, whether it is ethical to withhold/withdraw therapy, sometimes in an active way, allowing newborn/child, (presumed to be unable to lead a normal quality life) to die.[9] Legality depends upon facts and circumstances of each case and shall decide whether to initiate resuscitation or not; once resuscitation is started, when to withdraw or stop/withhold resuscitation in case of futility to continue.

Barriers in withdrawing and withholding is difficult

There are varied legal, ethical, moral, religious, social, economic and psychological barriers to withdraw a treatment in progress and withholding it. Some medical persons and parents/relatives might have more difficulty in stopping therapy once it has begun and makes situation litigation prone.

Persons deciding about discontinuing life support system since it amounts to passive euthanasia

SC in Aruna Shanbaug's case said decision regarding discontinuing life support system amounting to passive euthanasia has to be taken either by the parents/relatives or in the absence of any of them, such a decision could be taken even by a person or a body of persons acting as a next friend including doctors attending the patient. They have to apply to high court for discontinuing life support system.

The top court has prescribed a procedure, so that it cannot be violated. Under it high courts will rely on the opinion of independent panels of doctors and parents/relatives before deciding whether doctors can withdraw life support. This arrangement shall be in force till proper legislation comes to regulate active and passive euthanasia. Similar Law Commission's report is pending before government for enacting law on euthanasia.[10]

For legal safety inform about optimum duration of 'resuscitation' after birth without results.

Pediatrician should inform parents/relatives to allow stopping resuscitation if the heart rate is undetectable and remains so for 10 minutes after birth,[11] because both survival and quality of survival deteriorate precipitously by this time. Birth asphyxia causing brain damage and its severity, becomes progressively more as time elapses beyond 10 minutes. If parents/relatives decide to withdraw/withhold resuscitation, care should be taken to make baby's end-of-life situation comfortable and provide much needed psychological support to parents/relatives to avoid litigation.

Legally how much parents/relatives should know regarding unsalvageable newborn/child regarding "Do not resuscitate"(DNR)

Resuscitation is not indicated in birth weight ≤ 400 g, anencephaly, Trisomy 13 and 18 since it is associated with almost certain early death and/or unacceptably high morbidity.[12] Sometimes parents/relatives may file a case for not resuscitating with police under IPC S. 304-A saying death is caused by negligent "act" (IPC S. 32 says "acts" include illegal omissions also). Pediatricians can defend by saying that there is no legal obligation to resuscitate unsalvageable newborn/child.

Legal problems from unnoticed passive euthanasia

When payment is done by parents/relatives for ICU patient then two situation of acceleration of dying by passive euthanasia occur:

a. Slow attenuation of aggressive life support interventions may result due to failure to provide required medicines daily by parents/relatives causing acceleration of dying process.

b. Sometimes parents/relatives insist for discharge against medical advice (DAMA) or ask transfer, but do not take to other medical centre. Patient is taken home hastening death.

Passive euthanasia by accident / negligence

a. Infrastructure needed for resuscitation may fail, eg. Non availability of oxygen,[13] oxygen getting exhausted/empty cylinder,[14] oxygen tubes getting disconnected accidentally may cause acceleration of death.

b. Failure to raise alarm by monitoring system leading to failure to take proper remedial action causing acceleration of death.

End of life care situation

We suggest coining a term like "end-of-life care situation" (EOLS) and designate ICU for "end-of-life care

situation". This increases efficiency of regular ICU's and reduces legalities and litigation. EOLS circumstances are extreme prematurity, severe congenital anomaly, imminent death regardless of treatment, evidence of profound neurologic injury, irreversible coma, permanent vegetative state (PVS) or life not worth salvaging further. Such patients impede usual functioning of ICU because of legalities involved. Protocols/guidelines to withhold/withdraw life support interventions for EOLS based on SC decision in Aruna Shanbaug case for passive euthanasia are evolving. Execution of protocols/guidelines may be a time consuming procedure since it is mandatory to obtain high court permission. We suggest designating ICU for 'EOLS' (EOLS-ICU) to care for such EOLS patient, increasing efficiency of regular ICU. Thus newborn/child requiring EOLS shall not hinder regular medical care. It may be easy for parents/relatives to accept and allow pediatricians to administer successfully a passive euthanasia protocols/ guidelines ethically, legally and psychologically in EOLS-ICU, where even other patients are in similar situation. This will reduce psychological trauma to parents/ relatives and reduce cost of care for futile life support interventions and speed up legal procedures and reduce litigations.

Points to Remember

- ***Proper documentation is insisted***
- ***Informed consent of parents/relatives for 'do not resuscitate' and 'withhold/withdrawal of life support' should be based on institutional protocol as per 2011 Supreme Court judgement.***
- ***Full disclosure is a must about futility to resuscitate newborn/child or continue resuscitation thus discontinuing life support, in situations where there are 'no prospects of living', irreversible coma or permanent vegetative state and damaged /defective child considered as burden by parents/relatives.***

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CLIPPINGS

Dominguez SR et al. Preventing Coronary Artery Abnormalities: A Need for Earlier Diagnosis and Treatment of Kawasaki Disease. The Pediatric Infectious Disease Journal, 12/07/2012.

The majority of coronary artery (CA) abnormalities in children with Kawasaki disease (KD) were identified in the initial ECHO, during the first week of illness. Earlier diagnosis and treatment is needed to impact the incidence of CA abnormalities in children with KD. Increased clinical suspicion and earlier use of ECHO in the initial workup of children with suspected KD may lead to more rapid diagnosis and treatment.

