

# ANNALS OF THE INSTITUTE OF CHILD HEALTH CALCUTTA

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Generally children present to the emergency department more often than adults. Neonates and small children are more difficult to assess as most of the time they present with non-specific signs and symptoms. The vital signs like respiratory rate and heart rate are crucial points in examination. Unlike adults the children are unique in this sense as both these parameters change with age.

Early assessment and emergency triage is vital with regards to outcome of the children presenting in the emergency department. Triage includes early patient assessment, priority rating, first aid, control of patient flow, assignment of correct area of care, initiation of diagnostic measure and liaising with relatives and health care professionals. Many early hospital deaths can be prevented by an accurate triaging and thus instituting quick treatment.

Decision making in pediatric room is the synthesis of the whole process of history, examination, knowing when to trust the parents, intuition and maintaining objectivity. Sometimes the features are glaring and decision making is very easy, at other times there is no definite pointer but somehow one feels that everything is not right and these are the difficult situations. In neonatal and pediatric emergency probably a bit of over doing is better than taking a chance. When in doubt it is better to admit a patient for observation.

Pediatric emergency is a relatively new discipline in India. It is taking its shape over the last few years as a new speciality dealt by specialists interested in this discipline. It is time that institutes must focus towards training pediatricians in such an interesting field of pediatrics where in the first few golden moments at presentation to emergency department, a rational, stepwise and correct approach can not only save the child but also reduce the morbidity to a minimal.

Maya Mukhopadhyaya  
Jaydeep Choudhury

## Review Article

# Neonatal and Pediatric Emergencies

**Maya Mukhopadhyay**

*Professor and Head, Department of Pediatrics, Institute of Child Health, Kolkata*

Neonates and Children often present with non specific signs and symptoms which may turn out to be fatal and require early aggressive emergency life saving intervention. Physicians need to be aware of the emergency conditions.

The mnemonic “THE MISFITS” is helpful tool indicating the emergency situations. <sup>1,2</sup>

T = Trauma

H = Heart disease / Hypovolemia/hypoxia

E = Endocrine (Congenital adrenal hyperplasia, thyrotoxicosis)

M = Metabolic (Electrolyte imbalance)

I = Inborn error of Metabolism

S = Sepsis (Meningitis, Pneumonia, UTI)

F = Formula mishaps (Over or under dilution)

I = Intestinal catastrophes (Volvulus, Intususception, NEC)

T = Toxins/ poisons

S = Seizures

Another term an “Apparent Life Threatening Event” (ALTE) <sup>3</sup> indicates “an episode that is frightening to the observer that is characterized by some combination of apnea,

colour change, marked change in muscle tone, choking or gagging.” This also indicates emergency situations.

Important causes are as follows:

Acid based disturbances

Botulism

Child abuse

Disrhythmia

Electrolyte abnormality

GERD

Hypoglycemia

Hypothermia

Seizure

IEM

Intracranial Hemorrhage

Meningitis and Encephalitis

Pertussis

Pneumonia

Sepsis

Some important emergency conditions are highlighted as follows:

### **Trauma**

Trauma may be accidental or non accidental.

Head trauma may often be the sign of child

abuse without any other physical significant finding. Early diagnosis with neuroimaging – skull X-ray, CT scan, MRI may be helpful for early management and to prevent long term sequel. Child abuse needs to be excluded. The diagnosis of non-accidental head trauma or shaken baby syndrome (SBS)<sup>4,5,6</sup> is challenging because long term morbidity and mortality is high in these cases. Management includes ABC stabilization, IV access, thorough investigation CT/ MRI brain etc.

### **Heart disease / Hypovolemia/ Hypoxia**

Patient presenting with cyanosis should be differentiated for cyanotic heart disease, pulmonary causes, infections, CNS involvement or toxins. With 100% FiO<sub>2</sub> there is at least 10% increase in O<sub>2</sub> saturation in non cardiac diseases, where as in cyanotic heart diseases no such change is noted. Hypoplastic left heart, Transposition of the great arteries (TGA), Tetralogy of Fallot (TOF), Total anomalous pulmonary venous return (TAPVR), Tricuspid atresia (TA), Truncus arteriosus are important causes of cyanotic heart diseases. Detection of cyanotic heart disease is often delayed until there is anatomical closure of PDA by 2 weeks. Physical examination, detection of murmur, chest X-ray, ECG, ECHO are diagnostic. Acyanotic heart diseases e.g VSD, ASD, PDA, CoA, severe anemia, SVT can also present with heart failure. Respiratory causes e.g. bacterial pneumonia and LRTI from RSV, influenza, parainfluenza are important causes of bronchiolitis. Apnea and other causes of ALTE should be differentiated.

### **Endocrine causes**

Endocrine emergencies often present with signs and symptoms of shock, CNS infection or renal failure. Physicians must have high index of suspicion other wise it may be overlooked.

Common endocrine emergencies are:

Diabetic Keto Acidosis (DKA)

Hypoglycemia

Hypocalcaemia

Thyroid storm / Thyrotoxicosis

Adrenal insufficiency

CAH

Pheochromocytoma

Diabetic insipidus

Syndromes of inappropriate ADH (SIADH)

#### **DKA:**

DKA is defined as severe uncontrolled diabetes requiring urgent treatment with IV fluid and Insulin. It is characterized biochemically by blood glucose >250mg/dl, serum Ketons>3mmol/l, serum bicarbonate <15 mmol/l and blood PH < 7.3. DKA occurs in 20-40% children with first onset diabetes or in children with known diabetes due to lack of compliance. It may be mild, moderate or severe and the range of symptoms depends on depth of ketoacidosis (Table 1). There is a large amount of ketonuria, an increased ion gap, a decreased serum bicarbonate (or total CO<sub>2</sub>) and pH, and an elevated effective serum osmolality, indicating hypertonic dehydration.

**Table 1:** Classification Of Diabetic Ketoacidosis <sup>7</sup>

	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
CO <sub>2</sub> (mEq/L, venous)	20-28	16-20	10-15	<10
pH (venous)	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*Clinical features* – Features of DKA are dehydration, Kussaul breathing (rapid and deep breathing), abdominal pain, distension and vomiting. Patient gradually becomes drowsy and later develops coma.

In DKA, insulin deficiency produces hyperglycemia and ketonemia. There is increase in serum osmolarity causing osmotic diuresis with dehydration and electrolyte loss. Ketonemia results in sodium and potassium loss in urine. Paralytic ileus with vomiting, aggravates dehydration and electrolyte imbalance. Ketone bodies are neutralized by bicarbonates, resulting in acidosis with hyperventilation. Severe acidosis has a negative inotropic effect and causes peripheral vasodilatation which accentuates shock. Lactic acidosis is secondary to tissue hypoxia.

#### *Treatment* <sup>8</sup>

*Fluid replacement:* The sum of maintenance requirement + deficit + ongoing losses are calculated. In first 1-2 hours, 10-20ml/kg is given to bring circulatory stability. The remainder of calculated fluid is replaced over 36 – 48 hours.

*Maintenance:* 1,500 ml/m<sup>2</sup>/day for all ages or

120ml/kg (1-2yrs) 100ml/kg (3-6yrs), 80ml/kg (7-9yrs), 60ml/kg (<10yrs)

*Deficit:* Generally 10% is assumed.

*On going loss:* Urine output during first 5hours of treatment + loss of vomitus and gastric aspirate.

*Type of fluid:* Initially N saline or Ringerlactate is used. With gradual decline in plasma osmolarity, when blood glucose reaches 250mg/dL 5% dextrose is added to the fluid to reduce the risk of hypoglycemia.

Total fluid replacement should be as follows 1/3<sup>rd</sup> in the 1<sup>st</sup> 6 hours, 1/3<sup>rd</sup> in next 12 hours and the rest 1/3<sup>rd</sup> in next 18 hours.

*Potassium replacement:* Though initial serum level may be normal or high, with fluid and insulin therapy there is a marked fall in potassium level. So, total body potassium is depleted in all cases.

Potassium replacement is started after the 1<sup>st</sup> hour of fluid therapy. If the initial level is <3mEq/l earlier potassium replacement should be done irrespective of renal function as in these cases arrhythmias, respiratory muscle weakness or impaired CVS function

may be induced by insulin therapy. On the other hand if the patient is hyperkalemic early potassium before insulin may increase extra cellular potassium further and precipitate life threatening arrhythmias. An urgent ECG is suggested to monitor T wave abnormalities as serum potassium level may take time to be available. Potassium is replaced 20-30mmol/l of fluids, not exceeding 40-60mmol/l.

*Bicarbonate replacement:* With insulin and IV fluid therapy, ketoacid and lactic acid molecules are metabolized to bicarbonate. Routine use of bicarbonate may over correct acidosis and precipitate alkalosis. Hyponatremia and acute hypokalemia also results. CO<sub>2</sub> formed by interaction of H<sup>+</sup> ions with bicarbonate crosses the blood brain barrier leading to CNS acidosis. Monitoring of serum potassium and ECG is mandatory during correction. Only when serum PH is < 7.0 bicarbonate may be used as slow IV infusion and never as a bolus (as bicarbonate has high osmolarity) over a period of 2 - 4 hours and half correction is recommended.

*Insulin Therapy:* To be given after starting IV fluid. Continuous low dose insulin infusion is preferred. Infusion is made as 50units of short or ultra short acting insulin in 500ml of N saline and initial 50-60ml is run off through the tubing to saturate binding sites. Infusion is given through infusion pump and dose of insulin infusion is 0.1unit/kg/hour. If blood glucose does not fall by 50- 100mg/dl/hr in 2-3 hours, the infusion rate is doubled. When blood glucose reaches 250mg/dl glucose is added to infusion and continued till acidosis is corrected and ketone bodies have

disappeared. Half an hour before the insulin infusion is to be discontinued, subcutaneous regular insulin 0.25units/kg must be given. Following this a regimen of regular and intermediate acting insulin in 2 or more daily doses can be started. Oral feed is recommended within 4-12hours with improvement of patient's condition e.g. regaining of consciousness, disappearance of abdominal distension and no vomiting. It should be kept in mind that measurement of ketone bodies in urine may be fallacious. Beta hydroxybutarates produced in the initial phase of ketoacidosis can not be detected by ketodiastics which is sensitive to acetone acetoacetic acid. In the initial phase test may be weekly positive giving wrong impression of improvement. With improvement there is more production of acetone and acetoacetic acid giving strongly positive results which is false positive as even if the patient is improving the test result is strongly positive.

*Monitoring:* After initial investigation of glucose, electrolytes, blood gas, creatinin, serum osmolarity, blood count and C/S, further monitoring of glucose and electrolytes should be done 1-2hourly; ABG at 2,4,6,12 and 24hours and GCS monitored 2hourly.

*Complications of DKA:* Brain edema, hypokalemia, hypocalcemia, hypoglycemia, alkalosis are common complications of DKA.

Brain edema is suspected with deterioration of level of consciousness, appearance of bradycardia and convulsions. This is prevented by slow IV fluid over 48hours and use of isotonic solutions – to avoid hypotonic or

hypertonic solutions. Treatment includes manitol 20% IV in a dose of 0.5-1gm/kg (may be repeated every 15minutes), reduced rate of IV fluids, nursing in head up position and assisted ventilation.

**Hypoglycemia :**

A common problem in PICU and NICU. Hypoglycemia is defined as blood glucose below 40mg/dl (2.2mmol/l) in a neonate and 50 mg/dl (2.7mmol/l) there after.

*Clinical features in neonates –*

Lethargy, jitteriness, myoclonic, jerks or convulsion, apnea, respiratory distress, cyanosis, poor feeding, hypothermia

In older children: sweating, tremors, hunger, pallor, tachycardia, lethargy, ataxia, visual deficiency, convulsion, unconsciousness are usual findings.

*Classification –* It can be Ketotic or Non-ketotic. (Figure 1)

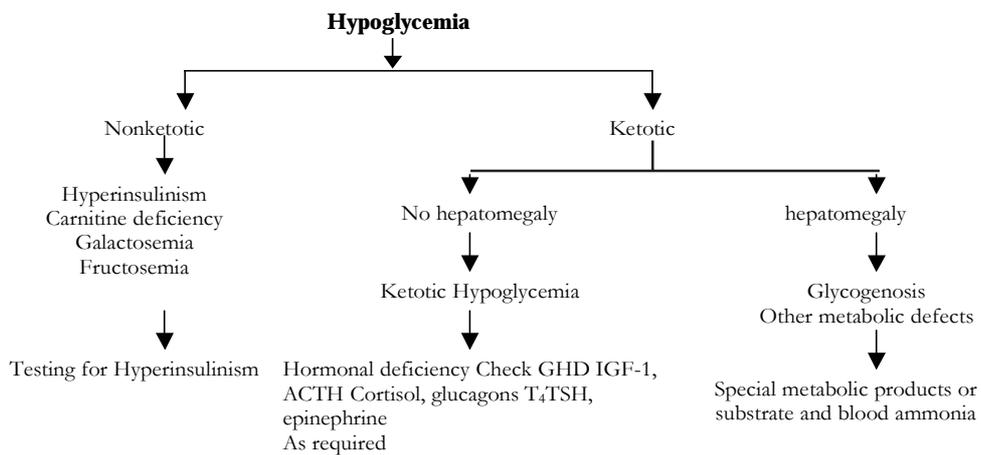
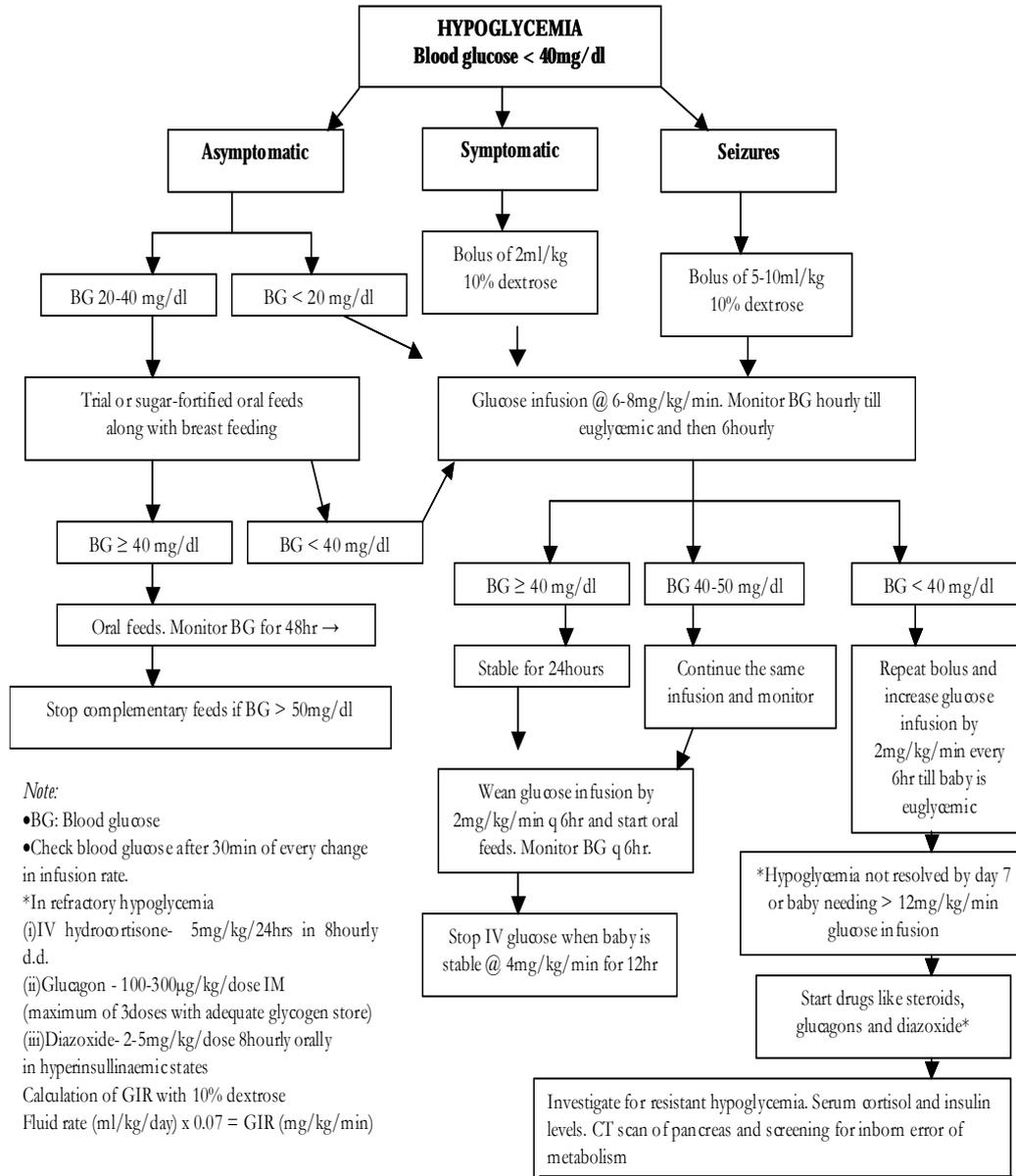


Figure 1: **Classification of Hypoglycemia**

**Investigation**

Blood Test	Urine Test
Glucose	Ketone bodies
Acetone	Reduceing substance
Cortisol	Amino acid and organic acid
Growth hormone	
Insulin	
Free fatty acid	
Lactate and pyruvate	

## Treatment <sup>9</sup>



**Figure 2: Algorithm for management of neonatal hypoglycemia**

**Hypocalcaemia<sup>10, 11, 12</sup> :**

Defined as serum calcium < 7.5mg/dl and ionized calcium < 4.0mg/dl. After delivery calcium level starts decreasing and reaches nadir of 7.5 – 8.5 mg/dl by day 2. This drop is due to peak in Calcitonin level which occurs by 12-24hrs. PTH gradually increases in first 48hrs. This transition results in early hypocalcaemia. Neonatal hypocalcaemia can be *Early onset* or *Late onset*

*Early onset* – During first 3days (within 72hrs). Commonly between 24-48hrs.

Etiology: Preterm and VLBW.

SGA

Infants of DM

Birth asphyxia

Clinical features:

Jitteriness, tremor, irritability, seizure, hyper-tonia, tachycardia/ tachypnea, apnea, poor

feeding, vomiting, hyperreflexia, clonus, carpopedal spasm/ Chvostek’s sign (less common), laryngospasm and inspiratory stridor.

Serum calcium to be screened at 12, 24, 48hrs after birth.

*Diagnosis* –

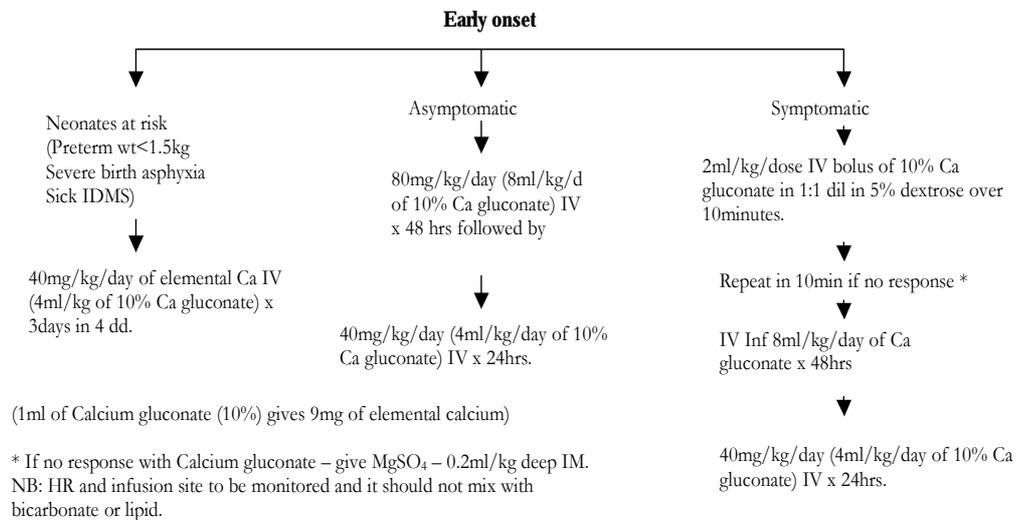
1. Total serum Ca: < 7.0mg/dl
2. ECG: QoTc >0.2 seconds or QTc >0.45 seconds

$$QTc = \frac{QT \text{ interval in seconds}}{\sqrt{R-R \text{ interval in seconds}}}$$

$$QoTc = \frac{QoT \text{ interval in seconds}}{\sqrt{R-R \text{ interval in seconds}}}$$

(QT interval is measured from origin of q wave to end of T wave on ECG

QoT interval is measured from origin of q wave to origin of T wave).