DRUG PROFILE

NEWER ANTI-AMOEBIC DRUGS

**** Jeeson C Unni***

Abstract: *The possibility of emergence of resistance of E histolytica to the first line drugs, mainly due to its over use, has resulted in search for newer anti-amoebic drugs and this article highlights the issues involved and touches upon some of the drugs in the pipeline.*

Keywords: *Amoebiasis; E histolytica; drug resistance; newer drugs; immunize.*

Amoebiasis is endemic India[1] but its incidence varies in different parts of the country and between areas with different socioeconomic strata.[2] Many animals are potential reservoirs of infection.[3] The parasite has been detected through identification of cysts and trophozoites[4] and through seroprevalence studies.[5] But various studies from developing countries, including India, suggest that it is not a major cause of acute watery diarrhea in infants and children.[4,6,7,8] Several anti-amoebic drugs are currently available, of which the most common ones are derivatives of 5-nitroimidazole including metronidazole and tinidazole.[9] Tinidazole has similar efficacy to metronidazole with shorter and simpler dosing and less frequent adverse effects.[10] These adverse effects include nausea, abdominal discomfort and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol[9] to prevent recurrence of invasive disease and to stop the shedding of E.histolytica cysts into the environment as it is of public health concern.[11] Diloxanide furoate can also be used in children above 2 years of age. However, these anti-amoebic drugs are less effective against the cyst of E.histolytica than the trophozoite and their indiscriminate use could result in development of resistance to commonly used drugs.[12] Development of new antiamoebic drugs is still in its infancy and vaccine development appears to be a distant dream. Reviews of some newer anti-amoebic drugs that are in the pipeline are discussed.

* Editor-in-Chief,
IAP Drug Formulary,
Cochin.

Drug resistance

Drug resistance to E. histolytica has been uncommon in India. However, differences in drug susceptibility between different isolates have been reported from Chandigarh[13] and elsewhere[14] indicating that a small percentage of amoebae are resistant to drugs. Reports of treatment failure with first line anti-amoebic therapy[15,16,17] further support the possibility of emerging of drug resistance. The fact that drug resistant clones have been generated in the laboratory[18,19,20] and drug resistance has been demonstrated in other anaerobic and microaerophilic parasitic protozoa, such as Giardia lamblia and Trichomonas vaginalis[21,22] also point to forthcoming metronidazole resistance in E. histolytica and have spurred the search for alternative chemotherapeutic agents.

Mechanism of drug resistance

Mechanisms of multiding resistance (MDR) in Entamoeba mutants have not been studied in detail. The various mechanisms of antimicrobial resistance in bacteria are well known, one of which may be the efflux of antimicrobials.[23] Loci such as the P-glycoprotein (Pgp) are involved in drug efflux from cells and the reactions for generating the energy for this efflux is inhibited by calcium channel blockers.[24] The EhPgp1 and EhPgp5 genes over expression has been demonstrated in the emetine resistant clone and their expression is regulated at transcriptional level.[25,26]

Amoebicide classes

E. histolytica may be found in the bowel lumen, in the bowel wall and in tissues, including the liver. Antiamoebic drugs vary in efficacy at the three sites where the parasites commonly exist and are generally divided into two classes based on their main site of activity. The luminal amoebicides act principally in the bowel lumen and the tissue amoebicides act principally in the bowel wall and the liver.

Luminal

1. Arsenical compounds: Carbarsone, acetarsone or acetarsol, treparsol, diphetarsone, glycobiarsol or bismuth glycolylarsanilate, stovarsol and thioarsenite, thiocarbarsone or thiocarabazone, arsthinol.

2. Hydroxyquinoline derivatives: Chiniofon or quinoxyl, clioquinol or iodochlorhydroxyquin, and iodoquinol or diiodohydroxyquin.

3. Dichloroacetamide derivatives: Diloxanide furoate or entamide furoate, clefamide, eticlordifene or ethylchlordiphene or etofamide or etophamide and quinfamide.

4. Benzylamine derivatives: Teclozan, chlorbetamide or mantomide, and chlorphenoxamide or mebinol.

5. Antibiotic amoebicides: Tetracycline, oxytetracycline, chlortetracycline, erythromycin, paromomycin and fumagillin.

6. Nithrothiazole salicylamide: Nitazoxanide

Tissue

1. Emetine and its derivatives: Emetine hydrochloride, emetine bismuth iodide, dehydroemetine dihydrochloride and dehydroemetine resinate

2. Aminoquinoline: Chloroquine

3. Thiazole derivative: Niridazole

4. Nitroimidazoles: Metronidazole, tinidazole, ornidazole, secnidazole and nimorazole

Secnidazole, ornidazole, panidazole and satranidazole

Single-dose secnidazole was compared with tinidazole for two days without any difference[27], metronidazole for 10 days with similar efficacy[28], and a combination of tetracycline and clioquinol given for five days.[29] Single-dose secnidazole resulted in greater resolution of clinical symptoms compared with five days of tetracycline and clioquinol. Trials comparing metronidazole with ornidazole, panidazole, and satranidazole were too small to detect any difference in clinical failure or parasitological failure.

Newer drugs under study

1. Cryptdin-2 exhibited potent in-vitro concentration dependent amoebicidal activity against E. histolytica at a minimum concentration of 4 mg/L.[30] The drug seems to have a membrane dependent amoebicidal activity and in addition, interferes with DNA, RNA as well as protein synthesis of E. histolytica exerting the highest effect against DNA synthesis. The drug may be useful by itself or as an adjunct to metronidazole and/or other available anti-amoebic drugs.