**Figure 3 : indicates the algorithm of management of neonatal hypocalcaemia**

*Late onset* –

It usually presents at the end of the first week.

*Etiology* –

1. Hypomagnesemia
2. Hyperphosphatemia  
Cow's milk intake
3. Hypoparathyroidism
  - a. Idiopathic, transient
  - b. Hypoplasia or aplasia of parathyroid glands (Di George's syndrome)
  - c. Pseudoparathyroidism
  - d. Maternal hyperparathyroidism
4. Vitamin D deficiency
  - a. Maternal Vitamin D deficiency
  - b. Maternal anti convulsant therapy
  - c. Liver disease
  - d. Renal insufficiency
5. Miscellaneous
  - a. Bicarbonate therapy
  - b. Exchange transfusion with CPD blood
  - c. Phototherapy
  - d. Hypoalbuminemia
  - e. Furosemide
  - f. Lipid infusion

*Investigation* – In Late Onset neonatal hypocalcemia or if hypocalcemia is unresponsive to adequate doses of calcium, following investigations to be done:

Serum magnesium – if  $< 0.8\text{mg/dl}$  – sug-

gests primary hypomagnesemia and should be treated.

Serum Phosphate – Phosphate levels are increased in renal failure, top feeding with cow's milk and hypoparathyroidism.

Alkaline Phosphatase - levels are increased in hypoparathyroidism

PTH levels - PTH is decreased in hypoparathyroidism.

Urine Calcium/ creatinine ratio ( $> 0.2$  suggests hypoparathyroidism)

Chest X-Ray - Absence of thymus shadow is suggestive of Di George's syndrome

Maternal phosphate, calcium, alkaline phosphatase levels are helpful in detecting maternal vitamin D deficiency.

*Treatment* – Treatment of Late Onset neonatal hypocalcemia is specific to etiology and in certain diseases may be life long.

Hypomagnesemia - hypocalcemia unresponsive to adequate doses of IV calcium therapy is usually due to hypomagnesemia. Two doses of  $0.2\text{ml/kg}$  of 50%  $\text{MgSO}_4$  injection, 12 hours apart, deep IM is followed by a maintenance dose of  $0.2\text{ ml/kg/day}$  of 50%  $\text{MgSO}_4$ , PO for 3 days.

Hypoparathyroidism - Parathormone insufficiency is indicated by elevated phosphate levels in the absence of exogenous phosphate load (cow's milk) and presence of normal renal functions. Treatment with calcium ( $50\text{ mg/kg/day}$  in 3 divided doses) and  $1,25(\text{OH})_2$  Vitamin D3 ( $0.5\text{-}1\text{ mg/day}$ ) is suggestive. In hypocalcemia secondary

to maternal hyperparathyroidism, treatment may be stopped after 6 weeks.

Vit D3 Deficiency – presents with hypocalcemia associated with hypophosphatemia due to an intact parathormone response on the kidneys. Treatment with Vitamin D3 supplementation 30-60 ng/kg/day is helpful .

Breast feeding to be encouraged and cow's milk should be discontinued.

### ***Thyrotoxicosis*<sup>13</sup> :**

Thyroid storm, a life threatening syndrome due to thyroid hormone excess is rare in children. Unlike congenital hypothyroidism which is permanent, neonatal hyperthyroidism is transient and results from transplacental transfer of maternal thyrotropin(TSH) receptor stimulating antibody. Fetal hyperthyroidism is suspected in presence of fetal tachycardia (HR > 160/min), IUGR and goiter. In neonate signs and symptoms are tachycardia, irritability, poor weight gain, prominent eyes, goiter. Rarely neonatal Graves Disease may present with thrombocytopenia, jaundice, hepatosplenomegaly and should be differentiated from congenital TORCH infection. Sudden death may result from arrhythmia and heart failure. In untreated cases along with significant mortality, long term sequel, e.g. cranial synostosis, failure to thrive and delayed development may results. Neonatal hyperthyroidism usually lasts for 2-3months. Low TSH and increase concentration of circulating free T<sub>4</sub>, T<sub>3</sub> and TSH receptor antibody is diagnostic. Increase blood sugar, alkaline phosphates and raised liver enzymes can occur. Aggressive

management is life saving. Temperature control to be done with acetaminophen. Salicylates should be avoided as it displaces thyroid hormone from binding protein. IV fluid and cold sponging is also supportive measures in cooling the body. Propylthiouracil (PTU), a rapid acting drug 5-15mg/kg/day is helpful. Lugols iodine can be used in 0.1 – 0.3 mg/kg/day to inhibit thyroid iodide transport, synthesis and hormone release. This can be used as short term therapy in severe thyrotoxicosis and thyroid storm. This should be given 2hours after PTU to prevent worsening of symptoms. Beta blockers e.g. propranolol 0.5-2mg/kg/day in 8 hourly divided doses are recommended to control adrenergic symptom. Hydrocortisone or dexametasone are helpful to prevent adrenal crisis and conversion of T<sub>4</sub> to T<sub>3</sub>. Role of Radio active iodine (RAI) which destroys thyroid follicular cell has its reservation in children. Surgery – Sub total thyroidectomy may be considered in refractory cases and complication like recurrent laryngeal nerve palsy to be kept in mind.

### ***Addisonian crisis*<sup>14</sup> :**

Adrenal failure, a life threatening emergency condition may be precipated by infection, trauma, stress or surgery. Addison's disease is due to low output of all adrenal steroids due to low production of adrenocorticotrophic hormone. It also results from destruction of adrenal cortices by autoimmune diseases or chronic infections like tuberculosis, HIV. Adrenal Crisis is the initial presentation of congenital adrenal hypoplasia, congenital ad-

renal hyperplasia and adrenal hemorrhage. Clinical features are anorexia, vomiting, abdominal pain, pyrexia, hypotension, dehydration, shock and circulatory collapse. Patient suddenly becomes cyanosed, cold, clammy extremities, weak and thready pulse, hypotension, rapid labored breathing. This is associated with hyponatrimia, hyperkalemia and hypoglycemia. Adrenal hemorrhage may be associated in fulminant infection e.g. meningococemia and other bacterial infection leading to endotoxic shock resulting in Waterhouse-Friedrichsen Syndrome. Traumatic delivery may cause adrenal hemorrhage in newborn leading to acute adrenal insufficiency. Ultra-sonography confirm the diagnostic. During recovery adrenal calcification is seen. Adrenal crisis is due to mineralocorticoid deficiency and not glucocorticoid deficiency.

Congenital adrenal hypoplasia may be of two forms. The first form is Autosomal recessive with small adrenal gland containing all the 3 zones and the second form is X-linked recessive disorder with structural disorganization of adrenal glands containing large vacuolated cells (cytomegalic hypoplasia). Congenital adrenal hypoplasia manifest as severe salt-wasting in the neonatal period but may be delayed. The first variety is associated with cerebral malformation and the second variety may be associated with hypogonadotropic hypogonadism and Duchene muscular dystrophy. Presence of hyperpigmented or hypopigmented patches, ambiguous genitalia, muscular hypertrophy, midline craniofa-

cial defect, achalasia etc. suggests adrenal insufficiency.

Acquired adrenal insufficiency results from autoimmune adrenalities. It can be Type 1 polyglandular autoimmune syndrome (PGA), having features of mucocutaneous candidiasis, hypoparathyroidism, Addison's disease, insulin dependent diabetes mellitus, hypothyroidism, gonadal failure, alopecia, vitiligo and Type 2 PGA, associated with thyroid disease and type 1 diabetes mellitus.

Tuberculosis is the common cause of Addison's disease, and is also common in HIV patients.

*Investigations* – Serum sodium is low and serum potassium is high. Blood glucose is low, BUN and creatinine is high. X-ray abdomen shows calcified adrenals in adrenal hemorrhage; CT scan and MRI is helpful.

*Hormonal study* – Measuring cortisol, ACTH, 17 hydroxyprogesterone, aldosterone during crisis are useful for definite diagnosis.

*Treatment* – After blood collection for endocrine assays IV hydrocortisone is given 5mg/kg 6hourly. Later 12-15mg/m<sup>2</sup>/day of hydrocortisone and Fludrocortisone 100mcg/m<sup>2</sup> is recommended. Glucocorticoid doses adjusted in infection and stress. In secondary disease mineralocorticoids are not required.

### ***Congenital Adrenal Hyperplasia (CAH)<sup>15</sup>:***

CAH is an autosomal recessive disorder of biosynthesis of cortisol. Cortisol deficiency

leading to increase secretion on ACTH results in adrenocortical hyperplasia and excess accumulation of intermediate metabolites. Features of incomplete virilization in males and virilization in females is evident along with laboratory findings of mineralocorticoid excess or deficiency depending on the stage of enzymatic block. Genital abnormalities may not be detected in male neonates and the infants may remain undiagnosed, till they present with shock during first 2 weeks of life.

The most common cause of CAH is deficiency of 21-hydroxylase enzyme. In the classic severe salt-wasting form both aldosterone and cortisol are deficient. The clinical features are evident in the first few weeks of life presenting with vomiting, hypoglycemia, dehydration, hypotension and shock. Electrolyte disturbances like hyponatremia, hyperkalemia is evident. If untreated shock, cardiac arrhythmia and death may occur. Routine neonatal screening (which analyzes 17-hydroxyprogesterone level) is helpful for early diagnosis.

*Management* – Beside ABC stabilization replacement of steroid with hydrocortisone 25-50mg/m<sup>2</sup> IV is lifesaving. Patient with salt-wasting disease required mineralocorticoid replacement with fludrocortisone 0.1-0.3mg/day in two divided doses. Serum electrolyte should be monitored and treated accordingly.

***Pheochromocytoma<sup>16</sup> :***

Rare tumor arising from chromaffin cell. They may arise from anywhere along the sympathetic adrenal system and may be situated on adre-

nal or extra adrenal location. These tumor secrete epinephrine, norepinephrine and occasionally dopamine. Secretion of norepinephrine predominates. Higher level of free catecholamines in plasma and urine and higher concentration of metabolites like metanephrine, normetanephrine and VMA have been found. Some also secrete vasoactive intestinal peptide, ACTH, serotonin, calcitonin, parathyroid like hormone, neurotensin and many other hormones leading to various manifestations. Hypertensive crisis tachycardia, arrhythmia are life threatening manifestation.

Management is surgical removal of the tumor. Preoperative control of blood pressure is done with beta-adrenergic blocker e.g. phenoxybenzamine 0.5-1.9mg/kg/12 hour or prazosin 0.1-0.4mg/kg/day in 6 hourly divided doses, sodium nitroprusside infusion @1µg/kg/min and nitroglycerin. Tachycardia and arrhythmia is controlled by beta adrenergic blockers propranolol but only after beta adrenergic blockage is established; as blockage of vasodilating beta-receptors without blocking vasoconstricting beta receptor results in aggravation of hypertension. To minimize hypertensive crisis beta adrenergic blockers should be used 2 weeks before surgery. Volume expanders and fluid replacement are used to correct hypovolemia. Regular monitoring of blood pressure, tachycardia, arrhythmia, and blood sugar is mandatory. Hydrocortisone should be used when both adrenal glands are removed. Plasma catecholamines metanephrin should be mea-

sured after 3-6months and there after annually for 5 years even in normotensive patients.

**Diabetes insipidus<sup>17</sup> :**

Diabetes insipidus is a condition where there is passage of large volume of dilute urine. It may be

- i. Central diabetes insipidus (CDI) or
- ii. Nephrogenic diabetes insipidus (NDI) or
- iii. Primary polydipsia (Psychogenic or dipsogenic i.e. defect in third centre)

CDI may be i) idiopathic, ii)genetic - autosomal dominant/ X-linked/ Wolfram syndrome or iii) acquired from – trauma, infection, neoplasm (craniopharyngioma), histiocytosis X, Intracranial hemorrhage, toxins and drugs etc.

NDI may be i) genetic – X-linked recessive or autosomal recessive or ii) acquired from electrolyte disturbances, drug or renal disorders e.g. chronic pyelonephritis, chronic renal failure, sickle cell disease, polycystic kidney etc.

*Clinical features* – In CDI polyurea and polydipsia is abrupt. Children present with enuresis, disturbed sleep, failure to thrive; neurological manifestations exists and anterior pituitary hormone deficiency coexist in organic lesion.

NDI is usually acquired. Kidney stones are suggestive of hypercalcemia; muscle weakness with constipation suggests hypokalemia. Onset is gradual in primary polydipsia.

*Diagnosis* – It is done by confirming polyurea by measuring intake and output. Urine output > 2L/m<sup>2</sup>/day is suggestive of polyurea. A serum osmolarity of >300mOsm/kg with urine osmolarity <300mOsm/kg confirms DI. Water deprivation test is done only when intial serum osmolarity is <300mOsm/kg. Blood pressure and hydration should be monitored during the test. Serum and urine osmolality and APV level are measured. The table 2 indicates the interpretation of the test.

**Table 2:** Interpretation of water deprivation test

	<i>Serum Osm. (mOsm/kg)</i>	<i>Urine Osm. (mOsm/kg)</i>	<i>AVP levels</i>	<i>Interpretation</i>
Basal	<270	>800		Rule out DI
	>300	<300		Suspect DI
After water Deprivation	<280	<300		Primary polydipsia
	>300	>800		Rule out DI
		<300		DI
		300-800	Low	Partial CDI
			High	NDI
After vasopressin		increased by more than 2times		CDI
		Less than double		NDI

In CDI – X -ray skull, CT/MRI , anterior pituitary function test are suggested.

In NDI – USG of KUB, voiding cystourethrography, IVP, serum electrolytes, urinary electrolytes, blood gases, blood urea cratinine, calcium, phosphorus, alkaline phosphatase etc. are necessary.

*Management –*

1. Free access to water
2. CDI: DDAVP 0.25 µg/kg intranasally once or twice per day and is individualized accordingly. Antidiuretic effects should be adequate for atleast 8hours; adverse effect include hypertension, nasal congestion, abdominal distension etc.
3. NDI: treated with treatment of known cause, dietary salt restriction, diuretics like hydrochlorothiazide 1-2mg/kg/day along with amiloride or indomethacin 2mg/kg/day. High doses of DDAVP may be useful in some.

***Syndrome of inappropriate ADH :***

Occasionally seen as a complication of meningitis or pneumonia. Excessive water

reabsorption from distal convoluted tubule results in hyponatrimia, hypokalemia. Clinically there may be edema, altered sensorium and convulsion. Sodium is low but potassium is normal with inappropriate low urine output. Serum osmolarity is <265 mmol/l and simultaneous urine osmolarity is high (> 800mmol/l).

*Treatment –* Restriction of two third of maintenance fluid. Frusemide administration and hypertonic saline infusion over 2-3hours for hyponatrimia may be helpful.

***Cerebral salt wasting :***

It is also another important complication of brain injury manifested as increase in urinary sodium excretion with increase urinary volume. It differs from SIADH by increase urinary volume, increase urinary loss of sodium and dehydration. ADH level is low in cerebral salt wasting where as it is high in SIADH.

Table 3 shows the distinguishing features among SIADH, Cerebral Salt wasting and Central diabetes insipidus.

**Table 3:** Distinguishing features of siadh, cerebral salt wasting, and central diabetes insipidus <sup>18</sup>

<b>CLINICAL PARAMETER</b>	<b>SIADH</b>	<b>CEREBRAL SALT WASTING</b>	<b>CENTRAL DI</b>
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Vasopressin level	High	Low	Low

DI : diabetes insipidus: SIADH : Syndrome of inappropriate antidiuretic hormone secretion.

### **Metabolic (Electrolyte imbalance) and Inborn errors of Metabolism (IEM) <sup>19</sup>**

Often present as emergency situation. Inborn Errors of Metabolism (IEM) comprise a group of disorders in which a single gene defect causes a clinically significant block in a metabolic pathway resulting either in accumulation of substrate behind the block or deficiency of the product. All IEMs are genetically transmitted typically in an autosomal recessive or X-linked recessive fashion.

Routine neonatal screening in newborns may be helpful to detect IEM in some cases but it is impossible to screen the total huge number of causes of IEM. The non specific symptoms like poor feeding, vomiting, tachycardia, tachypnea, failure to thrive, lethargy, irritability, seizures, hypoglycemia, apnea and acidosis should not be ignored. The major categories are:

#### ***Urea cycle defects :***

[e.g. ornithine-transcarbamylase deficiency, carbamyl phosphate synthetase deficiency, transient hyperammonemia of the neonate, argininosuccinate synthetase deficiency (citrulinemia), argininosuccinate lyase deficiency, arginase deficiency, N-acetylglutamate synthetase deficiency]

Normally when dietary protein is digested it is broken down to amino acid and nitrogen. Patients with this disorder are unable to detoxify nitrogen. Severe hyperammonemia and respiratory alkalosis, with a typical onset after 24 hours of age are characteristic features. Dietary treatment is to provide only

the amount of protein the body can utilize. Diet consist of fruits, grains and vegetables with low protein.

#### ***Amino acid metabolism defects :***

[e.g. MSUD, homocystinuria, nonketotic hyperglycinemia, phenylketonuria (PKU), hereditary tyrosinemia, pyroglutamic acidemia (5-oxoprolinuria), hyperornithinemia-hyperammonemia-homocitrulinemia syndrome, lysinuric protein intolerance, methylene tetrahydrofolate reductase deficiency, sulfite oxidase deficiency]

They have similar presentation as organic academia but are a very heterogeneous group of disorders. Hereditary tyrosinemia can present in the neonate with a bleeding diathesis due to liver disease, or later in infancy with a renal Fanconi syndrome. The severe form of nonketotic hyperglycinemia presents as intractable seizures with hypotonia and hiccoughs.

MSUD, is a disorder where the body is unable to use amino acid isoleucine, leucine and valine and excess accumulation of these amino acids and their metabolites in blood, urine and sweat giving odor of maple syrup. It classically presents at the end of the first week of life with feeding difficulties, lethargy, coma, seizures and have characteristic odor in urine. Restriction to food containing isoleucine, leucine and valine is the suggestive treatment.

PKU is the most common disorder of amino acid metabolism. The body can not utilize amino acid phenylalanine and excess amount

accumulates in blood. Clinical manifestation is seizure, mental retardation, eczema. Treatment is phenylalanine restricted diet.

***Organic acidemias :***

[e.g. methylmalonic academia, propionic academia, multiple carboxylase deficiency, glutaric acidemia type II, isovaleric acidemia, HMG-CoA lyase deficiency, 3-methylcrotonoyl-CoA carboxylase deficiency, 3-hydroxyisobutyric acidemia]

Common symptoms and signs include vomiting, signs of encephalopathy, neutropenia and thrombocytopenia. These are caused by abnormal metabolism of proteins, fats or carbohydrates and are characterized by marked metabolic acidosis with ketosis, often with elevated lactate and mild to moderate hyperammonemia.

***Carbohydrate metabolism defects :***

[e.g. galactosemia, hereditary fructose intolerance, fructose-1,6-diphosphatase deficiency, glycogen storage diseases]

These are caused by inability to metabolize specific sugars, aberrant glycogen synthesis, or disorders of gluconeogenesis and usually manifest with hypoglycemia, hepatosplenomegaly, lactic acidosis or ketosis.

*Galactosemia* – where body can not break down galactose and is accumulated in the body leading to liver damage, kidney damage, stunted growth, mental retardation and cataract. Restriction of galactose and lactose from diet, elimination of milk protein; also meat should not be taken because of stored

galactose in them.

*Glycogen storage diseases* – require different treatment according to specific enzyme defect of the various types. Type 1 A is commonest. Clinical features are seizure, hypoglycemia, poor growth, hepatomegaly, high level of fat, uric acid and lactic acid in blood. Treatment is frequent meals with high complex carbohydrate which is beneficial to prevent low blood sugar.

***Fatty acid oxidation defects:***

[e.g. short chain acyl-CoA dehydrogenase deficiency (SCAD), medium chain acyl-CoA dehydrogenase deficiency (MCAD), long chain acyl-CoA dehydrogenase deficiency (LCAD), acyl-CoA deficiency]

They are known as beta-oxidation defects, characterized by hypoketotic hypoglycemia, hyperammonemia, and cardiomyopathy, and may present clinically with Reye's syndrome. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) is among the most common of all IEMs and may account for 5% cases of SIDS.