2. Auranofin, used for treatment of rheumatoid arthritis, has been found to be 10 times more active against E. histolytica than metronidazole.[31] Transcriptional profiling and thioredoxin reductase assays suggested that auranofin targets the E. histolytica thioredoxin reductase, preventing the reduction of thioredoxin and enhancing sensitivity of trophozoites to reactive oxygen-mediated killing[31,32] proven in a mouse model of amoebic colitis and a hamster model of amoebic liver abscess. It has been granted orphan-drug status from the FDA for amoebiasis.

3. Recombinant form of EhCP4 generated in E.coli is being studied to immunize against E.Histolytica infection. Cysteine proteinases 4 (EhCP4) of Entamoeba histolytica are considered important for amoeba pathogenicity. The recombinant gene obtained by cloning and expression of the EhCP4 gene in heterologous host E. coli BL-21 (DE3), were studied in guinea pigs and found to produce protective specific anti-EhCP4 antibodies.[33]

Conclusion

Though newer anti-amoebic drugs are being researched due to the scare of development of resistance to the present first line drugs, tinidazole and metronidazole continue to be the drugs of choice for treatment of amoebiasis.

Points to Remember

- ***Amoebiasis in endemic in India but it is not a major cause of acute watery diarrhea in infants and children.***
- ***5-nitroimidazole including metronidazole and tinidazole remain the mainstay of treatment followed by treatment with a luminal agent, such as paromomycin or iodoquinol.***
- ***Their indiscriminate use could result in development of resistance.***
- ***Drug resistance to E. histolytica is not common in India.***
- ***However, reports of resistance have stimulated research into mechanisms involved (not fully elucidated as yet) and molecules that could be used for treatment of such resistant strains.***
- ***Cryptdin-2 and auranofin have been identified as drugs that may be useful in such cases.***
- ***Recombinant form of EhCP4 is being studied to immunize against E.histolytica infection.***

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NEWS AND NOTES

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Dr H Paramesh - 09845022689; Dr Major K Nagaraj - 09840230199; or Dr BP Karunakara - 09845263322

Secretariat

Department of Pediatrics

M.S. Ramaiah Medical Teaching Hospital

MSRIT Post, MSR Nagar, Bangalore City, Karnataka, India, Pin Code-560054

Ph-080-23609999/40502000, Email ID:bpkaruns2gmail.com

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DERMATOLOGY

PEDICULOSIS

** Anandan V*

Abstract: *Pediculosis is a common infestation in children. The blood sucking lice which infest the human can have various habitations like scalp (Pediculosis capitis), body (Pediculosis corporis), pubis (Pediculosis pubis) and eyelashes (Pediculosis palpebrarum). It not only sucks blood but also acts as a vector for louse borne diseases.*

Keywords: *Pediculosis, Capitis, Corporis, Pubis, Palpabrarum.*

Pediculosis and Phthiriasis infection are common in general pediatric practice. An effective knowledge is mandatory for the successful treatment of these conditions so as to avoid the diseases in which these organisms serve as vectors.

Interesting history

Pediculosis has been documented for thousands of years.[1] The existence of insects have been dated back to several million years. As on date 560 species of blood sucking lice have been identified.[2] These insects have been classified as pediculosis and Phthiriasis. These two genera of insects which infest humans are also found in gorillas and chimpanzees just because the fur is much like human hair and their blood is physiologically similar to humans.

The earliest reference quoted in Exodus 8:17 which records that Aaron "stretched out his hand with his rod and smote the dust of the earth and it became lice in men and beast". Ancient Egyptians priests shaved their bodies every three days to keep the lice away.[3] 16th century BC papyrus also gives instructions for the eradication of lice.

Dessicated lice and eggs have been identified from Egyptians mummies of 16th century BC.

Habitation

Pediculosis capitis is the infestation of scalp, Pediculosis corporis is that of the body, Pediculosis or Phthiriasis pubis is the infestation of pubic area, and Pediculosis palpebrarum is the infestation of the eye lashes.

Effects of pediculosis on the host

It is believed that the clinical symptoms and signs of pediculosis are due to the injected saliva at the time of feeding.

"Lousy feeling" is attributed to tiredness and irritability due to lack of sleep which in turn is due to the pruritus caused by the lice mainly nocturnally as the lice prefers to feed in darkness. Apart from nocturnal pruritus the affected child can present with fever, secondary bacterial infections, lymphadenopathy and anemia.

Pediculosis corporis

Pediculosis corporis is due to the infestation by pediculosis humanus (body lice). It was Culpepper in 1946 successfully reared a laboratory colony of body lice.[5] It is interesting and important to note that the lice spend most of their time in clothes and go to the body only to feed.

It is commonly seen with overcrowding, poverty and lack of hygiene. The body lice act as a vector for epidemic typhus, murine typhus, trench fever and relapsing fever.[4]

Clinically the bite site may produce erythematous papules, macules with typical flare and wheal formation which can occur within minutes to days. Pain may be variable but pruritus is the rule.

"Vagabond's disease" is characterized by severe excoriations, thickening of the skin, exaggerated skin markings and brownish hyper pigmentation commonly seen over trunk and abdomen.

Pediculosis capitis

Pediculosis capitis is the infestation of the scalp by P. capitis. It is interesting to note that it is also seen even in individuals with good hygiene and grooming habits.