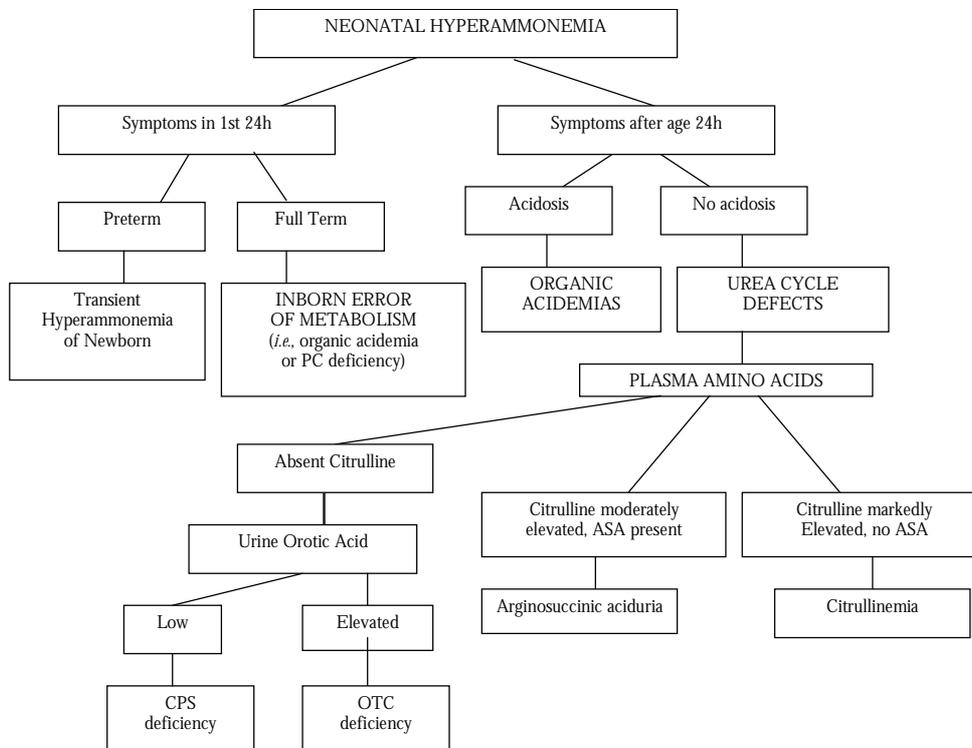
***Lysosomal storage disorders:***

(e.g., mucopolysaccharidosis, Tay-Sachs, Niemann-Pick disease, Gaucher's disease) are caused by accumulation of glycoproteins, glycolipids, or glycosaminoglycans within lysosomes in various tissues. They usually present later in infancy with organomegaly, facial coarseness and neurodegeneration and show a progressively degenerative course.

**Investigations :**

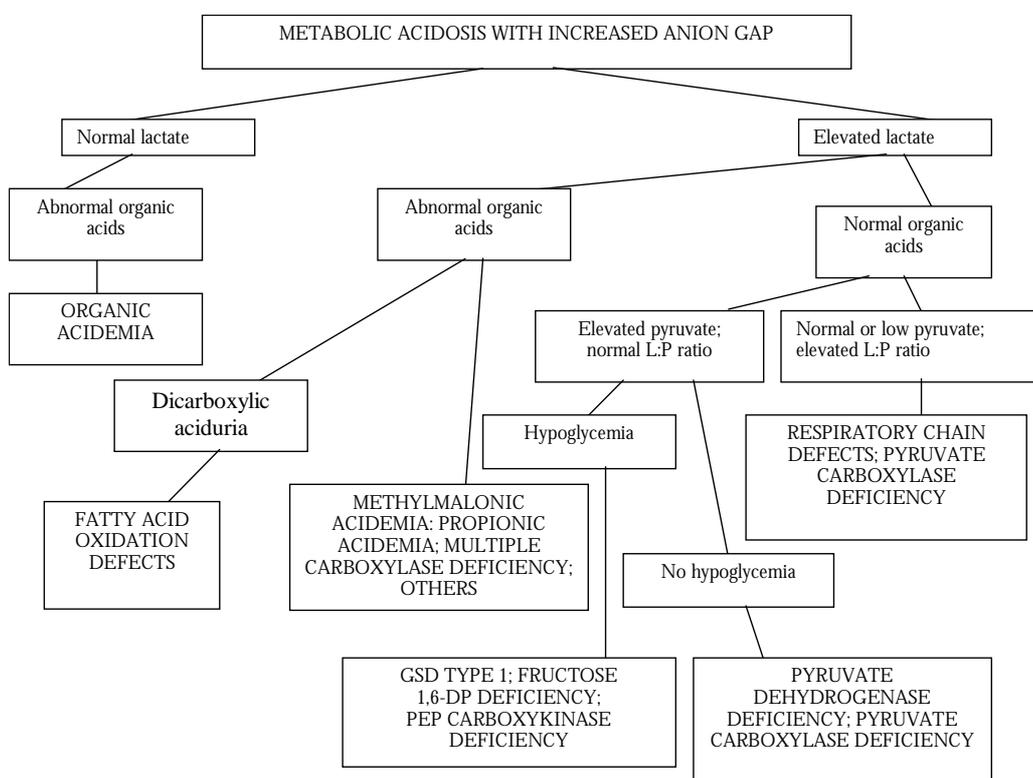
- (i) Blood: glucose, newborn screen, CBC with differential, platelets, pH and PaCO<sub>2</sub>, electrolytes for anion gap, liver function tests, total and direct bilirubin, PT, PTT, uric acid, ammonia. Blood ammonia, lactate and pyruvate, quantitative measurement of amino acid in plasma and urine.
- (ii) Urine: color, odor, pH, glucose, ketones, reducing substances (positive for galactosemia, fructose intolerance, tyrosinemia and others), ferric chloride reaction (positive for MSUD, PKU and others) and DNPH reaction (screens for alpha-keto acids), amino and organic acids.
- (iii) CSF: glycine (for nonketotic hyperglycinemia), lactate, pyruvate.
- (iv) Tissue biopsy: from liver, muscle, liver and bone marrow.
- (v) Specific DNA testing

Guthrie bacterial inhibition assay and Tandem Mass Spectrometry is helpful giving an indication for a disorder which can be confirmed by gas chromatography



**Figure 4: Flow chart for differential diagnosis of hyperammonemia <sup>20</sup>.**

(ASA, arginosuccinic acid; CPS, carbamyl phosphate synthetase; OTC, ornithine transcarbamylase; PC, pyruvate carboxylase). Chart is adapted from Burton BK: Pediatrics 102: E69, 1998



**Figure 5. Flowchart for evaluation of metabolic acidosis in the young infant <sup>20</sup>.**

(Fructose-1,6-DP, fructose-1,6-diphosphatase; GSD, glycogen storage disease; L:P ratio, lactate to pyruvate ratio) Chart is adapted from Burton BK: Pediatrics 102: E69, 1998.

**Management:**

- (i) Treatment defers for each specific disorder.
- (ii) Maintenance of hydration/nutrition/acid-base balance should be considered. IV fluid resuscitation is essential along with IV dextrose to prevent further catabolism. Oral intake should be stopped to eliminate protein, galactose and fructose.
- (iii) IV lipids after ruling out a primary or secondary fatty acid oxidation defect.
- (iv) All protein withheld for 48 to 72 hours, till an aminoacidopathy, organic aciduria or urea cycle defect has been excluded.
- (v) Significant acidosis (pH<7.22) is treated with a continuous infusion of NaHCO<sub>3</sub>.
- (vi) Elimination of toxic metabolites: Urgent treatment of hyperammonemia is essential.
- (vii) Hemodialysis is indicated in severe hyperammonemia and for intractable

- anion gap metabolic acidosis.
- (viii) Treatment of infection, thrombocytopenia etc.
- (ix) Cofactor replacement: biotin, vitamin B12, thiamine in selective cases.

### Sepsis

Sepsis is a syndrome of bacteremia with positive culture from blood, CSF or some other central fluid of the body. Neonatal sepsis can be (i) *early onset sepsis (EOS)* – where manifestation occurs before 72 hours, caused by organism prevalent in maternal genital tract or in delivery area and (ii) *late onset sepsis (LOS)* – which is manifested after 72 hours of delivery. Clinical manifestation – poor feeding, diarrhoea, vomiting, abdominal distension, jaundice, hypothermia/ hyperthermia, respiratory distress, apnea, cyanosis, oedema, hepatomegaly. Multiorgan system manifestation often results involving gastrointestinal, renal, respiratory, cardiovascular, neurologic, hematologic manifestations are common.

Systemic Inflammatory Response Syndrome (SIRS) – Sepsis is one of the causes of SIRS. When bacteria are not efficiently cleared by host defense mechanism a systemic inflammatory response is set into motion. If not diagnosed or treated early and aggressively, sepsis can lead to severe sepsis, septic shock, multiorgan dysfunction syndrome (MODS) and deaths.

SIRS is manifested by 2 or more of the following condition.

- (i) Temperature instability  $<35^{\circ}\text{C}$  or  $>38.5^{\circ}\text{C}$
- (ii) Respiratory dysfunction – tachypnea  $>2\text{SD}$  above mean for age. hypoxemia  $\text{PaO}_2 <70\text{mmHg}$  in room air
- (iii) Cardiac dysfunction - tachycardia  $>2\text{SD}$  above mean for age. delayed capillary refill  $>3\text{sec}$ . hypotension  $>2\text{SD}$  below mean for age.
- (iv) Perfusion abnormalities - urine output  $<0.5\text{ml/kg/hr}$

Sepsis screening should be done in all cases.

- (i) I/T ratio  $>0.2$
- (ii) Absolute neutrophil count  $>16,000$  or  $<5,000$
- (iii) Nutropenia  $>1750$
- (iv) CRP  $>1$
- (v) Micro ESR  $>15/\text{hr}$

A positive sepsis screen is indicated by  $\geq 2$  abnormal above results. It has a sensitivity of 93% and positive predictive value 39%.

Supportive test for sepsis include radiologic evidence of pneumonia, ileus, NEC and arterial blood gas analysis.

Diagnosis of sepsis is confirmed by demonstration of microorganism in a tissue or fluid; culture from blood, CSF etc; antigen detection in urine and CSF; maternal or neonatal serology (syphilis, toxoplasmosis).

Golden rules in management of sepsis is initiation of urgent and immediate treatment without loss of time; parenteral therapy

should begin immediately after sepsis screen and blood C/S; bactericidal antibiotic is preferred over bacteriostatic drug. Supportive therapy for fluid electrolyte and acidbase monitoring, maintenance of blood sugar, thermoregulation, oxygen for hypoxia/ventilatory support, blood transfusion/platelet transfusion in selected cases; anticonvulsant for management of seizure; adjuvant therapy e.g. IVIG, granulocyte transfusion; cytokine (CK) therapy with G-CSF; GM-CSF, TNS-á may be helpful.

Importance of exclusive breast feeding and maintenance of strict asepsis by six steps of effective handwashing should be kept in mind.

### **Formula Mishaps**

Inappropriate mixing of milk powder formula and water can give rise to overdilution of concentrated liquid or premixed formula which can result in life-threatening electrolyte disturbances and hyponatremia, seizures etc.

### **Intestinal Catastrophes**

Vomiting in neonatal period indicates pathologic process. It can be the manifestation of gastroenteritis, severe GERD or surgical causes. Bilious vomiting almost always indicates surgical cause. Malrotation with midgut volvulus, toxic megacolon, necrotizing enterocolitis, hypertrophic pyloric stenosis, tracheoesophageal fistula, omphalocele, congenital diaphragmatic hernia, testicular torsion are important causes.

*Malrotation with midgut volvulus:* presents in the first month of life with history of bilious

vomiting. Diagnosis is done from abdominal radiographs and USG. Management includes fluid replacement, NG tube placement, pediatric surgical consultation.

*Toxic Megacolon:* life threatening presentation of a patient with Hirschprung's disease. Failure to pass meconium in the first 24 hours of life with history of constipation is highly suspicious of Hirschprung's.

Presenting symptoms are poor feeding, vomiting, irritability, abdominal distention, hematochezia and shock. Enterocolitis (toxic megacolon) may develop in these patients and may simulate NEC. X-ray and USG abdomen demonstrate an enlarged or dilated section of colon. Along with Stabilization of ABC's, fluid resuscitation, broad-spectrum antibiotics, these patients require critical care management and surgical consultation.

*Necrotizing Enterocolitis:* classically disease of premature and LBW infants due to immaturity of gut. Perinatal hypoxia, active resuscitation, assisted ventilation, apnea, RDS, acidosis, shock, umbilical artery chaperization, early and large volume feeding are predisposing factors of NEC. Exact etiology is not known. Multifactorial etiology may be responsible. Intestinal mucosal injury from ischemia of mesenteric vessels due to "diving reflex" which diverts blood to vital organ may initiate the pathogenesis. Role of bacterial toxins from anaerobic organism and platelet activating factor (PAF) and other inflammatory mediators have also been well discussed. Mucosal necrosis and bleeding

results in intestinal obstructive features with bilious vomiting and abdominal distension, production of hydrogen gas from undigested food which enter the mucosal breach leading to pneumatosis intestinalis (air in the bowel wall). If not diagnosed and managed early end result is intestinal perforation, peritonitis, systemic endotoxemia and shock.

Investigation- serial x-ray abdomen every 12hours, sepsis screen, monitoring of electrolyte should be done for diagnosis and to know the prognosis of the disease.

Management – early withheld of oral feed, IV fluid, IV broad spectrum antibiotics, slow continuous gastric suction is indicated. IV metronidazole 7.5mg/kg 2times daily is advocated in anerobic infection. Supportive therapy is suggested with FFP, platelet, blood and other supportive measures. TPN may be

required in selective cases. With improvement gradual introduction of dilute enteral feed (breastmilk) is suggested. Surgical management is indicated in perforation, necrosis of bowel wall and peritonitis.

Hypertrophic pyloric stenosis, tracheoesophageal fistula, omphalocele, congenital diaphragmatic hernia, intususception, and other surgical causes and poisoning/toxins and seizures will be discussed in detail in coming issues of this journal.

The mnemonic “*THE MISFITS*” is a helpful tool which can be readily used by the general pediatricians and clinicians in the Emergency department for correct approach and diagnosis to the most common neonatal emergencies.

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## MRI Department, Institute of Child Health, Calcutta

### How long it is open?

It is open from 9 a.m. to 7pm on weekdays. On Sunday, it is open from 9am to 1pm.

### What is the usual time required for MRI scan?

About 30 minutes.

### How an appointment is made?

It is usually done at the reception of MRI department by personal visit or by telephone. Telephone No.s (033)2289-3526 and (033)6526-6969.

### What preparation is needed for MRI?

Usually no preparation is needed. For MRCP study 4-6 hours fasting is needed. For children, oral sedation is usually required. In some hyperactive, restless patients anesthesia is needed. We have fully equipped setup for anesthesia and extremely competent anesthetist for such patients. About 6 hours of fasting is needed prior to anesthesia.

### Apnea of Prematurity (AOP)

Rafiqul Hassan

*RMO-cum-Clinical Tutor, Department of Neonatology, Institute of Child Health, Kolkata.*

Uninterrupted breathing is vital for life. The transition from fetal to neonatal life requires infants to develop a stable respiratory pattern for successful gas exchange to occur. However in preterm infants immaturity of respiratory control almost invariably results in respiratory pauses of variable duration. If it's of shorter duration (<15 sec) usually it is not harmful – termed as periodic breathing and it is self limiting<sup>1</sup>. But if it is for longer duration, it can have serious consequences.

Apnea is defined as cessation of breathing for longer than 20 sec duration or shorter duration if accompanied by cyanosis or bradycardia<sup>2</sup>.

#### Types of Apnea<sup>3</sup>

- (i) *Central apnea* – characterized by total cessation of inspiratory efforts with no evidence of obstruction.
- (ii) *Obstructed apnea* – In obstructed apnea, the infant tries to breathe against an obstructed upper airway resulting in chest wall motion without airflow throughout the entire apnea.
- (iii) *Mixed apnea* – consists of obstructed

respiratory efforts usually following central pauses and is probably the most common type of apnea.

Mixed apnea typically accounts for more than half of all long apneic episodes followed in decreasing frequency by central and obstructed apnea.

Apnea in preterm infants is usually related to immaturity of central nervous system and is called apnea of prematurity (AOP)<sup>4</sup>. It can also occur secondary to other causes and is a common manifestation of most neonatal diseases. Secondary causes of apnea<sup>(4)</sup> include:-

- (a) *Temperature instability* – Hypothermia and hyperthermia.
- (b) *Neurological* – birth trauma, drugs, intracranial hemorrhage, seizures, CNS infection, perinatal asphyxia, congenital myopathies, neuropathies.
- (c) *Pulmonary* – Respiratory distress syndrome (RDS), Pneumonia, Pulmonary hemorrhage, pneumothorax, tracheal obstruction by neck flexion.
- (d) *Cardiac* – Congenital cyanotic heart disease,

hypotension / hypertension, PDA, Congestive heart failure.

- (e) *Gastrointestinal* – Gastroesophageal reflux, abdominal distension. Necrotizing enterocolitis (NEC).
- (f) *Hematological* – Anaemia.
- (g) *Metabolic* – Hypoglycemia, acidosis, hypo/hyponatremia, hypocalcemia. Inborn error of metabolism (IEM).
- (h) *Infections* – Sepsis, pneumonia, meningitis, NEC.

Apnea of prematurity is a diagnosis of exclusion and should be considered only after secondary causes of apnea have been excluded. Common causes of secondary apnea include sepsis, pneumonia, asphyxia, temperature instability and anaemia.

Incidence of AOP is inversely proportional to gestational age. It varies from 10% in infants born at 34 weeks of gestation to more than 60% in infants born at < 28 weeks of gestation<sup>5</sup>.

Apneic spells generally begin at 1 or 2 days after birth; if they do not occur during the first 7 days, they are unlikely to occur later. Apneic spells persist for variable periods postnatally and usually cease by 37 weeks' gestational age<sup>5</sup>.

Pathophysiology<sup>6</sup> : There are 2 aspects

- (i) Cessation of breathing.
- (ii) Response to cessation of breathing.

Basic function of Respiratory Control System

is to – maintain normal partial pressure of oxygen (PO<sub>2</sub>), partial pressure of carbon dioxide (PCO<sub>2</sub>) and hydrogen ion concentration (pH) in the face of large changes in O<sub>2</sub> consumption and CO<sub>2</sub> production. This complex control involves –

- (i) Central brainstem processing.
- (ii) Central and peripheral chemoreceptors.
- (iii) Irritant and mechanoreceptors.
- (iv) Endogenous neuroregulators – inhibit or stimulate respiration.

The foetal response to hypoxia is decrease in respiratory effort, response to hypercapnea is an increase in breathing depth but not frequency. These foetal reflexes change over the first few weeks of life to become more like the normal adult reflex<sup>6</sup>.

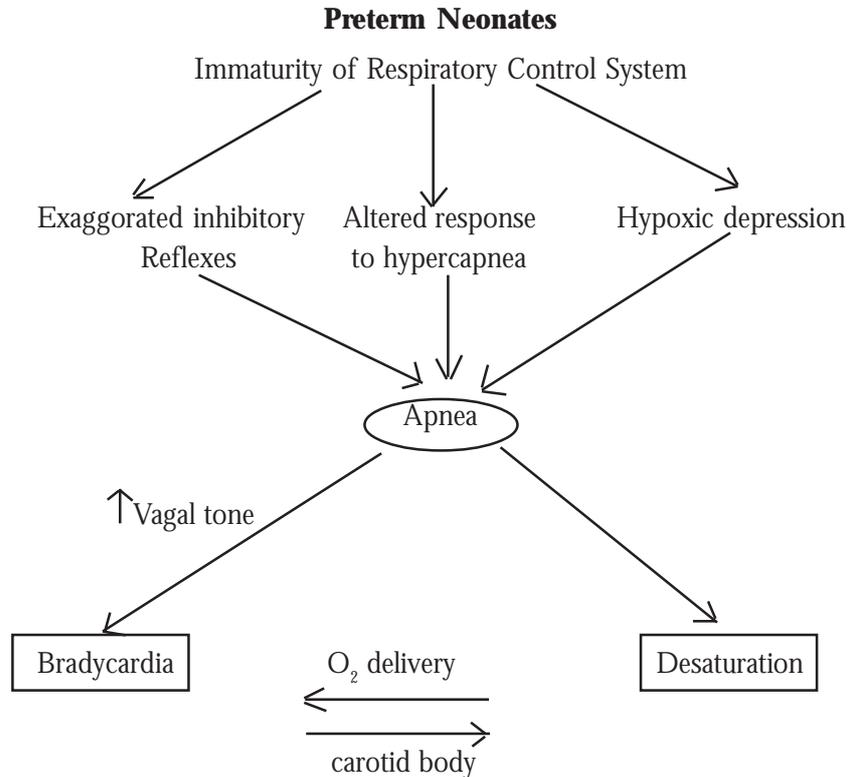
AOP is thought to be secondary to immaturity of brainstem centres that regulate breathing<sup>1</sup>.