High rates of infestations is seen both in developed and developing countries and in both in temperate as well as in tropical regions and nearly 90% of the children might

* Professor and Head of Dermatology,
Govt. Stanley Medical College,
Chennai.

have been affected at least once in their lifetime[6] most commonly between 2 to 11 years of age.[7] It is found to be more common in girls.[8]

Transmission is mainly by head to head contact and through fomites like towels, combs and head gears. Pruritus and secondary infection of the scalp with or without scaling and regional lymphadenitis marks Pediculosis capitis infestation.

Pediculosis pubis

Pediculosis pubis refers to infestations with crab lice or pubic lice which infest not only the pubic area but also any hair bearing areas and it gets transmitted through close body contacts. Crab lice affect all races and ethnic groups. They are relatively uncommon among Asians perhaps because of the sparse genital hair.[9] Children usually contract P.pubis by sharing a bed or towel with an infested member.[10] Lice tend to adapt color according to their surroundings and hence the lice in darker individuals are darker than those found on people of lighter color.Apart from the clinical features mentioned above the skin lesions which are peculiar to Pediculosis pubis are known as maculae caeruleae, which are nothing but bluish black pigmentation.

Pediculosis palpabrarum

Pediculosis palpabrarum is the infestation of the eyelashes caused by P.pubis and usually will be complicated by bacterial infections as evidenced by painful edema and erythema of eyelids. The presence of P.pubis in children should be viewed cautiously with high index of suspicion of sexual abuse.

Lice as disease vector

The body lice acting as vectors has already been highlighted. The head lice are found to carry streptococcus and staphylococcus on their exterior surfaces.

It is found that salmonellae can rapidly multiply in the gut of the lice in turn killing the lice within 48 hours. The bacilli have been known to remain alive in dead lice and their fecal pellets for at least one year. [11] It has been found that both body lice and head lice carried a yersinia pestis taken from diseased victims.

Diagnosis

Diagnosis is by the clinical features mentioned and demonstration of lice.

Therapy

1) Body lice

The clothing of the infected person is considered infectious and disinfection is recommended wherein it is fumigated with methyl bromide or simply machine washed in hot water and dried on a high heat of 65^0C for 15-30 minutes.

5% Permethrin topical cream is the safest and most effective therapy which is applied from head to toe for 8-14 hours and repeated after a week. Oral Ivermectin 200 microgram per kg single dose if necessary to be repeated after one week.is also effective. Dusting powders containing permethrin, malathion, temephos, propoxur and carbaryl are found to be very effective.

2) Head lice

The lice and nits are mechanically removed by brushing, combing, shampooing and toweling.

Medications used against lice are to be repeated a week after for the effective killing of the nymphs as most of the drugs do not have any action against the eggs.

Currently FDA has approved 1% gamma benzene hexachloride (GBHC) which is available as shampoo, lotion and cream.

Shampoo is easy to use and the recommended contact time is only 4 minutes.

1% Permethrin cream rinse has been approved by FDA and has to be applied for 15 minutes and repeated after a week.[12]

0.5% malathion lotion is the quickest and most ovicidal that has been approved by FDA around 20 years ago which recommends 8-12 hours application time.[13]

Carbaryl is available as 0.5% lotion and shampoo and the recommended contact time is 24 hours for lotion and 10-15 minutes for shampoo.

Oral ivermectin and cotrimoxazole are also used with success.[14]

Vinegar solution is found to be effective in mechanical nit picking.

3) Phthiriasis pubis

Application of GBHC lotion once for 4 minutes is a treatment of choice.

4) Phthiriasis palpabrarum

This is the infestation of the eye lashes with P.pubis and the safest treatment for this would be vaseline (petrolatum), applied 3-5 times a day for 10 days which clogs the breathing spiracles causing the lice to die of

suffocation and desiccation. Oral cotrimoxazole for 10 days is also useful in killing the lice. Oral ivermetin is useful in severe and resistant cases. Physostigmine 0.25% a mydriatic applied to the eye lashes frequently over a period of three days is found to be effective.

Conclusion

As pediculosis infestation at any habitat is considered as a social stigma and lice are also vectors for several diseases this infestation should be considered important and a thorough knowledge is essential to identify, classify and to treat appropriately and vigorously.

Points to Remember

- ***Close contact with the infested transmits the disease.***
- ***All the family members are to be treated simultaneously.***
- ***Repeat the treatment after a week where ever it is recommended.***
- ***P.humanus should be searched in the clothing rather than in the body.***
- ***Treatment of clothes is essential in P.corporis.***

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Contact:

Dr B K Hukkeri,

IAP Belgaum District Branch,

Department of Pediatrics,

K L E University's

J N Medical College, and Department of Pediatrics,

Belgaum Institute of Medical Sciences, Belgaum, Karnataka, India.

babannakh@hotmail.com Mobile: 98441 88212.

RADIOLOGIST TALKS TO YOU

TUMOUR AND TUMOUR-LIKE LESIONS IN THE SINUSES

** Vijayalakshmi G*
*** Malathy K*
**** Natarajan B*
**** Jaya Rajiah*
**** Kasi Visalakshi*

In the last issue we saw inflammation of the sinuses. Now we will move on to masses in the sinuses. These are very rare in children but the common malignant tumours arising in the extra cranial head and neck are rhabdomyosarcoma and lymphoma. Radiology has an important role in the diagnosis of tumours and tumour like lesions and follow-up evaluation to assess adequacy of treatment. CT allows rapid and detailed imaging. MRI is useful for intracranial extension. Positron emission tomography provides whole body functional imaging and coupled with CT (PET CT), it is increasingly being used in the staging and follow-up of lymphomas.

Fig.1 belongs to a 17 year old and shows a round opacity in the region of the right maxillary sinus. There is a displaced tooth high up within it. Fig. 2 is that of a 10 year old child with an opaque left maxillary sinus. Here also there is a displaced tooth. Further imaging reveals two very different conditions. Fig.1 is a dentigerous cyst. It is a benign, non-inflammatory odontogenic cyst. They usually present in the 2nd or 3rd decade but sometimes they occur earlier. The cyst encloses the crown of an unerupted tooth. The commonly involved teeth are mandibular 3rd molar and maxillary 3rd molar. Other teeth that are involved are the maxillary canines and central incisors. As the cyst grows other teeth may also be displaced. CT appearances are similar to that in x-ray. There is a unilocular radiolucent lesion with a sclerotic border and the relationship to the precise un erupted tooth is easily appreciated.

* Professor, Department of Radiology, ICH & HC, Chennai.

** Professor
Department of Radiology,
Madras Medical College, Chennai.

*** Asst. Professors, Department of Radiology, ICH & HC, Chennai.

Fig. 3 is a T2 weighted MRI image of the same patient as in Fig. 2. There is a hyper intense mass filling the maxillary sinus, eroding the medial wall and extending into the nasal cavity, displacing the nasal septum to the opposite side. It is clearly a malignancy. Biopsy showed that it was lymphoma. Lymphoma is the commonest malignancy involving the extra cranial head and neck.

Fig.4 shows an image of a mass in the left maxillary sinus. The mass has expanded the sinus, eroded its lateral wall and extended into the soft tissue of the cheek. The biopsy revealed a diagnosis of rhabdomyosarcoma. RMS is the commonest soft tissue sarcoma in children less than 15 years. 40% of RMS occur in the head and neck. Most cases occur in the first decade of life and there is a slight male preponderance. Imaging is essential for staging and long term follow-up. It will show the disease site that will categorize disease into more favourable orbital and non-para meningeal sites. Para meningeal sites are not so favourable and include the nasal cavity, para nasal sinuses, pterygoid fossa , nasopharynx and middle ear where they tend to be large and invasive. Cervical lymph node metastases may be seen. Orbital RMS is usually non-invasive and confined to the orbit and lymphatic spread and nodal metastases are rare. MRI is the modality of choice for assessment of disease in the head and neck. It allows accurate assessment of extent that will help in defining the field of radiotherapy. In T2 weighted images it is hyper intense just like the lymphoma in Fig. 3. In T1 images it is iso or mildly hypo intense to skeletal muscle. Following contrast the mass enhances moderately or brilliantly like the juvenile angiofibroma. However CT is essential for identifying bone erosion and therefore both CT and MRI are often necessary. Some patients may have metastatic disease on presentation. Chest CT, abdominal ultrasound and bone scintigraphy will complete the pre-treatment work-up of the patient. Likewise post-operative extent of residual disease will help to guide multi-pronged treatment with radiotherapy and chemotherapy.

Neuroblastoma is the third most common malignancy in childhood but rarely arises primarily in the head and neck. Metastatic disease is more common. Nasopharyngeal carcinoma is also rare in children. Most often they present with bulky disease with skull base erosion and cranial nerve