### **Consequences of Apnea**

Immediate consequences are hypoxia, hypercarbia, bradycardia, and changes in blood pressure (Fig 1). Delayed consequences are morbidity and mortality, irreversible neurological damage, blindness from bilateral retrolental fibroplasia sensorineural deafness and retardation. However, it is unclear if severe sequelae relate to apnea alone and linking recurrent apneas with poorer neurodevelopmental outcome is difficult<sup>4, 6,7</sup>.

### **Monitoring :**

All babies less than 34 weeks gestation should



**Fig 1. Consequences of Apnea**

be monitored for at least in the first week of life or till absence of apneic episodes for at least 7 days<sup>5</sup>.

- (i) Pulse oximeter : commonly used for monitoring of apnea. They detect changes in heart rate and / or saturation due to apneic episodes.
- (ii) Other apnea monitors include – movement sensors.
- (iii) Thoracic impedance based monitors.
- (iv) Respiratory inductive plethysmography.
- (v) Magnetometer.

Apnea monitors based on chest wall movements are likely to miss obstructive apnea. Monitors with facilities for measuring heart rate and oxygen saturation would be more useful in the monitoring of significant apnea in preterm infants<sup>8</sup>.

**Management**

The outline of the management is shown in Fig 2.

**Emergency treatment :**

- (i) Maintain airway, breathing, and circulation.
- (ii) Neck should be positioned in slight

- extension.
- (iii) Oropharynx gently suctioned, if required – Avoid vigorous suctioning.
  - (iv) Tactile stimulation.
  - (v) Oxygen by head box or nasal Canula.
  - (vi) If does not respond to tactile stimulation, ventilation with bag and mask using 100% oxygen.
  - (vii) If this fails, mechanical ventilation.

### **Clinical Evaluation**

After stabilization, the infant should be evaluated for a possible underlying cause. History should be reviewed for possible causes of secondary apnea including perinatal asphyxia, maternal drugs, neonatal sepsis. The infant should be examined for temperature instability, hypotension, jaundice, pallor, cardiac murmur for PDA and poor perfusion.

### **Investigation**

To exclude common causes of secondary apnea. Investigations should be considered include blood glucose, hematocrit, electrolytes, Sepsis screen, blood culture, arterial blood gas, Chest X-ray, abdominal X-ray, USG of Brain and other investigation depending on the history and physical examination.

### **Specific Measures for AOP**

Pharmacotherapy : Methylxanthine have been the mainstay of pharmacological treatment of AOP. <sup>(9)</sup> They act by –

- (i) Stimulating respiratory centre.
- (ii) Inhibiting adenosine receptors – that leads to increase minute ventilation, improve CO<sub>2</sub> sensitivity, decrease hypoxic depression of breathing, enhance diaphragmatic activity and decrease periodic breathing.

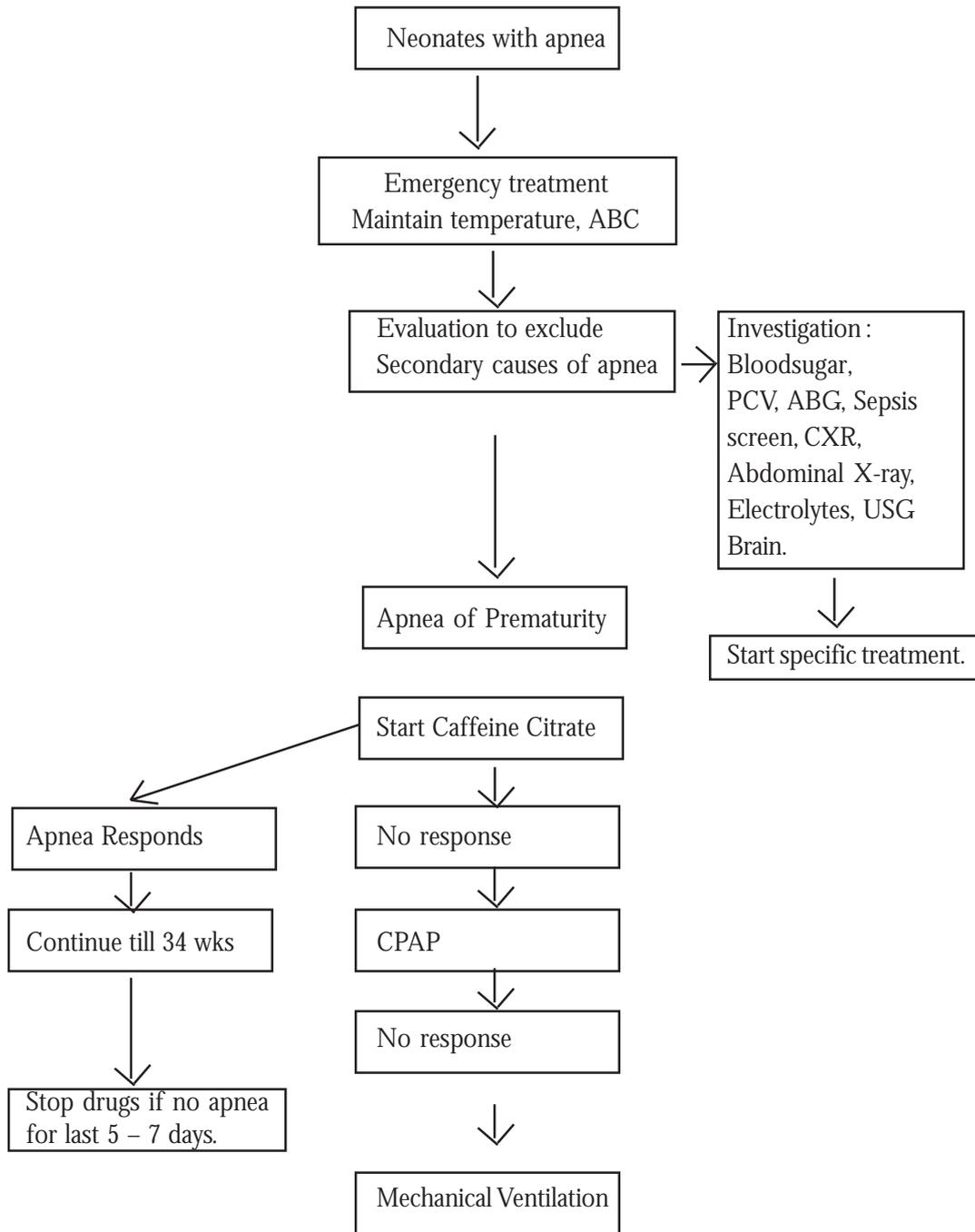
Methylxanthines used are –

- (i) Aminophyline – It is given as a loading dose of 5–7 mg/kg IV followed by maintenance dose 1.5 – 3 mg/kg every 6–8 hrs.
- (ii) Caffeine Citrate – drug of choice for AOP. It is given as a loading dose of 20 mg/kg orally or intravenously over 30 min. followed by maintenance dose of 5 to 8 mg/kg in one daily dose beginning 24 hours after the loading dose.

Caffeine is generally discontinued at 34 to 36 weeks postnatal age if no apneic spells have occurred for 5 to 7 days<sup>10</sup>.

### **Continuous Positive Airway Pressure (CPAP)**

CPAP usually administered using nasal prongs (NCPAP) is also an effective treatment of AOP and is typically used when apneic episodes persist despite optimal methylxanthine therapy. A CPAP of 5 cm H<sub>2</sub>O (4–6) is usually used. They usually decrease obstructive and mixed apnea. Adverse effects of CPAP include barotrauma, abdominal distension, feeding intolerance and local nasal irritation. <sup>(11)</sup>



**Fig 2. Algorithm for management of Neonatal apnea.**

Mechanical Ventilation – The infant should be ventilated if both pharmacotherapy and CPAP have been tried and significant apneas continue to occur. This method is effective in all forms of apnea. Stop drugs if no apnea for last 5 – 7 days. Mechanical Ventilation.

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## Management of Childhood Hypertension

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The incidence of hypertension in children is increasing more so because of increasing awareness of measuring blood pressure in children. Most cases of hypertension in children are secondary and treatable causes can be found in many. The incidence of essential hypertension is increasingly being identified in children nowadays. All children above 3 yrs should have their BP measured atleast once annually.

According to the 1996 task force hypertension is defined with respect to age, sex and height.

- (i) Blood pressures (systolic or diastolic) more than 95th centile is labeled **hypertension**.
- (ii) BP between 90th and 95th centile is **high normal**.
- (iii) BP more than 99th centile with target organ damage is **hypertensive emergency**.
- (iv) BP more than 99th centile without target organ damage is **hypertensive urgency**.

A standardized method of recording BP is of utmost importance. Upper right arm used with the child sitting erect and arm supported at heart level. The child should be relaxed and

comfortable. Mercury sphygmomanometer still preferred. The bladder cuff width should be 40% of the midarm circumference and should encircle 80-100% of the arm circumference. BP should be high on atleast 3 consecutive measurements at weekly intervals. It should be recorded twice on each occasion after 3-5 minutes rest. Blood pressure standards are based on gender, age and height.

Ambulatory Blood pressure monitoring (ABPM) is being increasingly used in some centres as a tool for investigating hypertension. The device is simple, portable and can be programmed to measure blood pressure timely round the clock in home setting with normal activity. It has the advantage of ruling out "white coat hypertension", gives more accurate BP readings by giving multiple readings, assess circadian BP profile and useful in hypertensive children taking antihypertensive medications.

### **Evaluation**

If BP recording > 90th centile for age/sex/Ht repeat BP measurement atleast on 3 occasions weeks apart. If BP recordings persist between 90-95th centile without any symptoms- follow-up.

If symptomatic or with target organ damage with BP recordings between 90-95th centile or recordings > 95th centile - always evaluate. Evidence of end organ damage should be seen in the form of encephalopathy, ocular changes, echocardiography suggestive of LVH.

### **Causes**

Secondary causes like renal parenchymal disease account for 60-80% and renovascular causes in 5-25%. Therefore every effort should be made to rule out these causes before looking for endocrine ones (Table 1).

### **Phase I Investigations**

Complete blood counts, urea, creatinine, sodium, potassium (atleast on 2 occasions), uric acid, calcium, urine routine and microscopy, ECHO/ CXR and ECG, renal ultrasonography. If urine microscopy abnormal (proteinuria, hematuria, casts)- consider ASLO, C3, ANA, anti dsDNA, renal biopsy- consider AGN, chronic glomerulonephritides, lupus nephritis. If on USG hydronephrotic or scarred kidney- consider MCU, DMSA to rule out obstructive/ reflux uropathy. If on USG normal or small kidney- consider doppler USG, captopril primed DTPA, MRA, DSA, conventional renal angiography to rule out renal artery stenosis.

If all phase I investigations are negative-

### **Phase II investigations**

Lipid profile, plasma cortisol (morning 8:00 AM sample), DOCA levels, TSH, urinary 24 hours catecholamines, MRI for adrenals/ MIBG scan. If persistent hypokalemia- consider plasma aldosterone levels, plasma

renin activity. If all these investigations are negative- consider essential hypertension as a likely diagnosis.

### **Treatment of Hypertension**

All patients with BP >95th centile with target organ damage should receive antihypertensives irrespective of the cause. Patients with BP between 90-95th centile or > 95th centile without target organ damage should be managed with non-therapeutic measures initially for 3-6 months and if these measures are ineffective consider antihypertensives. If BP more than 99th centile at presentation even without target organ damage consider antihypertensives.

#### ***Non pharmacological methods:***

Salt restriction 1meq/kg/day. Regular exercise 30-60 minutes/day for atleast 3 days per week. Restrict fatty, junk food.

#### ***Pharmacotherapy:***

ACE inhibitors like enalapril, lisinopril, ramipril should be considered as the first line drugs in patients with renal parenchymal diseases like glomerulonephritides, lupus, mild to moderate CRF, obstructive uropathy. Enalapril can be given in doses of 0.2-1 mg/kg/day. However ACE inhibitors should be avoided till a renovascular cause has been sufficiently ruled out. Patients with transient hypertension like poststreptococcal glomerulonephritis can be managed with diuretics like frusemide (2-8 mg/kg/day) alone. Diuretics like frusemide and thiazides can be used for patients with renal conditions associated with fluid retention like nephrotic syndrome, mild to moderate chronic renal failure. If the hypertension is not controlled

on these drugs add either beta blockers like atenolol (1-2 mg/kg/day single dose) or calcium channel blockers like amlodipine (0.1-0.5 mg/kg/day). Plain nifedipine should not be used for management of chronic hypertension. It can be used for control of BP in hypertensive urgency without target organ damage. It should not be used in patients with encephalopathy as it may cause further damage and predispose to bleed by sudden reduction of BP. If the hypertension is not controlled on maximum doses of these drugs consider alpha receptor blocker like prazosin (30-150 µg/kg/dose in 6-8hrly doses) or central adrenergic agonist like clonidine (15-30 µg/kg/day in 6-8hrly doses). Managing Hypertensive emergency can be very challenging. It can be managed with sodium nitroprusside drip at doses of 0.5-5 µg/kg/min for the first 48-72 hours and further control can be managed with the above-mentioned drugs. IV Labetalol infusion (1 - 3 mg/kg/hr) is also the drug of choice in hypertensive emergency. The aim should be to reduce BP gradually, one third of the planned reduction over first 6 hours, next third over 12-36 hours and the last third over 36-72 hours. Once BP is controlled to a safe level maintenance oral medications should be gradually added according to the underlying cause. Drugs like Nifedipine, ACE inhibitors and B blockers are useful. Hydralazine, clonidine and prazosin may be used. All possible efforts should be made to identify the cause of hypertension and treat the underlying etiology.

**Table 1. Salient causes and features of pediatric hypertension**

<b>Cause</b>	<b>Presentation</b>	<b>Investigations</b>
Glomerulonephritis	If acute transient HTN, edema, proteinuria, hematuria	ASO, C3, Renal biopsy
Lupus nephritis, vasculitis	Rash, joint pains, edema, hematuria	ANA, ANCA, anti dsDNA
Renovascular (RAS, aortoarteritis)	HTN, abdominal bruit, asymmetric pulses	USG Doppler, captopril DTPA, MRA, Angiography
Coarctation of aorta	Upper limb hypertension	ECHO, CXR
Reflux/ obstructive uropathy	Urinary stream abnormalities/ antenatal detection, UTI	MCU, DMSA, DTPA
Phaeochromocytoma	Headaches, palpitations, sweating	24 hrs urinary catecholamines, MIBG/MRI
Congenital adrenal hyperplasia (11β and 17α)	HTN around puberty	Plasma cortisol, DOCA
Primary hyperaldosteronism	HTN, hypokalemia, weakness, cramps	Aldosterone, PRA levels
Glucocorticoid remediable aldosteronism	HTN, hypokalemia, alkalosis	PRA levels, aldosterone suppressed by dexamethasone
Liddle's syndrome	Early onset HTN, hypokalemia, cramps, alkalosis	Aldosterone, PRA levels, HTN responds to triamterene and amiloride
Pseudohypoaldosteronism type 2	HTN, hyperkalemia	Aldosterone normal, PRA levels

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## **Overview of Atopic Dermatitis from Indian perspective**

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### **Epidemiology of Atopic Dermatitis in India**

Overall prevalence of AD is low in India. However, AD comprises one third of total pediatric skin disease in major institutes and tertiary referral centers. The incidence of AD is on the rise. Majority of patients have milder disease (80-85%), while moderate and severe forms are seen in 7-8% respectively. Incidence of AD in adult is quite low<sup>1-7</sup>.

### **Atopic Dermatitis: Clinical Diagnosis and Diagnostic Criteria**

The diagnosis of Atopic dermatitis (AD) is based on a constellation of signs and symptoms as there is no laboratory 'gold standard'. It depends to a great extent on clinical experience and expertise of a doctor dealing with cases of AD. There are different diagnostic criteria viz., Hanifin and Rajka's and UK working party's diagnostic criteria<sup>8-17</sup>. In India, simple clinical criteria of UK working group are easy to apply in day to day practice while Hanifin and Rajka's criteria are recommended for research purpose.

### **Severity scoring of atopic dermatitis :**

A number of severity indices are based on

the assessment of clinical features of the disease activity. The three most tested 'objective' clinical indices are the SCORAD index, the Eczema Area and Severity Index (EASI) and the Six Area, Six Sign Atopic Dermatitis index (SASSAD).

For day to day clinical use in primary or secondary care, the Three Item Severity score, based on the assessment of erythema, oedema/papulation and excoriations (maximum score 9) is very useful. We need to decide how to grade of mild, moderate and severe type of AD as these criteria will be used for algorithmic treatment plan. These criteria need to take into consideration extent of disease as well<sup>5-7</sup>.

### **Relevant investigations in atopic dermatitis :**

The diagnosis of atopic dermatitis (AD) is rarely aided by investigations. Estimation of total serum IgE, specific radioallergosorbent tests (RASTs) and prick tests usually serve to confirm the atopic nature of the individual. It is possible that such confirmation may be of value occasionally in adult onset dermatitis. However, one must remember that 20% of

patients with AD have normal total IgE levels and negative RASTs, whereas 15% of apparently healthy individuals may have raised IgE<sup>9-12</sup>.

*Value of investigations for trigger factors of atopic dermatitis* – The value of investigations in identifying trigger factors in AD is disputed. How helpful are the specific RASTs to food items or aeroallergens for disease management is unclear. However, it is suggested if they are negative, allergy is unlikely. It may be that skin prick test positivity to food allergens in young children with severe AD and a high serum IgE indicate a high risk of developing allergic respiratory disease later. Patch testing may also help to identify a contact allergen responsible for deterioration of skin condition, particularly in adults. The ‘atopy patch test’ for aeroallergen and foods in AD and skin application food test (SAFT) in the management of IgE contact urticaria in children with AD are recommended by some authorities<sup>13-17</sup>.

### **Management**

There is a difference between Evidence based medicine (EBM) and guidelines. EBM is based on systematic literature reviews; in particular considering those publications on therapeutic interventions which are double-blind placebo-controlled or head-to-head comparisons with sufficient statistical power. Guidelines may or may not be evidence based. In the words of Hywel Williams “guidelines are just that guidelines”.

Guidelines help general dermatologists, pediatricians and family physicians to have a consistent approach in order to optimize the treatment outcome in Atopic Dermatitis (AD). In India, we have very limited published data on different aspects of AD (except on epidemiology). Thus the next best option is to have experts in this field to bring out a consensus algorithmic approach in the treatment of AD. ISPD has taken the initiative and invited experts in this field to prepare this guidelines.

The first half will discuss individual therapy and its place in the treatment of AD. The second half will outline the treatment algorithm for mild, moderate and severe type of AD.

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore these guidelines should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

This report reflects the best available data at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

**Topical steroids :**

Topical corticosteroids have been the mainstay of treatment for atopic dermatitis and will continue to have an important role in its management(19-22).

- (i) Topical steroids are first line of therapy in AD
- (ii) Very potent steroids can be given to children with severe AD for 7-10 days pediatric age group
- (iii) Moderate potency steroids to be used only for short time (10-14 days), do not use on face and genitals
- (iv) In very severe
- (v) Use mild steroids on face and genitals
- (vi) Long-term application of a potent preparation increases the risk of unwanted local effects on the skin. Apply steroids intermittently or use steroid sparing agents for long term use.
- (vii) Apply steroids twice/once daily
- (viii) Apply adequate amount to cover the treatment site with a thin, invisible layer of medicine.
- (ix) Proper and adequate application emollients will help to reduce the potency and quantity of TC usage
- (x) Taper topical steroid potency wise rather than suddenly stopping them, to prevent sudden flare up
- (xi) If moderate to potent TC's need for long term (>4weeks), they should be used intermittently(once/twice weekly)
- (xii) Taper TC potency wise (on an average 2-3 weeks), rather than suddenly stopping them, to prevent sudden flare.
- (xiii) Avoid steroid –antibiotic combinations in routine practice, and if required prescribe for short period i.e. 2-3 weeks.

Topical Calcineurin inhibitors TCIs (Tacrolimus and pimecrolimus)<sup>23-29</sup>.

- (i) It is recommended in patients of AD who are unresponsive to or intolerant of other conventional therapies.
- (ii) TIMs should be applied over the affected areas twice daily.
- (iii) Both 0.03% and 0.1% formulations are recommended for the use in adults, whereas only 0.03% formulation is recommended for use in children aged 2-15 years.
- (iv) Often first line therapy for lesions over the face and intertriginous areas and genitalia
- (v) Useful in early flare
- (vi) Continue treatment till disease clears (approximately 1 month), continue later as per the need
- (vii) Useful for maintenance therapy
- (viii) Long term intermittent treatment can be continued for 1-2 years.
- (ix) They should not be used under occlusion, in children younger than 2 years, in pregnant ladies and nursing mothers.
- (x) They should not be used in Netherton's syndrome, over mucous membranes

- (x) The long term effect of these compounds on immune system is not known and hence they should not be used in patients with compromised immune system.
- (xi) During treatment it is better to avoid direct sunlight exposure as far as possible<sup>30-36</sup>.