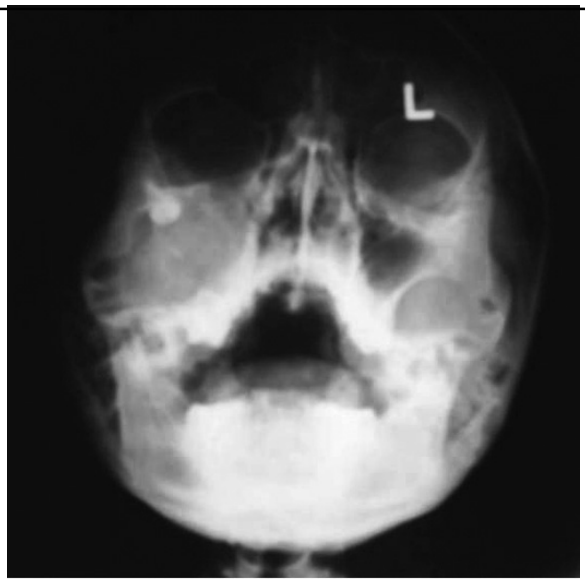


Fig.1. Dermoid cyst- Right maxilla

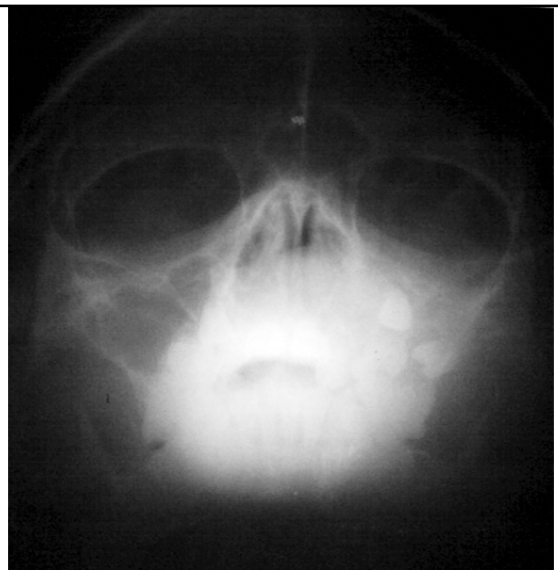


Fig.2. Swelling in left maxilla- Lymphoma

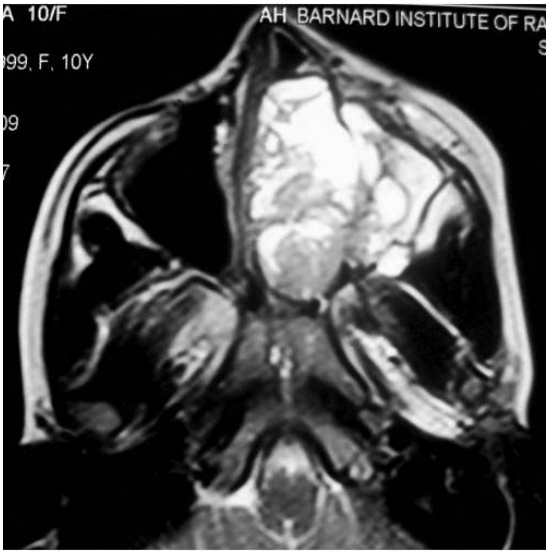


Fig.3. Same patient as Fig 2. MRI- Lymphoma

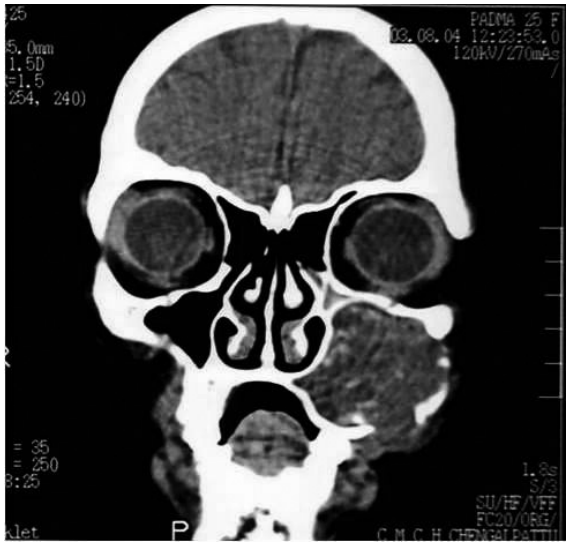


Fig.4. Mass – Left maxilla – RMS

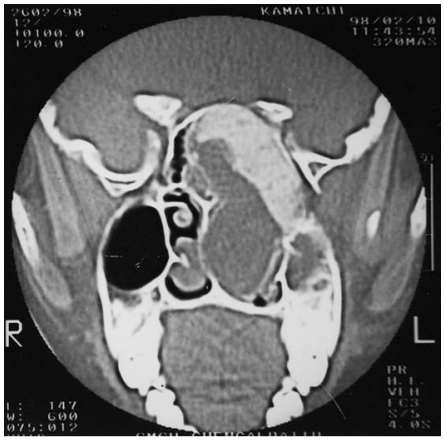


Fig.5. Fibrous dysplasia- Left ethmoid and turbinates

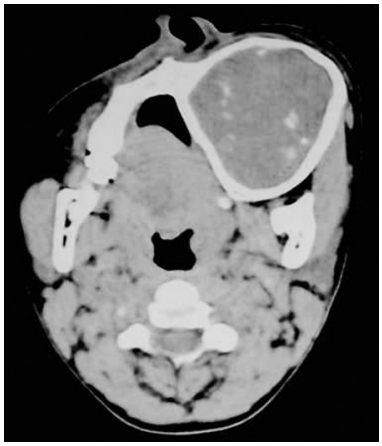


Fig 6. Fibrous dysplasia- cystic type- in the left maxilla

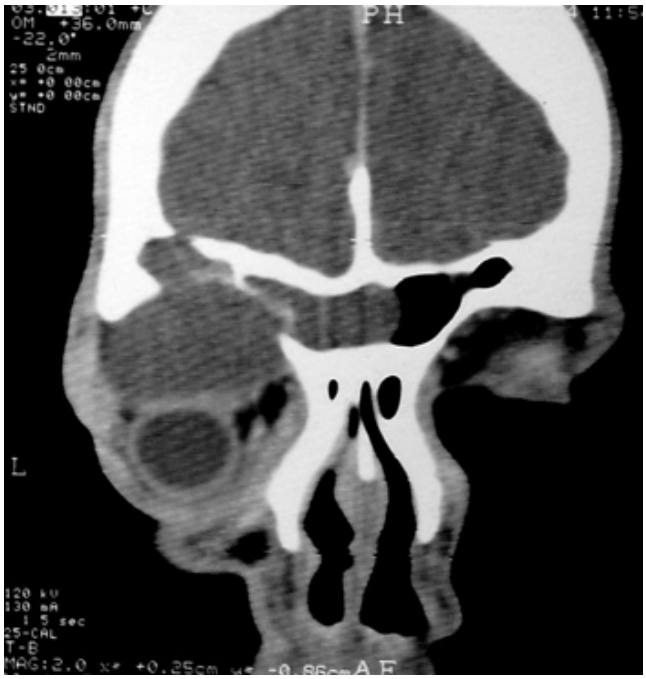


Fig 7. Mucocele – Right frontal sinus

palsy. While it is squamous cell carcinoma in the adult it is undifferentiated round cell type in children.

Fibrous dysplasia is a benign condition occurring in the region of the sinuses. Craniofacial involvement occurs in about 25% of mono-ostotic fibrous dysplasia and 50% of poly-ostotic disease. X-rays will show expansile lesions with a ground glass density. CT will better delineate anatomical extent . Fig.5 shows fibrous dysplasia involving the ethmoid sinuses and turbinates on the left. The ground glass density is characteristic of the disease. The bone is expanded and is compressing the sphenoid sinus and blocking the ostium of the left maxillary sinus causing sinus opacification. Fig. 6 is a typical appearance of cystic type of fibrous dysplasia found in the craniofacial region. There is a radiolucent area bound by sclerotic rind of bone.

Another benign condition is a sinus mucocele. It rarely occurs in children less than 10 years. There may be a history of cystic fibrosis. Frontal sinuses followed by ethmoidal sinuses are affected. The mucocele is an expanded sinus filled with pent up secretions. They have the ability to erode through adjacent bone and into the cranium. The mucocele in Fig.7 has eroded the roof of the orbit and caused displacement of the globe.

The clinical presentation of some benign conditions occurring in the sinuses and facial region may overlap with those of malignancy. Therefore imaging plays an important role in diagnosis, management and follow-up.

CASE STUDY

DUODENAL WEB -A RARE CASE OF RECURRENT VOMITING IN AN YOUNG INFANT

***Sumathi B**
** **Nirmala D**
*** **Bhaskar Raju B**
**** **Senthil Nathan SV**

Abstract: *Duodenal obstruction is a common surgical condition that causes vomiting in neonates. Most common site of duodenal obstruction is the second part of duodenum. This condition may result from atresia, stenosis or rarely due to membrane containing a pinhole orifice. Anomalies like intestinal malrotation, preduodenal vein and annular pancreas can be associated. Significant proportion of children can have late onset of symptoms. Most of the cases have been diagnosed by barium contrast studies. In our child duodenal web with a pinhole was identified by upper gastrointestinal endoscopy followed by barium contrast study.*

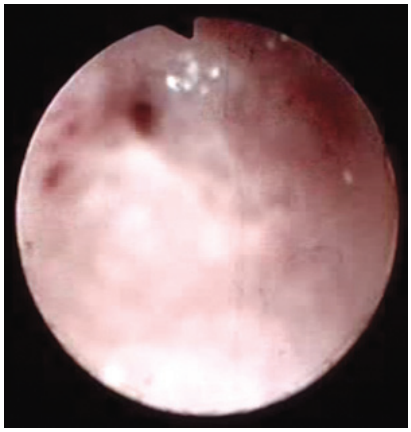
Keywords: *Recurrent vomiting, Duodenal web, Fenestrated duodenal membrane.*

Recurrent vomiting in infants and young children can occur due to many conditions like gastroesophageal reflux disease, food intolerance, metabolic disorders, central nervous system disorders and surgical causes. Presence of alarming signs and symptoms like failure to thrive, anemia and visible gastric, intestinal peristalsis should make one to suspect surgical causes of recurrent vomiting like esophageal stenosis, pyloric obstruction and intestinal web/ atresia. Most of the cases are being diagnosed by barium studies. These correctable conditions warrant early diagnosis and intervention for achieving normal growth and development of the child. The clinical presentation of duodenal web can be early or late. Late presentation may vary from less specific clinical features like failure to thrive, gastro esophageal reflux, epigastric fullness and recurrent pulmonary aspiration.[1] Most of the cases reported in the literature have been diagnosed by barium contrast studies.[2]

* Assistant Professor of Pediatric Gastroenterology,
** Professor & Head Department of Gastroenterology
*** Retired Professor & Head, Department of Gastroenterology
**** Professor & Head Department of Pediatric Surgery
ICH & HC, Chennai.

Case Report

One year and three months old female child born to non-consanguinous parents was brought by the mother to pediatric gastroenterology out patient clinic in April 2009 with history of regurgitation and vomiting since birth. Vomiting was more pronounced after one year of age when solid foods were introduced and most episodes were non-bilious. There was no history of passing hard stools. Mother gave history of recurrent wheeze suggestive of recurrent aspiration. Child was on exclusive breast feed till six months of life. Cow's milk was introduced after sixth months of age and solid diet was introduced after one year. On examination, child was weighing 8 kg with grade 1 PEM and anemia. There was epigastric fullness after feeds. Plain X- Ray abdomen showed a dilated stomach. Hemoglobin was 8gm/kg. Renal parameters and serum electrolytes were normal. Ultrasound examination showed distended stomach. Upper GI scopy was done after 24 hours nasogastric decompression, using modified fibreoptic endoscope N30 fitted with a video adapter and the pictures were recorded on a computer. On endoscopy, a web was seen with an eccentrically and medially placed orifice measuring 3-4 mm in size beyond second part of duodenum suggestive of fenestrated duodenal membrane (Fig.1 & 2). Stomach was dilated with stasis gastritis and distal esophagitis. This was followed by barium contrast study, which revealed dilated stomach with contrast filling beyond (Fig.3). Surgery was done. Intra operative findings showed grossly dilated stomach and proximal duodenum. Ring of pancreatic tissue was seen encircling second part of duodenum suggestive of annular pancreas and there was malrotation. Web was seen at second part of duodenum producing a wind sock defect into third part. The web was excised and duodeno duodenostomy was done and malrotation was corrected. The post-operative period was