***Role of oral antihistamines in AD :***

- (i) There is little evidence that sedating or nonsedating antihistamines are effective in relieving itch associated with AD
- (ii) Sedative antihistamines may have a role for patients in whom pruritus interferes with sleep.
- (iii) Antihistamines may be prescribed when urticaria or allergic rhinitis co-exists along with atopic dermatitis.

***Role of oral corticosteroids in the management of AD :***

- (i) Oral or intramuscular corticosteroids are neither safe nor practical except for brief, 1-week courses to control severe
- (ii) Short reducing courses of oral prednisolone (rapidly excreted) can be given for controlling severe AD. Reduced rate of growth (height) may occur while the child is taking the medication.

***Role of phototherapy in treatment of AD:***

- (i) The treatment is best introduced after the stabilization of an acute flare
- (ii) Children need to be at least old enough to comply with phototherapy.
- (iii) NB-UVB (311 nm) is superior to

conventional broadband UVB therapy  
(iv) NB-UVB therapy is preferably administered thrice a week, although five times weekly may achieve faster response<sup>32-40</sup>.

(v) Narrow-band UVB therapy is safe and effective therapy for older children with AD.

(vi) In acute flares, it is best instituted after initially controlling the process with systemic agents. Relapse after discontinuing NB-UVB therapy is frequent. ( should we recommend it at all in acute flare ?)

Azathioprine and Cyclosporine in Atopic dermatitis

Systemic immunosuppressives - when to use?

Severe recalcitrant atopic dermatitis, refractory to conventional therapies

Erythroderma due to atopic dermatitis

Disease causing significant compromise in Quality of life (QOL)

***Steroid dependent patient :***

- (i) Usual starting dose – 50mg twice daily in adults – 2.5mg/kg/day in children
- (ii) CBC, Liver functions – pretreatment and every month thereafter
- (iii) Duration of therapy – up to 12-16 weeks
- (iv) Improvement is slow -usually at 4-6 weeks; peak efficacy at 3 months or longer

***Cyclosporine in Atopic Dermatitis :***

- (i) Doses – 3-5mg/kg/day

- (ii) Symptomatic relief within 2 weeks
- (iii) Relapses on cessation of therapy occur
- (iv) Short-course therapy (12 weeks) is usually
- (v) Few patients may require(37-41)
- adequate for most patients to prevent cumulative exposure to the drug
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## View Point

### The Concept of Hearing Screening and Basic Hints for Parental Approach-Personal Practice

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Unlike many disabling conditions hearing impairment does not have any overtly visible feature to the common person and sometimes even to doctors and other professionals. Hearing impairment is often mistaken as mental retardation. The invisible nature of this disabling condition strikes the heart of communication system used by humans and affects not only the receptive and expressive language but also social, emotional and cognitive development.

One feature of hearing impairment not widely appreciated is the severity of sensory loss. It can vary from fluctuating temporary conductive loss of minor degree only slightly affecting the linguistic and educational progress to severe to profoundly deaf child failing to acquire proper speech and language. Other important feature of hearing loss is to rightly define the frequency of loss. Distortion or omission of certain sounds due to specific frequency loss leads to unclear speech and these children are often misdiagnosed as slow learners and/or educationally subnormal children.

Due to hidden nature of the condition, and

its irreversible damage it causes on child's behavior, speech and language development, it is particularly important to detect congenital hearing impairment during early critical period of language development. Although the need for early detection is well defined the current practice for neonatal hearing screening is far from ideal in our setup.

Any screening procedure is likened to fishing a flowing stream with a net, the size of which must be suited to the intended catch. Too fine a mesh size may lead to unnecessary large quantity catch and a waste of time in sorting them out. Conversely, large mesh may fail to take the largest desired fish.

An economical, less time consuming and a compromised approach is called for best results. A good hearing screening programme should have high SENSITIVITY (picking up all true positives) together with high degree of SPECIFICITY (releasing all true negatives). The formula for quantifying these two descriptors of validity are:

Sensitivity =  $a/a+c$  and specificity =  $d/b+d$  where (table -1)

a=impairment present test positive:  
 b= impairment absent but still test positive:  
 c= impairment present ,test negative :  
 d=impairment absent ,test negative.

Screen result	Verified disease state	
	Disea sestate	No disease
Fail(positive)	True positive(a)	False positive (b)
Pass(negative)	False negative(c)	True Negative(d)

Sensitivity=  $a/a+c$   
 Specificity =  $d/d+c$

An ideal screening test should be 100% sensitive and specific. A realistic objective would be to achieve 90% specificity and sensitivity where one in 10 with impairment would be missed and one in 10 caught in the net will have normal hearing. The adverse consequences of those with impairment missed by the screen will be greater than those incorrectly caught<sup>1</sup>.

Clear identification must be made between a test of screening and a test of confirmation of hearing loss. A screening test does not and should not confirm the presence or degree of hearing loss. It should be rather relatively simple and economical means to suspect a disorder and filter it out from the population along pathway to confirmation.

Unfortunately in our set there is no defined protocol for neonatal hearing screen. It is generally practiced on an individual case basis and some referrals from the high risk register. Ringing the bell or clapping is no more

advised to make any conclusion on a babies hearing .

Table -1 lists the sounds which are known to have indefinable broad band frequency spectra and not recommended for screening tests.

**Table-1 Sounds of broad frequency spectrum unsuitable for hearing screening purposes.**

- 
- (i) Stirring a cup with a spoon
  - (ii) Crinkling a tissue paper.
  - (iii) Whispered or voiced speech
  - (iv) Clapping /ringing the bell by the side of ears.
  - (v) Baby rattles
  - (vi) Watch Tick
- 

In the absence of set defined screening protocols it is mandatory to at least increase the parental and professional awareness through simple methods like following the checklist of reactions to sounds. Numerous workers have demonstrated that parents observation of babies reactions to sounds are generally very reliable indicators of resence of hearing disorders<sup>2</sup>.

It is difficult for parents to answer a question 'can your baby hear normally compared to when asked "can your baby hear various environmental sounds. Further if parents are given clues to get more detail information about baby"s reactions to sounds , then their answers were more refined and clear.

The checklist should not cause greater anxiety in minds of parents whose babies can hear ( indicating good specificity) and it should also

be able to bring in attention the babies with hearing loss(indicating good sensitivity).

Increasing the parental awareness should be justified purely on the grounds that it provides a reference from which suspicion or satisfaction about the baby's reactions to sounds can be gauged simply and economically within the existing health care system. The hints for parents approach serves as a valuable adjunct and safety catch net for use along side some form of other definite screening programme in use. While using approach, this care should be taken in cases of fluctuating, progressive and sudden onset deafness.

Despite its simplicity and being economic this approach cannot be used in isolation as a definitive screening method for following reasons:

- (i) It is insensitive for selective frequency losses.
- (ii) It is more reliable for more than moderate losses.

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**Parental checklist : ( produced by Dr. Barry McCormick . Childrens hearing assessment center, Nottingham general hospital).**

**Here is a checklist of some of the general signs you can look for in your baby's first year.;**

**Shortly after birth**

Your baby should be startled by a sudden loud

- (iii) All parents cannot be reached because of reading and language difficulties and /or poor motivation.

**Conclusion.**

Parental checklist for reactions to sounds offers the simplest and most convenient way for suspecting hearing problems in a baby .

The objectives of a hearing screening programme have been discussed and now with the introduction of various electronic devices into hearing screening along with the use of parental checklist, a high specificity and sensitivity can be attained along with possibility of establishing uniformity and standardization. Ideal approach in our setup would still screening all the high risk newborn babies with in 6-8 weeks ( at CGA of 36 weeks) followed by checklist of sounds given to the parents and a follow up at 8-10 months as a part of surveillance.

Depending on the high risk register, care should be taken while following the type of screening protocols and not to miss out cases of Auditory neuropathy.

lot study for detecting hearing impairment in young. Midwife health visitor and community nurse 16,370-4.

noise such as a hand clap and a door slamming and should blink or open his eyes widely to such sounds.

**By 1 month**

Your baby should be beginning to notice sudden prolonged sounds like the noise of a vacuum cleaner and he should pause or listen to them when

they begin.

**By 4 months**

He should quieten or smile to the sound of your voice even when he cannot see you. He may also turn his head or eyes towards you if you come up from behind and speak to him from the side.

**By 7 months**

He should turn immediately to your voice across the room or to very quiet noises made on each side if he is not too occupied with other things.

**By 9 months**

He should listen attentively to everyday familiar sounds and search for very quiet noises made out of sight. He should also show pleasure in babbling loudly and tunefully.

**By 12 months.**

He should show some responses to his own name and to other familiar words. He may also respond when you say 'NO' or 'BYE BYE' even when he cannot see accompanying gesture.

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The Institute of Child Health, affirms that the organization has the following goals:

- (i) To help cure diseases and offer protection to the physical and mental health of every child regardless of the child's economic circumstances.**
- (ii) To carry on research in pediatrics.**
- (iii) To offer training to doctors, nurses, technicians and social workers.**
- (iv) To help build a healthy population in India.**

The institute is a non-profit organization and consultants hold honorary posts. Many pediatricians of Kolkata happily offer voluntary services to the patients of the institute in the area of surgery as well as in the area of medicine. Fees received from the patients merely help meet the expenses of the daily running of the hospital. The members of the institute feel constrained, however, as medical science is advancing fast and medical services in nursing homes and private hospitals, have improved considerably. They feel when the doctors are so skilled the amenities should do justice to them. Besides, the University of Calcutta urges the institute to follow its guidelines. Thus, certain life-saving and diagnostic equipment have to be installed for the institute to be able to offer sophisticated treatment to the patients. But, these are expensive and the resources of the institute, as indicated above, are limited. Doctors, employees, trustees and members of the governing body of the institute seek to raise funds, modernize services and better the academic atmosphere. They aspire to offer the best treatment available to the ailing children.

## View Point

# **$\beta$ -Lactam/ $\beta$ -Lactamase Inhibitor Combinations: Possible Role in the Management of Bacterial Infections**

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### **Introduction**

The use of antibiotics in combating bacterial infections has been hampered by production by many bacterial pathogens of  $\beta$ -lactamases that render them resistant to  $\beta$ -lactam antibiotics. Since susceptibility to the  $\beta$ -lactam appears crucial in attaining a clinical response in Gram-negative bacteraemia, regimens that inhibit the activity of  $\beta$ -lactamases are desirable. Although many

$\beta$ -lactamase inhibitors, such as sulbactam or tazobactam, can result in irreversible inhibition of bacterial  $\beta$ -lactamase in vitro, careful selection of dosage, as well as testing in models of infection mimicking that in patients, is required.

### ***Mechanism of action of $\beta$ -lactam antibiotics:***

$\beta$ -Lactam antibiotics exhibit their bactericidal effects by inhibiting enzymes involved in cell wall synthesis. The integrity of the bacterial cell wall is essential to maintaining cell shape in a hypertonic and hostile environment<sup>1</sup>. Osmotic stability is preserved by a rigid cell wall comprised of alternating N-acetylmuramic acid (NAM) and N-acetyl

glucosamine (NAG) units. These glycosidic units are linked by transglycosidases. A pentapeptide is attached to each NAM unit, and the cross-linking of two D-alanine–D-alanine NAM pentapeptides is catalyzed by PBPs, which act as transpeptidases<sup>2,3</sup>. This cross-linking of adjacent glycan strands confers the rigidity of the cell wall. The  $\beta$ -lactam ring is sterically similar to the D-alanine–D-alanine of the NAM pentapeptide, and PBPs “mistakenly” use the  $\beta$ -lactam as a “building block” during cell wall synthesis<sup>4</sup>. This results in acylation of the PBP, which renders the enzyme unable to catalyze further transpeptidation reactions<sup>5</sup>. As cell wall synthesis slows to a halt, constitutive peptidoglycan autolysis continues. The breakdown of the murein sacculus leads to cell wall compromise and increased permeability. Thus, the  $\beta$ -lactam-mediated inhibition of transpeptidation causes cell lysis, although the specific details of penicillin's bactericidal effects are still being unraveled<sup>6</sup>.

### ***Resistance to $\beta$ -lactam antibiotics:***

There are four primary mechanisms by which bacteria can overcome  $\beta$ -lactam antibiotics<sup>7</sup>.

- (i) Production of  $\beta$ -lactamase enzymes is the most common and important mechanism of resistance in Gram-negative bacteria and will be the focus of this review.
- (ii) Changes in the active site of PBPs can lower the affinity for  $\beta$ -lactam antibiotics and subsequently increase resistance to these agents, such as those seen in PBP2x of *Streptococcus pneumoniae*<sup>8</sup>. Through natural transformation and recombination with DNA from other organisms, *Neisseria* spp. and *Streptococcus* spp. have acquired highly resistant, low-affinity PBPs<sup>9</sup>. In a related manner, penicillin resistance in *Streptococcus sanguis*, *Streptococcus oralis*, and *Streptococcus mitis* developed from horizontal transfer of a PBP2b gene from *Streptococcus pneumoniae*<sup>10</sup>. Methicillin resistance in *Staphylococcus* spp. is also a significant clinical challenge. While there are many reasons for this resistance, the  $\beta$ -lactam resistance phenotype is also conferred by acquisition of the *mec A* gene which produces PBP2a (also denoted PBP2 ' )<sup>11</sup>. PBP2a can assemble new cell wall in the presence of high concentration of penicillin and cephalosporin.
- (iii) Decreased expression of outer membrane proteins (OMPs) is another mechanism of resistance. In order to access PBPs on the inner plasma membrane,  $\beta$ -lactams must either diffuse through or directly traverse porin channels in the outer membrane of Gram-negative bacterial cell walls. Some Enterobacteriaceae (e.g., *Enterobacter* spp., *Klebsiella pneumoniae*, and *Escherichia coli* ) exhibit resistance to carbapenems based on loss of these OMPs; the loss of OprD is associated with imipenem resistance and reduced susceptibility to meropenem in the nonfermenter *Pseudomonas aeruginosa*<sup>12</sup>. Resistance to imipenem and meropenem has also been associated with the loss of the CarO OMP in clinical isolates of multidrug-resistant *Acinetobacter baumannii*<sup>13</sup>. Point mutations or insertion sequences in porin-encoding genes can produce proteins with decreased function and thus lower permeability to-  $\beta$ -lactams<sup>14</sup>. Of note, the disruption of porin proteins alone is not always sufficient for producing the resistance phenotype, and typically this mechanism is found in combination with  $\beta$ -lactamase expression<sup>14</sup>.
- (iv) Efflux pumps, as part of either an acquired or intrinsic resistance phenotype, are capable of exporting a wide range of substrates from the periplasm to the surrounding environment<sup>15</sup>. These pumps are an important determinant of multi drug resistance in many Gram-negative pathogens, particularly *P.aeruginosa* and *Acinetobacter* spp. In *P.aeruginosa*, upregulation of the MexA-MexB-OprD system, in combination

with the organism's low outer membrane permeability, can contribute to decreased susceptibility to penicillins and cephalosporins, as well as quinolones, tetracycline, and chloramphenicol<sup>16</sup>. To illustrate, an increase in the carbenicillin MIC from 32 µg/ml to 1,028 µg/ml is associated with over production of this efflux pump (17). Additionally, an upregulated efflux pump (e.g., AdeABC, an RND-type efflux pump, in *Acinetobacter baumannii*) can augment the carbapenem resistance conferred by a catalytically poor β-lactamase (e.g., OXA-23)<sup>18</sup>.

### **β -lactamases :**

The first β-lactamase enzyme was identified in *Bacillus (Escherichia) coli* before the clinical use of penicillin. In a sentinel paper published nearly 70 years ago, E.P.Abraham and *E.Chain* described the *B.coli* "penicillinase".

The enzyme was not thought to be clinically relevant, since penicillin was targeted to treat staphylococcal and streptococcal infections, and Abraham, Chain, and their colleagues were unable to isolate the enzyme from these Gram-positive organisms. It is sobering now to consider the ramifications of this observation.

Four years later, Kirby successfully extracted these cell-free "penicillin inactivators" from *Staphylococcus aureus*, which foreshadowed the emergence of a significant clinical problem. The growing number of β-lactam antibiotics has since increased the selective pressure on

bacteria, promoting the survival of organisms with multiple β-lactamases<sup>19</sup>. Currently, more than 850 β-lactamases are identified.

### **Classification:**

Two major classification schemes exist for categorizing β-lactamase enzymes: Ambler classes A through D, based on amino acid sequence homology, and Bush-Jacoby-Medeiros groups 1 through 4, based on substrate and inhibitor profile<sup>20,21</sup>. A "family portrait" reveals the structural similarity of class A, C, and D serine β-lactamases. Class B β-lactamases ("a class apart") are metallo-β-lactamases (MBLs)<sup>22</sup>. MBLs possess either a single Zn<sup>2+</sup> ion or a pair of Zn<sup>2+</sup> ions coordinated to His/Cys/Asp residues in the active site.

### **β -lactamase inhibitors:**

Bacterial resistance due to β-lactamase production maybe reversed by a β -lactamase inhibitor combined with a β-lactam. Three inhibitors currently in use are clavulanic acid, sulbactam and tazobactam. The three main mechanisms by which β-lactamases may be inhibited are: competitive, non-competitive (time-dependent), and suicide inhibition. Livermore<sup>23</sup> has described the kinetic steps of β-lactam inhibition. In the presence of β-lactamase, inhibitors can form an initial high affinity complex. However, this interaction fails to acylate the serine residue on the enzyme and does not result in opening of the β-lactam ring. This is a competitive inhibition process where by the inhibitor competes with the enzyme for the substrate and inhibition

might be overcome with excess enzyme concentration. Alternatively, a stable enzyme-inhibitor complex that fails to hydrolyze the inhibitor (non-competitive inhibition) can form. In this case, the inhibitor binds to a different site from the active site of the enzyme and, hence, remotely modulates the binding of the enzyme to substrate. The resultant enzyme-inhibitor complex is often very stable, but the process is reversible. Sometimes, the enzyme-inhibitor interaction yields a stable (E-I) complex that does not hydrolyze to release the active enzyme; then the inhibition is 'suicidal' in that enzyme can not be recycled and the active site is permanently perturbed<sup>23</sup>. Thus, while competitive and non-competitive inhibition mechanisms are reversible processes, suicide inhibition is an irreversible process that results in the formation of a covalent non-hydrolyzed bond between the enzyme and hydrolyzed inhibitor, stopping the hydrolytic potential of the enzyme. The potency of the  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination depends on a number of factors. Measures of efficiency of inhibition include the IC<sub>50</sub> of the inhibitor (the inhibitor concentration required to achieve 50% loss of enzyme activity), affinity (measured by K<sub>m</sub>), the induction potential of the inhibitor (to paradoxically induce the production of the enzymes) and the 'turn over number'<sup>24</sup>. The 'turnover number' refers to the number of molecules of inhibitor required to inactivate one molecule of  $\beta$ -lactamase enzyme. The more efficient suicide inhibitors have a low

turnover number (i.e., need less inhibitor to inactivate a molecule of  $\beta$ -lactamase). Tazobactam has been reported as 10 times more potent than other  $\beta$ -lactamase inhibitors.

### ***$\beta$ -lactam- $\beta$ -lactamase inhibitor combinations in clinical use :***

Generally, the inhibitors do not inactivate PBPs, but notable exceptions include (i) the intrinsic activities of sulbactam against *Bacteroides* spp., *Acinetobacter* spp., and *N.gonorrhoeae*; (ii) clavulanate action against *Haemophilus influenzae* and *N.gonorrhoeae*; and (iii) tazobactam inhibition of PBPs in *Borrelia burgdorferi*<sup>25</sup>. As these "anti bacterial effects" are relatively weak, the inhibitors are always combined with  $\beta$ -lactam antibiotics for clinical use. Currently, there are five  $\beta$ -lactam-  $\beta$ -lactamase inhibitor formulations available. Amoxicillin-clavulanate, Ticarcillin-clavulanate, ampicillin-sulbactam, and Piperacillin-tazobactam are available in the United States. Cefoperazone-sulbactam is used in several European countries, Japan, and India but is not available in the United States. Importantly, as in clinical usage, the  $\beta$ -lactamase inhibitors are combined with  $\beta$ -lactams for in vitro susceptibility testing. The composition of these formulations can have a major impact on susceptibility results, which may or may not reflect clinical efficacy.