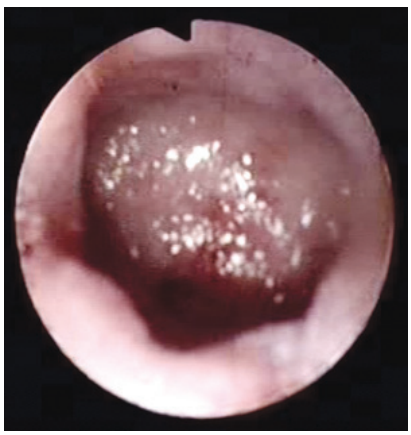


Fig. 1 & 2 showing endoscopic pictures of duodenal web with the hole which is eccentrically placed

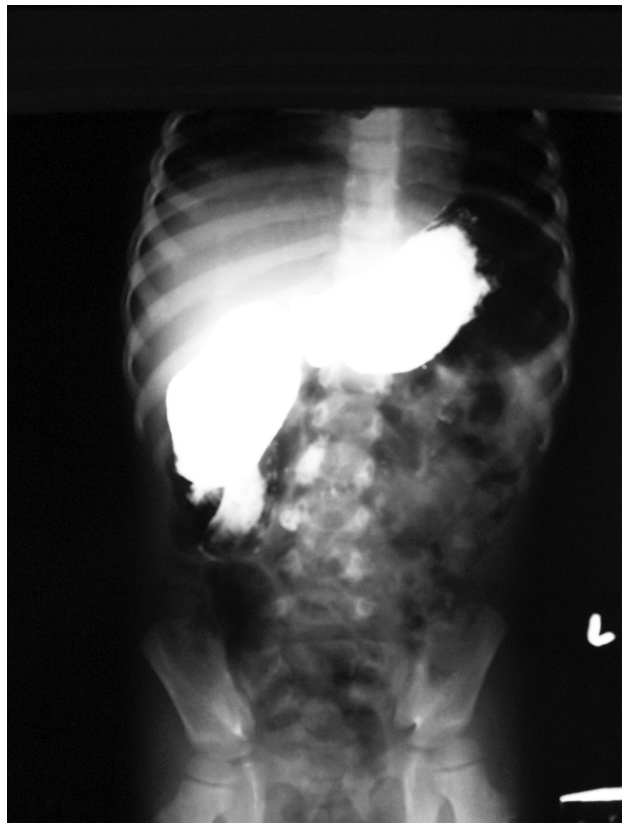


Fig.3. Barium contrast study showing dilated duodenum with minimal barium spill distally through the hole

uneventful. Child was started initially on liquids and solids were introduced gradually. Child is on regular follow up in our clinic.

Discussion

Duodenal web is a rare anamoly and so far nearly 100 cases have been reported in literature.[3] The second part of the duodenum is the most common site, seen in 85% to 90% of all duodenal web cases. The third and fourth parts of the duodenum may show a web in 20% and 10% of cases, respectively.[3,4] The embryology of the duodenum as described by Boyden, et al[5] supports the Tandler theory for this localisation and the central ampullary epithelium being the last one to canalize during cephalo-caudal wave of epithelisation. The residual barrier may be complete or less commonly at times containing a small orifice resulting in a fenestrated duodenal membrane. The position of the opening may vary and may be central, eccentric or even may be multiple and of varying size ranging from pinpoint to about 1 cm.[6] Due to constant prograde peristalsis, the membrane may be prolapsed into third or fourth part of duodenum and very rarely into proximal jejunum. This is the mechanism, which causes "Aviation Windsock" effect as described by Bill and Pope causing dilatation of the bowel distally.[7] Polyhydramnios may be seen in 50% of cases antenatally. Associated anomalies such as intestinal malrotation and a preduodenal portal vein are well recognized. Pancreatitis has also been reported in individuals with intraluminal duodenal diverticula.[4,8] Superior mesenteric artery syndrome is a very rare condition in childhood, most frequently resulting in duodenal obstruction in the adult population. Annular pancreas can be a rare association.

The clinical presentation may be delayed if the obstruction is incomplete. One important factor is that the child may be asymptomatic when on liquid diet and the child may show symptoms in the form of vomiting, epigastric fullness, recurrent chest infections and failure to gain weight when solids are introduced. Non bilious vomiting has been documented in 50% of cases in one study.[2] Clinical presentation of fenestrated duodenal membranes

Table.I Presentation of fenestrated duodenal membranes[2]

Early (neonatal) (n=6)	(n=6)	Delayed (5 wk to 14 yrs) (n=10)	n(%)
Bile-stained vomiting	4	Failure to thrive	6
Non-bile stained vomiting	2	Non-bile stained vomiting*	5
		Bile-stained vomiting*	2
		Epigastric distension	4
		Recurrent chest infections	4
		Hematemesis*	3
		Distension / constipation	1

*In 9 out of 10 cases, the vomiting was of sudden onset and short duration (< 1 wk)

are illustrated in the Table I. Surgery is most often required with excision of the membrane. Our child had web excision along with transverse duodenostomy. Okamatsu, et al have reported that identification of membrane and incision via an endoscope using high frequency laser wave. Care should be taken during excision to avoid ampullary damage or incision through the duodenal wall.[9]

The possibility of a fenestrated duodenal membrane must be considered whenever a child presents with recurrent vomiting resembling pyloric stenosis, gastroesophageal reflux disease, failure to thrive and recurrent pulmonary aspiration syndrome. Presence of epigastric fullness is a valuable clinical sign. Isolated membrane has good prognosis. Only few cases have been diagnosed by endoscopy as per literature. Most of the cases are diagnosed by barium contrast radiography.

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Workshop On Neonatal CPAP, Pune, Maharashtra

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Contact

Dr Sandeep Kadam,

Cell: 09850609628, E-mail:drsandeepkadam@yahoo.com