#### **(i) *Amoxicillin-clavulanate:***

Amoxicillin-clavulanate was the first  $\beta$ -lactam-  $\beta$ -lactamase inhibitor combination introduced into clinical practice, in 1981 in

the United Kingdom and in 1984 in the United States, and remains the only combination available for oral use. The activity of amoxicillin against susceptible bacteria that do not possess a  $\beta$ -lactamase (e.g., streptococci, enterococci, *E. coli*, and *Listeria* spp.) is not improved by the use of clavulanate. However, the addition of clavulanate significantly expands amoxicillin's spectrum to include penicillinase-producing *S. aureus*, *H. influenzae*, *Moraxella catarrhalis*, *Bacteroides* spp., *N. gonorrhoeae*, *E. coli*, *Klebsiella* spp. and *P. mirabilis*<sup>26</sup>. The oral availability of amoxicillin-clavulanate makes it well suited for the outpatient clinic, and this  $\beta$ -lactam- $\beta$  lactamase inhibitor combination exerted its greatest impact on the treatment of community-acquired respiratory infections<sup>26</sup>. Additionally, amoxicillin-clavulanate is sometimes used as an oral equivalent ("step-down therapy") of ampicillin-sulbactam or ticarcillin-clavulanate in the treatment of skin, soft tissue, abdominal, and gynecological infections. Intravenous formulations of amoxicillin-clavulanate are available in Europe and have been studied primarily for their efficacy against ESBL-producing *E. coli* bacteremia.

**(ii) Ticarcillin-clavulanate:**

When introduced in 1985, ticarcillin-clavulanate was the first  $\beta$ -lactam  $\beta$ -lactamase inhibitor combination available for parenteral administration. Similar to the case for amoxicillin, the addition of clavulanate does not increase activity against pathogens for which ticarcillin alone is effective, such as

non  $\beta$ -lactamase-producing *Haemophilus* spp., *E. coli*, *Proteus* spp., *Enterobacter* spp., *Morganella* spp., *Providencia* spp. and *P. aeruginosa*. However, the combination of ticarcillin and clavulanate does increase activity against  $\beta$ -lactamase-producing staphylococci, *E. coli*, *H. influenzae*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., *Providencia* spp., *N. gonorrhoeae*, *Moraxella catarrhalis*, and *Bacteroides* spp.<sup>26</sup>. Surprisingly, ticarcillin-clavulanate exhibits activity against the multidrug-resistant, non-lactose-fermenting *S. maltophilia*, and the use of this combination in addition to other antimicrobials (e.g., aztreonam or trimethoprim-sulfamethoxazole) leads to synergistic killing<sup>27</sup>. This phenomenon may represent a very interesting opportunity to study the activity of ticarcillin-clavulanate against *S. maltophilia*. Clavulanate induces the expression of chromosomally mediated AmpC- $\beta$  lactamases in many Enterobacteriaceae and can antagonize the antibacterial effects of ticarcillin as a partner  $\beta$ -lactam<sup>28</sup>. This ticarcillin antagonism was observed in laboratory checkerboard studies with *E. cloacae* and *Morganella morganii* strains<sup>28</sup>. However, the impact of  $\beta$ -lactamase induction in the clinic is very hard to measure. When testing or evaluating antibiotics in preclinical or clinical trials,  $\beta$ -lactamase induction may bear importance as an eventual predictor of efficacy. In our opinion, the ability of  $\beta$ -lactamase inhibitors to induce cephalosporinase production should be carefully examined and defined before clinical trials are performed.

In response to the potential for increased AmpC production due to  $\beta$ -lactam inducers (such as clavulanate, but including also ceftazidime, imipenem, and ceftazidime) as well as the relatively poor performance of amoxicillin-clavulanate and ticarcillin-clavulanate against ESBL-expressors, Livermore et al. and Nikaido et al. have proposed the combination of clavulanate with a cephalosporin, such as cefepime or ceftazidime, that is more stable against AmpC enzymes<sup>29</sup>. Cefepime-clavulanate and ceftazidime-clavulanate combinations, with a constant concentration of 4  $\mu$ g/ml clavulanate, were effective at 1  $\mu$ g/ml against ESBL-producing Enterobacteriaceae<sup>29</sup>. The combination of cefepime and clavulanate enjoys a particular advantage due to the inability of class C enzymes to hydrolyze cefepime and the ability of clavulanate to inhibit ESBLs. Currently, there are important obstacles to combining these agents (i.e., all three agents are at the end of patent protection, and the required trials of the formulations would be very expensive), but provided that the clinical research can be performed, these combinations may be an attractive alternative to carbapenem treatment of ESBL-producing organisms.

**(iii) Ampicillin-sulbactam:**

Ampicillin shows activity against most streptococci, enterococci, *Listeria* spp., and strains of *S.aureus*, *H.influenzae*, *E.coli*, *P.mirabilis*, *Salmonella* spp., and *Shigella* spp. that are devoid of  $\beta$ -lactamases (an important exception are ampicillin-resistant strains of

*H.influenzae* that do not contain a  $\beta$ -lactamase and often have substitutions in PBP sequences). In combination with sulbactam, the activity extends to  $\beta$ -lactamase-containing *S.aureus*, *H.influenzae*, *M.catarrhalis*, *E.coli*, *Proteus* spp., *Klebsiella* spp. and anaerobes<sup>30</sup>. When the combination of ampicillin at 2.0g and sulbactam at 1.0g was marketed in 1987, this broad-spectrum activity made ampicillin-sulbactam ideal therapy for polymicrobial infections such as abdominal and gynecological surgical infections, aspiration pneumonia, odontogenic abscesses, and diabetic foot infections. The early clinical success of this combination (and susceptibility of many pathogens to ampicillin-sulbactam and ticarcillin-clavulanate) established confidence in the role of  $\beta$ -lactam- $\beta$ -lactamase inhibitor therapy. Unfortunately, the resistance to ampicillin-sulbactam among clinical isolates of *E.coli* is increasing. Sulbactam is not well absorbed orally and must be administered parenterally. However, the intravenous ampicillin-sulbactam combination is well tolerated, with very few reported side effects<sup>31</sup>.

**(iv) Piperacillin-tazobactam:**

Piperacillin in combination with tazobactam became available in the United States in 1993. Piperacillin is a broad-spectrum penicillin that is bactericidal against many Gram-positive and Gram-negative aerobes and anaerobes<sup>32</sup>. As a single agent, piperacillin demonstrates activity against *P.aeruginosa*, pneumococci, streptococci, anaerobes, and *Enterococcus faecalis*, and this activity is retained in

combination with tazobactam. Clinicians must remember that the addition of tazobactam does not always increase susceptibility of *P.aeruginosa* and other Gram-negative bacilli expressing AmpC-  $\beta$ -lactamases<sup>32</sup>. However, tazobactam does extend piperacillin's activity against most  $\hat{\alpha}$ -lactamase producing strains of Enterobacteriaceae, *H.influenzae*, *N.gonorrhoeae*, and *M.catarrhalis* and has the potential to lower MICs against these strains expressing ESBLs<sup>26</sup>.

Several recent retrospective studies of clinical outcomes from *E.coli* and *K.pneumoniae* ESBL-producing isolates argue for the efficacy of piperacillin-tazobactam in the treatment of these infections<sup>33</sup>. Gavin et al. showed that when in vitro testing revealed susceptibility to piperacillin-tazobactam (=16/4 $\mu$ g/ml), successful outcomes were seen in 10 out of 11 non-urinary tract infections. An examination of 43 blood stream infections caused primarily by CTX-M ESBL-producing *E.coli* isolates revealed that piperacillin-tazobactam, amoxicillin-clavulanate (i.v.), or carbapenem treatment led to lower mortality than with cephalosporin or fluoroquinolone treatment (9% versus 35%)<sup>34</sup>. Another study, including infections caused by SHV and TEM -type ESBL-producing *K.pneumoniae*, established that empirical therapy with  $\beta$ -lactam-  $\beta$ -lactamase inhibitor combinations was validated by in vitro susceptibility testing in 75% of cases, compared to 0% for oxymino-cephalosporin treatment<sup>33</sup>. Furthermore, initial treatment with an adequate antibiotic was

associated with lower mortality rates (37%) than inadequate empirical therapy (67%). While this analysis did not stratify the outcome data based on ESBL type, other authors have reported that TEM-type ESBLs are more susceptible to piperacillin-tazobactam than are SHV-type ESBLs<sup>35</sup>.

Several observational studies have strongly suggested that the replacement of extended-spectrum cephalosporins with piperacillin-tazobactam can help lower the rates of infection from Gram-negative ESBL producers and vancomycin-resistant *Enterococcus spp.*<sup>36</sup>. While the mechanism for decreasing ESBL-producing isolates is not clear, it must be noted that the efficacy of  $\beta$ -lactam-  $\beta$ -lactamase inhibitor combinations may be reduced for organisms producing multiple ESBLs, particularly if they also have an AmpC-  $\beta$ -lactamase. For this reason, there is a caution against the use of piperacillin-tazobactam for the treatment of ESBL-producing pathogens.

So, why do the in vitro susceptibility data and the clinically cited data suggest that piperacillin-tazobactam can be used in the treatment of ESBL producers? The reasons for this contradiction include that piperacillin, as a partner  $\beta$ -lactam for  $\beta$ -lactamase inhibitors, is relatively resistant to hydrolysis by certain plasmid-mediated  $\beta$ -lactamases (e.g., TEM) compared to amoxicillin, ampicillin, or ticarcillin. This substrate stability may be due, in part, to piperacillin's lower affinity for and lower turnover by these enzymes and also piperacillin's greater affinity for bacterial PBPs

. It is likely that the high serum concentrations combined with the superior activity of piperacillin and the relatively “better” inhibitory activity of tazobactam versus clavulanate or sulbactam is enough to inhibit a majority of  $\beta$ -lactamases in a complex  $\beta$ -lactamase background (class A and C  $\beta$ -lactamases)<sup>37</sup>. However, this efficacy is not always clinically certain, and the physician must be aware that the susceptibility pattern of an infecting Gram-negative pathogen does not always reveal the number and complexity of the  $\beta$ -lactamases present. Moreover, the formulation that is tested in the lab may not mirror what is administered to patients.

The other combinations like Cefoperazone – Sulbactam (supported by EGAST Study in India) and Cefepime – Tazobactam are also widely used BL+BLI molecule; both are extensively used against polymicrobial infections and in second (i.e. Cefepime –

Tazobactam) case now the drug is widely being advocated for combating ESBLs and MDR Pseudomonads.

### Summary

Antibiotic resistance is a continuing problem in the treatment of hospital-acquired infections. Combinations of  $\beta$ -lactam/ $\beta$ -lactamase inhibitors such as piperacillin plus tazobactam provide broad coverage against these pathogens. The main challenge in  $\beta$ -lactamase inhibitor development is discovering

novel inhibitors with activity against a broad spectrum of inhibitor-susceptible and resistant enzymes from multiple classes<sup>38</sup>. New inhibitors must also target carbapenemases (serine and metallo), as carbapenems are still the most potent  $\beta$ -lactams available for clinical use.

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## Current Topic

### Latex Allergy – An Often Overlooked Phenomenon

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It has been known for a long time that latex a component of many medical and surgical equipment can cause hypersensitivity reactions. A wide spectrum of symptoms from contact urticaria to life threatening systemic manifestations are caused by latex allergy<sup>1</sup>.

Latex allergy is a matter of concern to pediatricians as it is one of the important causes of anaphylaxis in children in a hospital set-up<sup>2,3</sup>. Anaphylaxis is the most severe manifestation of immediate type hypersensitivity or IgE mediated type I hypersensitivity reaction.

The first case of type I reaction to latex proteins was described for the first time in 1979<sup>4</sup> and since then an increasing number of local reactions to contact with latex in health care personnel and anaphylactic reaction in patients undergoing surgery are being reported.

The incidence of latex hypersensitivity among children is increasing, the high risk population being children with Spina bifida, genitourinary malformations and children undergoing multiple surgical procedures<sup>5</sup>.

#### Latex Allergens

Natural rubber is obtained from the rubber tree *Havea braziliensis*. Latex is the milky sap of this plant. It contains a rubber matrix of cis-1-4-poly-isoprene, some proteins and water. During processing, the poly-isoprene chains are cross linked and many chemicals are added (vulcanizers, stabilizers etc.) The final product contains at least 16 proteins, which are responsible for IgE mediated Type I hypersensitivity reactions and certain chemicals which are responsible for Type IV delayed hypersensitivity reactions like contact dermatitis<sup>6,7</sup>.

Latex is a widely used product and is present in various articles used both in a hospital setting as consumer products. The list of most important ones relevant for children are listed below<sup>8</sup>.

#### *(A) In hospital setting :*

- (i) Gloves
- (ii) Sticking plaster
- (iii) Catheters
- (iv) Dental mouth guards.

**(B) Consumer product :**

- (i) Balloons
- (ii) Pacifiers
- (iii) Rubber toys and teethingers
- (iv) Athletic shoes

It is worth while to remember that latex allergens show

cross reactivity to fruit allergens. About 50% of latex-allergy patients report allergic reaction to fruits, namely banana, papaya, tomato and exotic fruits like kiwi and avocado<sup>9</sup>.

**Risk Factors to Latex Allergy in Children<sup>10</sup>**

- (a) *Atopic status* – Most individuals with latex hypersensitivity have an atopic background . A positive association has been found between atopic status i.e. positive S.P.T(Skin Prick Test) to major aero allergens and the risk of developing latex allergy.
- (b) Patients undergoing multiple operations and patients being chronically exposed to latex medical devices. These patients have a considerable risk of developing IgE mediated Type I reactions. The highest risk is among children with gross genito urinary defect and children with Spina bifida.

Latex sensitization occur after skin or mucosal contact with latex. Peritoneal contact during intra abdominal surgery from the surgeons gloves and inhalation of aerosolized particles with latex particles on their surface (corn starch

used for packing surgical gloves) are important factors<sup>8</sup>.

**Clinical Features of Latex Allergy<sup>5</sup>**

**Three distinct types of reactions are noted with latex hypersensitivity.**

- (a) Mild itching and irritation of the site of contact.
- (b) Contact dermatitis (type IV reaction) usually occurs with the latex adhesive in children shoes.
- (c) Contact urticaria – This is a classical picture of Type I IgE mediated reaction. Diffuse erythema and urticaria occur at the site of contact, e.g. site of attachment of sticking plaster during dressing of wounds or for keeping tubing in position.
- (d) Respiratory – Symptoms of sneezing, coughing,itching eyes and breathing distress occur within minute of exposure in sensitive individuals. Latex protein is absorbed by the particles of corn starch used for packaging of gloves. Whenever a pair of gloves is unpacked the powder get air borne and cause symptoms in sensitive individuals.
- (e) Systematic manifestation – This is the least frequent but the most severe and threatening condition. Majority of severe reaction have occurred during surgery. Typically anaphylaxis has occurred due to contact with surgeons gloves during intra-abdominal surgery. Many patients have experienced more than one episode as the first one usually goes unrecognized or unexplained.

Anaphylactic reactions following tracheal intubations and catheterization are also on record<sup>11</sup>.

### **Diagnosis<sup>12</sup>**

- (1) Meticulous clinical history is a good pointer to alert the physician regarding latex allergy.
- (2) Skin prick test (SPT) is the easiest readily available and reliable test for latex allergy. It can be performed with either extract of raw latex or that of a finished product.
- (3) Skin patch test are usually done to detect contact allergy to latex, due to chemical present in finished latex goods.
- (4) Airway and conjunctival challenge with exposure to powder in the latex gloves packages are not advocated routinely as there remains more than a fair chance of severe systemic reactions.
- (5) Invitro tests: RAST and / or ELISA test though not as sensitive as SPT can be done to detect IgE antibodies to latex proteins.

### **Differential Diagnosis**

When allergic reaction occurs during surgery, hypersensitivity to muscle relaxants and drugs used during general anesthesia, plasma expanders etc should be ruled out.

### **Management<sup>10</sup>**

The corner stone of management of latex allergy remains PREVENTION of contact with latex.

- (a) *Primary prevention* – Ideally latex products

should be entirely avoided in children with atopic background, eczema, Spina bifida, children under going multiple operations and children requiring repeated/ chronic catheterization (genito-urinary defects).

- (b) *Secondary prevention* – This is to prevent symptoms in sensitized children. Secondary prevention is a difficult proposition as latex is not only present in medical equipments but it is also present in various consumer durables.

However alerting the surgeon or dental surgeon regarding the patients sensitivity and educating parents, care givers and school officials regarding latex allergy goes a long way in preventing adverse symptoms.

### **Conclusion**

The dramatic rise in the use of latex gloves by surgeons, dental surgeons and clinicians in the casualty room in hospitals for protection against HIV and Hepatitis virus may have caused a rise in frequency of latex allergy.

The symptoms of latex allergy varies from urticaria to anaphylaxis.

Children with atopic status , Spina bifida, genitourinary defects are more prone to latex allergy. The later two due to repeated surgery and or chronic catheterization.

Latex is obtained from the sap of rubber tree *Havea brasiliensis* then processed by cross-linking and adding chemicals to produce furnished goods. Latex contains 16 proteins responsible for producing Type I IgE mediated reactions. The chemicals present in

finished products are usually responsible for contact dermatitis.

Latex is a ubiquitous component of many medical types of equipment and also of consumer durables.

Clinical features of latex allergy are – Contact dermatitis, contact urticaria, and various respiratory symptoms and last but not the least, anaphylaxis.

Prevention remains the corner stone of management of latex allergy.

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## *Nivedita Challenged Center*

Since 1975 Child Guidance Clinic is probably the only specific institutional centre in Kolkata that provides complete child psychiatric services through psychometry, pharmacotherapy, behaviour therapy, counseling, speech therapy etc, at inexpensive rates. It runs a special school for challenged children and carries out regular academic, research and public awareness activities.

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## Children are Not Small Adults! A Brief Report on Pediatric Reference Ranges

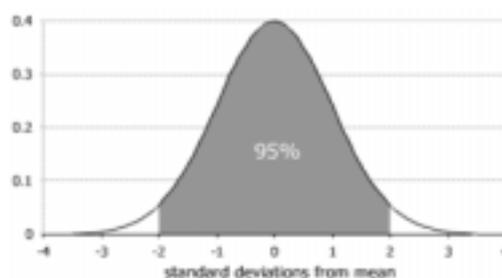
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It is a well known fact that each population has its unique biological reference interval for laboratory tests/ biomarkers of disease. The population may be divided by space (geographical location and ethnicity) or by time (neonates, children, adults etc.).

Healthcare is critically dependent on the availability of “reference intervals” (or “normal values”) to allow appropriate clinical interpretation of medical laboratory data. It is an important aspect of decision making, by comparison with reference values, to arrive at a correct diagnosis. To establish a more scientific basis, the term “normal values” has now been replaced with “biological reference interval”<sup>1</sup>. Cutting a long story short, establishing a reference interval is a mammoth task – it has various components that can be broadly classified as selection of reference individuals, specimen collection, analysis and quality control measures and statistical treatment of reference values. It suffices to add here that the reference interval are bounded by a pair of reference limits – upper and lower -which are obtained by cutting off 2.5% of the values ( $\pm 2$  standard

deviations from mean) at both ends of a *Gaussian* reference distribution (Fig 1). A reference interval is the *central 95% values* obtained by observation or measurement of a particular quantity on reference individuals.



**Fig 1.** Gaussian distribution of measured values of an analyte in a reference population. Value at  $\pm 2$  SD of mean (at 0 on X-axis) form the upper and lower limits of the reference interval. The bell shape area indicates that greater percentage of reference population have values around the mean.

India is a diverse nation. It has extreme heterogeneity in terms of ancestry, race, ethnicity, food habits, etc. However, laboratory reference intervals used have often been derived from predominantly North American and European (largely Caucasian) populations<sup>2</sup>.

Accrediting and licensing organizations/ regulatory bodies governing medical

laboratory best practices, such as the International Standards Organization (ISO) and Clinical and Laboratory Standards Institute (CLSI) require that individual laboratories establish or verify reference intervals for all quantitative test methods; the exception being for tests that employ decision cut-off limits (e.g. glucose, cholesterol, hemoglobin A1C)<sup>3,4</sup>. The undertaking in terms of time, resources, and costs to each laboratory is herculean. This is especially strenuous in the pediatric populations that require several age divisions based on child development. Apart from age, sex, and ethnicity-based partitions, biomarkers may also be affected by other physiological factors such as body mass index (BMI) and sexual development (Tanner) stage. These are significant reasons why India has been lacking in establishing its own reference intervals.

The west has been extremely radical and compliant with reporting pediatric reference intervals<sup>5,6</sup>. We borrow these reference intervals, primarily established on Caucasian reference population, in the absence of our own reference intervals<sup>7</sup>. In spite, reporting pediatric reference interval data is almost a non-existent practice. Very few laboratories realize the importance of providing age and gender specific reference intervals for the pediatric population. While regulatory authorities in India such as National Accreditation Board of Laboratories (NABL) have spelt out the need for an appropriate reference interval as a Quality System Essential (QSE 5.10/ ISO 15189)<sup>8</sup>, it

has hardly translated to global practice [*personal experience and internal communication*].

In the month of May, 2012 a very relevant article<sup>9</sup> has been published by the team of Dr. Khusrow Adeli that provides pediatric reference ranges from newborn to 18 years of age for 40 serum biochemical markers (see Table 1 for a few selected biomarkers). The focal point of this paper lies in the applicability of the data; as it was established in a healthy multiethnic pediatric population (n=2188) that included Caucasians, East Asians, and South Asian participants. This effort, called the Canadian Laboratory Initiative in Pediatric Reference Intervals (CALIPER), will now serve a new comprehensive database of pediatric reference intervals for the Canadian population and with further analysis can be extrapolated to local ethnic populations as well. Statistically significant differences were observed in 7 specific biomarkers with respect to ethnicity.

The CALIPER publication has certainly closed the current gap in pediatric reference intervals by addressing several critical issues:

- (i) Comprehensive (new born to 18 yrs) and adequately partitioned (gender, ethnicity) reference intervals
- (ii) Intervals for new biomarkers (e.g. high sensitive CRP)
- (iii) Reference population: healthy non-hospitalized multiethnic pediatric population recruited from three centres in Ontario, Canada.

(iv) Derived on accurate state of the art laboratory analyzers (Abbott Architect c 8000) using up to date methodologies.

One drawback that has been widely criticized in the CALIPER project has been the use of establishing intervals on a specific analytical platform, rather than building “common reference intervals”. One way to resolve this problem would be to take up *transference* studies i.e. to extrapolate the data that was generated on Abbott Architect in the CALIPER project to one’s own laboratory’s analytical platform. This is again difficult and costly.

While using reference intervals established on a multi-centric diverse population may alleviate reporting woes to a certain extent, it is best to create one’s own reference interval. The medical community which includes pediatricians and laboratorians should address national needs for the same. After all, validating a laboratory test without an appropriate reference is not a trivial matter, nor is it to treat on the basis of invalid results, as it can result in patients’ being taken off medication, being discharged too early or other worse

negative outcomes.

A publication in the *American Heart Journal*<sup>10</sup> stated that the reference interval for creatine kinase (CK), a test commonly performed to monitor statin therapy, could be off by as much as a factor of 3. As a result, many patients were incorrectly advised to discontinue their medications, causing their cholesterol levels to return to their original abnormal levels and putting them at increased risk for coronary heart disease.

The CLSI advises laboratories to *validate* the reference ranges (on 20 healthy individuals) provided by manufacturers’ of reagents and instruments, which is easier as opposed to establishing reference intervals (on at least 120 reference individuals for each age and gender)<sup>3</sup>. However, in pediatric populations where age and gender partitions are manifold, it is cost intensive. It may prudent for clinical laboratories to engage with Indian Council of Medical research and other allied bodies to surely and slowly validate or, for better, create Indian pediatric reference intervals. It is equally important for the laboratories to remember - Children are not small adults!

Table 1 Pediatric Reference Intervals of some important clinical chemistry analytes published at www.caliperdatabase.com

Age	Female Reference Interval		Male Reference Interval		Samples	Upper Limit	Lower Limit	Higher CI	Lower CI	Higher CI
	Lower Limit	Upper Limit	Lower CI	Upper Limit						
Albumin (g/dl) (Bromocresol green)	0 - 14 days 3.3	4.5	191	(3.2 - 3.3)	191	4.5	(3.2 - 3.3)	(4.4 - 4.6)	(3.2 - 3.3)	(4.4 - 4.6)
	15 days - < 1 yr 2.8	4.7	156	(2.6 - 3.0)	156	4.7	(2.6 - 3.0)	(4.5 - 5.3)	(2.6 - 3.0)	(4.5 - 5.3)
	1 - < 8 yrs 3.8	4.7	298	(3.8 - 3.9)	298	4.7	(3.8 - 3.9)	(4.6 - 4.7)	(3.8 - 3.9)	(4.6 - 4.7)
	8 - < 15 yrs 4.1	4.8	388	(4.1 - 4.1)	388	4.8	(4.1 - 4.1)	(4.8 - 4.9)	(4.1 - 4.1)	(4.8 - 4.9)
	15 - < 19 yrs 4	4.9	119	(3.9 - 4.1)	123	5.1	(4.1 - 4.2)	(5.0 - 5.2)	(4.1 - 4.2)	(5.0 - 5.2)
Alanine Transaminase (ALT) (U/L) (Without Pyridoxal Phosphate)	0 - < 1 yr 5	51	177	(5 - 5)	177	51	(5 - 5)	(42 - 54)	(5 - 5)	(42 - 54)
	1 - < 13 yrs 11	30	503	(10 - 12)	503	30	(10 - 12)	(28 - 32)	(10 - 12)	(28 - 32)
	13 - < 19 yrs 8	24	171	(6 - 10)	173	33	(5 - 12)	(31 - 34)	(5 - 12)	(31 - 34)
Amylase U/L	0 - 14 days 3	10	129	(2 - 3)	129	10	(2 - 3)	(10 - 10)	(2 - 3)	(10 - 10)
	15 days - < 13wks 2	22	62	(2 - 3)	62	22	(19 - 24)	(19 - 24)	(2 - 3)	(19 - 24)
	13 wks - < 1 yr 3	50	235	(2 - 3)	235	50	(2 - 3)	(47 - 53)	(2 - 3)	(47 - 53)
	1 - < 19 yrs 25	101	938	(23 - 28)	938	101	(23 - 28)	(98 - 105)	(23 - 28)	(98 - 105)
Antistreptolysin-O (ASO) (IU/mL)	0 - < 6 months 0	0	63	(0 - 0)	63	0	(0 - 0)	(0 - 0)	(0 - 0)	(0 - 0)
	6 months - < 1 yr 0	30	58	(0 - 0)	58	30	(0 - 0)	(62 - 193)	(0 - 0)	(62 - 193)
	1 - < 6 yrs 0	104	127	(0 - 0)	127	104	(0 - 0)	(309 - 383)	(0 - 0)	(309 - 383)
	6 - < 19 yrs 0	331	603	(0 - 0)	603	331	(0 - 0)	(152 - 167)	(0 - 0)	(152 - 167)
Aspartate Aminotransferase (AST) (U/L) (Without Pyridoxal Phosphate)	0 - 14 days 32	162	210	(27 - 42)	210	162	(27 - 42)	(152 - 167)	(27 - 42)	(152 - 167)
	15 days - < 1 yr 20	67	140	(14 - 22)	140	67	(14 - 22)	(62 - 70)	(14 - 22)	(62 - 70)
	1 - < 7 yrs 21	44	262	(20 - 23)	262	44	(20 - 23)	(42 - 48)	(20 - 23)	(42 - 48)
	7 - < 12 yrs 18	36	236	(16 - 18)	236	36	(16 - 18)	(33 - 37)	(16 - 18)	(33 - 37)
	12 - < 19 yrs 13	26	208	(13 - 14)	197	35	(13 - 15)	(31 - 38)	(13 - 15)	(31 - 38)

Alkaline Phosphatase (4-Nitrophenyl Phosphate) (ALP) (U/L)	0 - 14 days	90	273	155	(83 - 104)	(257 - 274)	90	273	155	(83 - 104)	(257 - 274)
	15 days - < 1 yr	134	518	147	(108 - 153)	(466 - 570)	134	518	147	(108 - 153)	(466 - 570)
	1 - < 10 yrs	156	369	391	(145 - 170)	(362 - 391)	156	369	391	(145 - 170)	(362 - 391)
	10 - < 13 yrs	141	460	154	(114 - 171)	(424 - 476)	141	460	154	(114 - 171)	(424 - 476)
	13 - < 15 yrs	62	280	68	(56 - 68)	(254 - 301)	62	280	66	(112 - 149)	(481 - 546)
	15 - < 17 yrs	54	128	74	(50 - 58)	(122 - 133)	54	128	64	(84 - 97)	(329 - 388)
	17 - < 19 yrs	48	95	40			48	95	54		
	0 - 14 days	0.33	0.71	171	(0.29-0.36)	(0.67-0.73)	0.33	0.71	171	(0.29-0.36)	(0.67 - 0.73)
	15 days - < 1 yr	0.05	0.3	108	(0.05-0.06)	(0.27-0.33)	0.05	0.3	108	(0.05-0.06)	(0.27 - 0.33)
	1 - < 9 yrs	0.05	0.2	281	(0.05-0.05)	(0.18-0.20)	0.05	0.2	281	(0.05-0.05)	(0.18 - 0.20)
9 - < 13 yrs	0.05	0.29	181	(0.05-0.10)	(0.28-0.33)	0.05	0.29	181	(0.05-0.10)	(0.28 - 0.33)	
13 - < 19 yrs	0.1	0.39	177	(0.05-0.11)	(0.34-0.46)	0.11	0.42	170	(0.10-0.12)	(0.40 - 0.43)	
Bilirubin Direct(mg/dL)	0 - 14 days	0.19	16.6	166	(0.10-0.29)	(15.04-17.88)	0.19	16.6	166	(0.10-0.29)	(15.04-17.88)
	15 days - < 1 yr	0.05	0.68	245	(0.05-0.10)	(0.63-0.73)	0.05	0.68	245	(0.05-0.10)	(0.63 - 0.73)
	1 - < 9 yrs	0.05	0.4	270	(0.05-0.05)	(0.36-0.42)	0.05	0.4	270	(0.05-0.05)	(0.36 - 0.42)
	9 - < 12 yrs	0.05	0.55	135	(0.05-0.10)	(0.50-0.61)	0.05	0.55	135	(0.05-0.10)	(0.50 - 0.61)
	12 - < 15 yrs	0.1	0.7	161	(0.05-0.10)	(0.64-0.81)	0.1	0.7	161	(0.05-0.10)	(0.64 - 0.81)
	15 - < 19 yrs	0.1	0.84	219	(0.05-0.11)	(0.81-0.89)	0.1	0.84	219	(0.05-0.11)	(0.81 - 0.89)
C-reactive protein - High Sensitivity (CRP) (mg/L)	0 - 14 days	0.3	6.1	139	(0.2 - 0.4)	(5.4 - 6.3)	0.3	6.1	139	(0.2 - 0.4)	(5.4 - 6.3)
	15 days - < 15 yrs	0.1	1	653	(0.1 - 0.1)	(0.9 - 1.1)	0.1	1	653	(0.1 - 0.1)	(0.9 - 1.1)
	15 - < 19 yrs	0.1	1.7	196	(0.1 - 0.1)	(1.6 - 1.9)	0.1	1.7	196	(0.1 - 0.1)	(1.6 - 1.9)
Calcium(mg/dL)	0 - < 1 yr	8.5	11	259	(8.4-8.7)	(10.8-11.1)	8.5	11	259	(8.4 - 8.7)	(10.8 - 11.1)
	1 - < 19 yrs	9.2	10.5	897	(9.1-9.2)	(10.5-10.6)	9.2	10.5	897	(9.1 - 9.2)	(10.5 - 10.6)
Carbon Dioxide (CO2) (mEq/L)	0 - 14 days	5	20	178	(5 - 5)	(19 - 25)	5	20	178	(5 - 5)	(19 - 25)
	15 days - < 1 yr	10	24	147	(9 - 11)	(22 - 25)	10	24	147	(9 - 11)	(22 - 25)
	1 - < 5 yrs	14	24	146	(13 - 16)	(23 - 25)	14	24	146	(13 - 16)	(23 - 25)
	5 - < 15 yrs	17	26	488	(17 - 17)	(26 - 27)	17	26	488	(17 - 17)	(26 - 27)
	15 - < 19 yrs	17	26	122	(16 - 18)	(25 - 27)	18	28	121	(17 - 19)	(27 - 29)

Cholesterol (mg/dL)	0 - 14 days	46	125	101	(42 - 52)	(120 - 127)	42	109	108	(41 - 47)	(103 - 112)
	15 days - < 1 yr	64	237	152	(51 - 85)	(224 - 245)	64	237	152	(51 - 85)	(224 - 245)
	1 - < 19 yrs	112	208	931	(110 - 114)	(206 - 211)	112	208	931	(110 - 114)	(206 - 211)
Complement C3 (C3) (mg/dL)	0 - 14 days	50	121	155	(42 - 57)	(118 - 130)	50	121	155	(42 - 57)	(118 - 130)
	15 days - < 1 yr	51	160	151	(31 - 55)	(150 - 165)	51	160	151	(31 - 55)	(150 - 165)
	1 - < 19 yrs	83	152	877	(82 - 87)	(151 - 157)	83	152	877	(82 - 87)	(151 - 157)
Complement C4 (C4) (mg/dL)	0 - < 1 yr	7	30	353	(5 - 8)	(28 - 32)	7	30	353	(5 - 8)	(28 - 32)
	1 - < 19 yrs	13	37	864	(12 - 13)	(36 - 38)	13	37	864	(12 - 13)	(36 - 38)
Creatinine (Enzymatic) (mg/dL)	0 - 14 days	0.33	0.93	147	(0.27-0.40)	(0.89-0.97)	0.33	0.93	147	(0.27-0.40)	(0.89 - 0.97)
	15 days - < 2 yrs	0.1	0.36	168	(0.10-0.12)	(0.35-0.37)	0.1	0.36	168	(0.10-0.12)	(0.35 - 0.37)
	2 - < 5 yrs	0.2	0.43	155	(0.18-0.21)	(0.41-0.45)	0.2	0.43	155	(0.18-0.21)	(0.41 - 0.45)
	5 - < 12 yrs	0.31	0.61	321	(0.29-0.32)	(0.60-0.62)	0.31	0.61	321	(0.29-0.32)	(0.60 - 0.62)
	12 - < 15 yrs	0.45	0.81	183	(0.37-0.46)	(0.76-0.85)	0.45	0.81	183	(0.37-0.46)	(0.76 - 0.85)
	15 - < 19 yrs	0.49	0.84	161	(0.48-0.51)	(0.80-0.88)	0.49	0.84	161	(0.53-0.66)	(1.06 - 1.12)
Creatinine (Jaffe) (mg/dL)	0 - 14 days	0.42	1.05	158	(0.33-0.48)	(0.97-1.06)	0.42	1.05	158	(0.33-0.48)	(0.97 - 1.06)
	15 days - < 1 yr	0.32	0.53	130	(0.31-0.33)	(0.51-0.54)	0.32	0.53	130	(0.31-0.33)	(0.51 - 0.54)
	1 - < 4 yrs	0.38	0.54	121	(0.38-0.41)	(0.54-0.55)	0.38	0.54	121	(0.38-0.41)	(0.54 - 0.55)
	4 - < 7 yrs	0.44	0.64	146	(0.43-0.45)	(0.62-0.67)	0.44	0.64	146	(0.43-0.45)	(0.62 - 0.67)
	7 - < 12 yrs	0.52	0.69	234	(0.52-0.53)	(0.67-0.71)	0.52	0.69	234	(0.52-0.53)	(0.67 - 0.71)
	12 - < 15 yrs	0.57	0.8	184	(0.55-0.58)	(0.80-0.86)	0.57	0.8	184	(0.55-0.58)	(0.80 - 0.86)
	15 - < 17 yrs	0.59	0.86	77	(0.58-0.61)	(0.84-0.87)	0.59	1.04	68	(0.63-0.68)	(1.00 - 1.07)
17 - < 19 yrs	0.6	0.88	88	(0.59-0.61)	(0.86-0.90)	0.69	1.1	86	(0.67-0.71)	(1.07-1.13)	
Direct HDL-Cholesterol (HDL) (mg/dL)	0 - 14 days	15	42	147	(10-17)	(40 - 47)	15	42	147	(10 - 17)	(40 - 47)
	15 days - < 1 yr	12	71	146	(8 - 18)	(66 - 77)	12	71	146	(8 - 18)	(66 - 77)
	1 - < 4 yrs	32	63	97	(32 - 34)	(61 - 64)	32	63	97	(32 - 34)	(61 - 64)
	4 - < 13 yrs	36	73	407	(34 - 37)	(70 - 74)	36	73	407	(34 - 37)	(70 - 74)
	13 - < 19 yrs	32	72	203	(29 - 37)	(69 - 76)	32	68	197	(30 - 33)	(66 - 72)

Gamma-Glutamyl Transferase (U/L)	0 - 14 days	23	219	171	(10 - 35)	(210 - 255)	23	219	171	(10 - 35)	(210 - 255)
	15 days - < 1 yr	8	127	141	(7 - 9)	(116 - 145)	8	127	141	(7 - 9)	(116 - 145)
	1 - < 11 yrs	6	16	438	(6 - 7)	(16 - 17)	6	16	438	(6 - 7)	(16 - 17)
	11 - < 19 yrs	7	21	444	(7 - 8)	(20 - 22)	7	21	444	(7 - 8)	(20 - 22)
Iron (ug/dL)	0 - < 14 yrs	16	128	588	(15 - 21)	(123 - 138)	16	128	588	(15 - 21)	(123 - 138)
	14 - < 19 yrs	20	162	143	(13 - 31)	(138 - 185)	31	168	138	(11 - 42)	(153 - 184)
Lactate Dehydrogenase (LDH) (U/L)	0 - 14 days	309	1222	197	(267-360)	(1116-1257)	309	1222	197	(267 - 360)	(1116 - 1257)
	15 days - < 1 yr	163	452	145	(94 - 173)	(428 - 483)	163	452	145	(94 - 173)	(428 - 483)
	1 - < 10 yrs	192	321	370	(189 - 199)	(314 - 333)	192	321	370	(189 - 199)	(314 - 333)
	10 - < 15 yrs	157	272	141	(130 - 162)	(258 - 308)	170	283	125	(138 - 175)	(277 - 286)
	15 - < 19 yrs	130	250	227	(124 - 142)	(239 - 257)	130	250	227	(124 - 142)	(239 - 257)
	0 - < 19 yrs	4	39	946	(3.9-6.0)	(37.0-40.0)	4	39	946	(3.9 - 6.0)	(37.0 - 40.0)
Magnesium (mg/dL)	0 - 14 days	1.99	3.94	183	(1.80-2.19)	(3.77-4.11)	1.99	3.94	183	(1.80-2.19)	(3.77 - 4.11)
	15 days - < 1 yr	1.97	3.09	145	(1.85-2.11)	(3.01-3.21)	1.97	3.09	145	(1.85-2.11)	(3.01 - 3.21)
	1 - < 19 yrs	2.09	2.84	897	(2.09-2.11)	(2.82-2.87)	2.09	2.84	897	(2.09-2.11)	(2.82 - 2.87)
Phosphate (mg/dL)	0 - 14 days	5.6	10.5	204	(5.4-5.9)	(10.2-10.7)	5.6	10.5	204	(5.4-5.9)	(10.2-10.7)
	15 days - < 1 yr	4.8	8.4	144	(4.2 - 5.0)	(8.1 - 8.6)	4.8	8.4	144	(4.2 - 5.0)	(8.1 - 8.6)
	1 - < 5 yrs	4.3	6.8	184	(4.0 - 4.5)	(6.5 - 7.4)	4.3	6.8	184	(4.0 - 4.5)	(6.5 - 7.4)
	5 - < 13 yrs	4.1	5.9	352	(4.1 - 4.2)	(5.9 - 6.0)	4.1	5.9	352	(4.1 - 4.2)	(5.9 - 6.0)
	13 - < 16 yrs	3.2	5.5	95	(3.0 - 3.3)	(5.4 - 5.7)	3.5	6.2	95	(3.4 - 3.6)	(6.0 - 6.3)
	16 - < 19 yrs	2.9	5	187	(2.7 - 3.1)	(4.9 - 5.6)	2.9	5	187	(2.7 - 3.1)	(4.9 - 5.6)
Rheumatoid Factor (IU/mL)	0 - 14 days	9	17.1	164	(9.0-9.0)	(16.2-17.7)	9	17.1	164	(9.0-9.0)	(16.2-17.7)
	15 days-<19 yrs	9	9	1016	(9.0 - 9.0)	(9.0 - 9.0)	9	9	1016	(9.0 - 9.0)	(9.0 - 9.0)
Total Protein (g/dL)	0 - 14 days	5.3	8.3	158	(5.0 - 5.4)	(8.0 - 8.5)	5.3	8.3	158	(5.0 - 5.4)	(8.0 - 8.5)
	15 days - < 1 yr	4.4	7.1	152	(4.2 - 4.6)	(6.9 - 7.4)	4.4	7.1	152	(4.2 - 4.6)	(6.9 - 7.4)
	1 - < 6 yrs	6.1	7.5	209	(5.8 - 6.2)	(7.5 - 7.6)	6.1	7.5	209	(5.8 - 6.2)	(7.5 - 7.6)

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## Immunization and Antibiotic Policy in Children Suffering from Malignancies

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Children suffering from various malignancies are immunocompromised. Consequently their vaccination and their treatment with antibiotics are different from that of immunocompetent individuals. Over the years the numbers of children surviving with or recovering from various malignancies are increasing specially as of late the cancer chemotherapy and radiotherapy has been substantially intensified in children suffering from malignancies. As acute leukemia is the commonest childhood malignancy, so this discussion mostly refers to acute leukemia in children.

### **Immunization in children with malignancies**

Many children with malignancies receive corticosteroids. Children receiving oral corticosteroids in high doses eg, prednisolone 1-2 mg/kg/day for more than 14 days should not receive live virus vaccines until the steroid has been discontinued for at least one month. Killed vaccines are safe but may be partially effective in such situations<sup>1</sup>.

#### **Live vaccines:**

*Measles vaccine* – Measles infection which is quite

common has high mortality in patients with cancer. Even there may be loss of immunity in children treated for leukemia previously vaccinated against measles. Immunization with live, attenuated vaccine is contraindicated because of risk of severe side effects in cancer patients undergoing chemotherapy. Immunization with live vaccines like measles might be considered in cancer patients not receiving active chemotherapy in epidemiologic situations when the risk for measles is increased<sup>2</sup>.

*Varicella vaccine* – Varicella virus infection is associated with high mortality in children with cancer. The existing vaccine is live, attenuated and based on Oka strain. The vaccine has been shown to be safe and effective in children with leukaemia who are in remission<sup>3</sup>. The frequency of side effects from the vaccine is low and breakthrough vaccine disease can usually be treated effectively with acyclovir. The risk of herpes zoster after vaccination is lower compared to that in patients who had natural varicella disease<sup>2</sup>.

Household exposure to varicella is associated with more extensive infection in secondary

cases. Healthy seronegative family members may be immunized when the child with cancer is undergoing intensive therapy and a live vaccine cannot be given.

*Oral polio vaccine* – The oral poliovirus vaccine can induce paralytic disease in immunocompromised patients and should not be used for immunization against poliomyelitis.

*Other live vaccines* – There is limited data on immunization with BCG, mumps, measles and rubella vaccines in cancer patients. These vaccines are not recommended during active cancer therapy<sup>2</sup>.

#### ***Killed vaccines:***

*DTP vaccines* – The protection against diphtheria, tetanus and pertussis is low in cancer patients undergoing chemotherapy. The loss of specific immunity is related to the intensity of given chemotherapy. Most children respond well to vaccination after chemotherapy for malignancies<sup>2</sup>.

*Inactivated poliovirus vaccine* – As the protection against polio virus is low in immunocompromised patients and oral polio vaccine cannot be used, inactivated poliovirus vaccine should be used for immunization of the patients with cancer. The poliovirus vaccine strain might be transferred from the healthy family members, so the use of inactivated vaccine when relatives are immunized is recommended.

*Hepatitis B virus vaccine* – Hepatitis b virus infection is a major cause of morbidity and mortality, more so in immunocompromised

patients. Immunization of patients against hepatitis B virus is indicated in countries like India where the prevalence of hepatitis B virus is high.

*Haemophilus influenzae type b (Hib) vaccine*– Children with leukaemia are at a greater risk for Hib infection compared to normal children. Immunization with conjugated Hib vaccine is indicated in children with cancer, preferably early during anticancer therapy.

*Pneumococcal vaccine* – Pneumococci are important causes of infection in patients with hematological malignancies. Lymphoma patients with poor antibody responses to polysaccharide vaccine have an increased risk for severe pneumococcal infections. So the vaccines which are able to induce better immune responses such as the conjugate pneumococcal vaccines are probably more immunogenic. Immunization of patients with hematological malignancies including lymphoma against pneumococcal infections is recommended as early as possible after diagnosis and before chemotherapy and / or radiotherapy is initiated<sup>2</sup>.

*Influenza vaccine* – The mortality and morbidity of influenza vary in different types of cancer patients. The most severe consequences occur in acute leukaemia patients undergoing induction chemotherapy. Influenza vaccination with inactivated vaccine is recommended in immunocompromised patients<sup>4</sup>. Two doses might give a better immune response.

*Meningococcal vaccine* – Vaccination should also be considered against meningococcal

infections.

*Human papilloma virus vaccine* – As of now there is no robust data on use of human papilloma virus vaccine in children suffering from malignancies. But the antigens of the vaccine are based on the L1 capsid proteins of certain types of human papilloma virus (HPV) assembled into virus-like particles (VLPs). The L1 capsid proteins self-assemble into VLPs that mimic the original HPV viruses but are not infectious and contain no oncogenic HPV DNA. Hence this vaccine can be used in children with malignancies as any other killed vaccines.

***Household contact vaccination:***

Household and other close contacts of immunocompromised patients should receive all age appropriate vaccines except live oral poliovirus vaccine<sup>2</sup>. This is also termed as cocoon strategy or ring immunization.

There are no effective vaccines available against several infections which are of great importance in these patients such as CMV, adenovirus and aspergillus infections.

***Infection in children with malignancies***

Children suffering from various malignancies are at increased risk of infection. Besides blood stream and other invasive infections, they suffer frequently from skin and soft-tissue infection. As they are caused by a wide range of pathogens and are often part of a widely disseminated infection, they frequently pose a very difficult clinical problem.

Infection prevention is of utmost importance

in children suffering from malignancies. When infections do develop, it is critical to establish a specific etiologic diagnosis as very often the infection is nosocomial and are caused by pathogens with increased antibiotic resistance. Even the skin lesions no matter how small and trivial should be carefully evaluated. The gross appearance of any skin lesion is frequently altered by decreased inflammatory response<sup>5</sup>. It is very important to thoroughly investigate any infection. Blood culture should always be done.

The current treatment protocols for cancer patients are very intense which frequently expose the patients to episodes of neutropenia. Even though several arms of the immune system can be affected, neutropenia is the major abnormality in children with cancer. During these episodes the patients are at increased risk of developing potentially fatal invasive infections. Antibiotic therapy should be initiated on the basis of important clinical parameters identified and the most likely offending pathogens.

***Causative organisms:***

Few years back the gram-negative organisms were the leading cause of infection in neutropenic patients. Over the years with the use of antibiotics to cover the gram-negative organisms, gram-positive organisms have become the predominant cause of infections, currently accounting for more than 60-70% of isolates<sup>6</sup>. In some centres though gram-negative infections have become common probably due to misuse of vancomycin.

The common gram-positive organisms are coagulase negative staphylococci, *Staphylococcus aureus*, *Streptococcus viridans*, *S. pneumoniae*, *Enterococci* and sometimes bacillus and corynebacterium species. The frequent gram-negative organisms isolated are *E. coli*, *Klebsiella*, *Pseudomonas* species and sometimes *Proteus* species, *Acinetobacter*. Anaerobic organisms seen are bacteroides and fusobacterium. The common fungal infections encountered are *Candida albicans* followed by *Aspergillus fumigatus*.

**Initial antibiotic therapy:**

Febrile neutropenia in cancer patients is one of the indications of empirical antibiotic therapy as blood stream infections in these patients can be rapid and fatal. The following are the three options for initial antibiotic therapy<sup>6</sup>.

- (i) *Single antibiotic therapy without vancomycin* – The single antibiotic used should cover gram-negative infection including *Pseudomonas*. The options are ceftazidime, cefipime, carbapenem or piperacillin-tazobactam. Aminoglycosides and quinolones should not be used as a single drug<sup>6</sup>.
- (ii) *Two drug combinations without vancomycin* – It is preferred in complicated cases and to achieve better coverage and reduce drug resistance. The options are addition of aminoglycoside to the previous regime or ciprofloxacin with amoxicillin-clavulanic acid.

- (iii) *Vancomycin plus 1 or 2 drugs* – Vancomycin is not recommended as the first line drug except the following situations. Catheter induced sepsis, complicated patients with high fever and hypotension, culture showing infection with drug resistant gram-positive organism, a patient known to be colonised with such an organism in the past. Vancomycin should be used in combination with other first line drugs. Linezolid is equally effective as vancomycin.

**Antibiotic therapy in initial 5-7 days:**

The culture report is expected after 48-72 hours. If the culture report is positive, the antibiotics should be adjusted still keeping broad spectrum coverage<sup>6</sup>. Usually it takes 3-5 days for response to the first line of antibiotics. In the mean time if the patient deteriorates one may have to add or change the antibiotics even before 72 hours. If vancomycin is started initially and the organism shows sensitivity to other drugs, vancomycin should be stopped.

Occasionally the situation may be such that culture is negative but the patient is still febrile on day 3 after initial antibiotics. It may be a case of delayed response as some patients may take up to 5 days for response. The presence of an organ infection and abscess somewhere or sub-optimal dose of antibiotics has to be ruled out. The possibility of a non-bacterial infection, drug resistant organism or fungal infection should be considered.

***Duration of antibiotics:***

When the patient is afebrile for more than 2 days, clinically stable without any complications, no organism is isolated on culture and absolute neutrophil count is above 500 cells/cu mm of blood, one can stop the antibiotics<sup>6</sup>. If the patient is afebrile but absolute neutrophil count continues to be low, one should ideally continue antibiotics till the neutrophil count is normal. But even in such situations antibiotics can be stopped after 5-7 days.

Infections occur in children with cancer even without neutropenia, usually these are viral etiology. *P. carinii* can cause pneumonitis

regardless of neutrophil count. Cotrimoxazole prophylaxis is an effective preventive strategy<sup>7</sup>.

It is utmost important to use antimicrobials judiciously in any children, more so in children who are suffering from malignancies. Globally antibiotic resistance is spreading like wildfire and when the multiple drug resistant organisms attack these immunocompromised children they are at greater risk. Though infection cannot be completely prevented in children who have defects in one or more arms of their immune system, but some measures can decrease the risk of infection and make treatment fruitful.

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## Control of Measles Infection

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The Millennium Development Goal (MDG) 4, is to reduce the under five mortality rate by 2/3<sup>rd</sup> between 1990 and 2015 in the world. One of the key interventions, to reduce the same and accelerate achievement of the goal is to strengthen measles control activities. WHO's Global strategy is for **sustainable measles mortality reduction**. At the outset, in May 2003, the 56<sup>th</sup> World Health Assembly had unanimously adopted a resolution to reduce measles death by 50% by the end of 2005 compared to 1999 levels. Later on in 2005, the World Health Assembly again set a for global measles control: a 90% reduction in measles mortality by 2010 compared with 2000 levels<sup>1</sup>.

Measles deaths worldwide fell by 78% between 2000 and 2008. North America has achieved elimination of measles in 2002, while European, Eastern Mediterranean and Western Pacific regions have targeted measles for elimination. WHO defines **elimination of measles** as the absence of endemic measles for a period of = 12 months in the presence of adequate surveillance. The strategy in Africa and South East Asia focuses

on **measles control** that is reduction of measles morbidity and mortality in accordance with the target<sup>1</sup>.

In India, measles is a major cause of morbidity and a significant contributor to childhood mortality. The Million Death Study in collaboration with Registrar General and Census Commissioner of India estimated that 92,000 children (99% CI: 79000 to 104000) died in 2005 due to measles, accounting for 4% of all under five deaths in India. Currently the National plan proposes to reduce measles mortality by 95% by 2013 compared to 2000 estimates<sup>2</sup>.

Consistent with WHO's Global strategy for **sustainable measles mortality reduction India strategic plan 2005-2010** addresses the issue of measles mortality reduction by 2/3 within 2010 compared to 2000 estimates<sup>3</sup>.

The key strategies comprises of

- 1. Strong routine immunization with the first dose of measles vaccine** of >90% of target population in 80% of the districts of the country by 2009<sup>2</sup>.

2. To establish **effective measles surveillance** that provides good quality epidemiological data about number of measles cases and measles death and its prevalence in particular age group and the vaccination status of the cases.
3. Active surveillance will help to identify any outbreak of measles and **to conduct outbreak investigation** supported by laboratory confirmation.
4. As soon as measles case has been identified proper case management including Vitamin-A supplementation and adequate treatment of complications.
5. Providing a **second opportunity of measles containing vaccine (MCV2)** to appropriate age group of children through either **second routine dose** of MCV or through **supplemental immunization activities (SIA)**<sup>1</sup>.

In accordance with National Technical Advisory Group on Immunization (NTAGI) recommendations, MCV2 is being introduced through mass catch-up vaccination campaigns in 14 states where routine first dose measles vaccination coverage is less than 80% according to District level Household Survey 3. **Catch-up vaccination** (launched in late 2010) as a part of SIA, is defined as a onetime nationwide vaccination campaign targeting usually all children aged between 9 months to 10 years, irrespective of previous immunization status or occurrence of measles disease. The remaining 21 states and Union Territories with MCV1 coverage = 80% are

introducing MCV2 through the routine programs. Delhi, Goa, Puducherry and Sikkim are already using MMR vaccine as MCV 2 in their routine immunization<sup>1</sup>.

**Key elements of Surveillance system are:**

- (i) Detection and timely notification of all measles cases.
- (ii) Investigation and confirmation (epidemiological, clinical, laboratory) of suspected measles cases
- (iii) Collection analysis and interpretation of data
- (iv) Feedback and dissemination of results
- (v) Prevention and control measures
- (vi) Timely detection of an outbreak and outbreak investigation

**Measles Surveillance Structure:**

All states in India have a well established polio surveillance network since 1997. The same structure has been utilized for measles surveillance also.

**Case definition of suspected measles:**

Any person with fever and maculo-papular rash with cough, coryza or conjunctivitis (either of the 3C's) or any person in whom **clinician suspects** measles infection.

1. **Clinically diagnosed measles** is a case which has occurred within the last 3 months
2. **Epidemiologically linked measles:** A case that meets the clinical case definition and is linked epidemiologically to a laboratory confirmed case for the

purpose of epidemiological investigation.

- 3. Laboratory Confirmed disease:** A case that needs the clinical case definition and presence of measles specific IgM antibodies in the serum.

**Reporting units (RU):**

Reporting is done through a network of reporting units which may be a hospital or any health care centres. Medical officers, General Physicians (GP), Pediatricians, Nurses, Health worker who come across suspected measles cases should inform the **designated nodal officer** immediately upon identification of the case. In fact any individual who come across measles cases can notify it to the district. The nodal officer at each RU should report to the district by Monday of each week sending details of the case in the VPD-H0002 form. Even if there is no case **zero reporting** should be sent using the same form<sup>3</sup>.

The DIO (District Immunization Officer) should send his report routinely to the state EPI officer by Tuesday. The DIO should analyze the available district data on a weekly basis using and reconciling case information from different surveillance systems such as IDSP to identify suspected outbreaks of measles. If suspected outbreaks are identified measles outbreak investigation should be initiated.

**Measles outbreak detection and Investigation:**

A suspected measles outbreak is said to occur when number of clinically diagnosed measles

cases are greater than the number normally expected in the geographic area for the same period of time. The details of investigation of suspected measles case should be made at the district level.

= 5 clinical cases of measles in a block in a week

Or

Any measles associated death in a block in a week

Or

= 5 clinical cases in an area bordering more than one adjacent block. (emphasis given to clustering of cases in adjacent blocks of 2 or more districts)

**Objective of Outbreak investigations:**

- (i) To study the epidemiology of measles and to identify the population at risk
- (ii) To review the dynamics of measles infection and impact of measles vaccination
- (iii) To suggest ways to improve measles vaccine coverage
- (iv) To reduce complications and deaths due to measles.

**Laboratory confirmation of the outbreak:**

The correct timing of sample collection with respect to the clinical signs is important for interpreting results and arriving at an accurate conclusion. Detection of measles specific IgM antibodies confirm that the outbreak is due to measles. IgM Elisa test are very sensitive

between 4 and 28 days after the onset of rash. A single positive serum sample obtained within 28 days after the onset of measles is considered adequate for confirmation of a measles case.

IgM detection is done only at WHO accredited laboratories by using Standardized ELISA kits. The results will be provided within 7 days. Measles specific IgM antibodies appear within the first few days of the rash and decline rapidly after one month. Their presence provides strong evidence of recent measles infection. IgM is also produced on primary vaccination and although it may decline more rapidly than IgM produced in response to the natural disease. Therefore vaccine induced IgM and wild virus induced IgM cannot be distinguished by serological test. Therefore a vaccination history is essential for interpretation of test results. At least 5 samples should be tested for measles IgM. All measles negative sera should be further tested for rubella specific IgM antibody<sup>3</sup>.

Send the outbreak investigation report to concern district and state government officers.

#### **Indicators of adequate surveillance**

- (i) At least 80% of reporting sites should report each week on the presence or absence of measles cases.

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2. World Health Organisation: AFP ALERT, Na-

- (ii) At least 80% of surveillance sites should report one or more clinically confirmed measles cases per year

- (iii) Proportions of outbreaks investigated against the threshold level identified by the Epidemic Response Team

WHO NPSF has worked closely with GOI AND State governments to plan and implement measles control programme. Using the AFP Surveillance reporting network, WHO NPSF has supported the establishment of laboratory enhanced measles outbreak surveillance since 2006. The network is providing important epidemiological information related to age distribution and vaccination status of confirmed measles cases. Data generated from this system illustrated that 90% of cases were less than 10 years of age in low coverage states, and was the basis of the NTAGI recommendation to target children 9 months to 10 years for the MCV2 catch up campaigns. Another important fact came out of this surveillance that many of the outbreaks are due to Rubella infection. Therefore there is recommendation is to introduce MR (Measles Rubella vaccine) in National immunization programme as MCV2 in select well performing states.

3. Field Guide: Measles Surveillance and Outbreak Investigation, September 2006, Government of India, Department of Family Welfare, New Delhi.

## Periodic Fever Syndrome

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These syndromes refer to diseases that cause periodic (episodic) fever that do not have an infectious (virus, bacteria) cause. In general children with these syndromes are well between episodes. Many of these syndromes are hereditary and result from a mutation in a gene. The syndromes are defined by the defect in gene as well as by the clinical features of the syndrome, the parts of the body affected in addition to fever, the age of the child when the syndrome starts, and the ethnicity (the area of the world where the child or parents come from) of the child and parents. Many of these syndromes have a specific treatment, often based on understanding the problem caused by the genetic defect. Under this heading the following diseases can be reviewed:

- (1) **Familial Mediterranean Fever (FMF)**,
- (2) **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)**,
- (3) **Hyperimmunoglobulin D syndrome (HIDS)**, also called *Mevalonate Kinase Associated Periodic Fever Syndrome*,
- (4) **Neonatal Onset Multisystem**

**Inflammatory Disease (NOMID)**, in Europe called **Chronic Inflammatory Neurological Cutaneous Articular (CINCA)** syndrome and related diseases,

- (5) **Muckle-Wells syndrome and Familial Cold auto inflammatory syndrome and**
- (6) **Periodic fever, Aphthous-stomatitis, Pharyngitis, Adenitis Syndrome (PFAPA)**.

### A. Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) is the most common periodic fever syndrome. Patients suffer from recurrent episodes of fever, accompanied by abdominal, chest and joint pain and swelling. The disease generally affects people of Mediterranean and Middle Eastern descent, typically Sephardic Jews, Turks, Arabs and Armenians. Since the discovery of the gene defect, it is being diagnosed more frequently, even among populations where it was thought to be very rare, such as Italians, Greeks and Ashkenazi Jews. FMF episodes start before the age of 20 years in approximately 90% of the patients

of which in more than half of them it appears before the age of 10 years.

FMF is an **autosomal recessive** disease. The responsible gene is called the **MEFV gene**, named after the Mediterranean Sea, and it affects a protein called **pyrin**, which plays a role in the natural control of inflammation. When this gene has a defect, the regulation of inflammation cannot be done properly and patients experience episodes of fever and other symptoms. Infection, trauma, menstruation or psychological stress may be the trigger factors.

#### ***Clinical features :***

The main symptoms of the disease are recurrent fever, accompanied by abdominal, chest, or joint pains. Not all children will have all symptoms and symptoms may change over time. Episodes resolve without treatment and usually last between one and four days. Most children are totally normal between episodes, but some children have frequent episodes, from which they do not fully recover and as a result do not grow properly. Some of the attacks may be too painful to seek medical help. For example, severe abdominal attacks may mimic acute appendicitis and therefore some patients may undergo abdominal surgery, such as an appendectomy. The chest pain may be so severe that it may be difficult to breathe deeply.

Usually, only one joint is affected at a time, most commonly an ankle or a knee. The joint may be so swollen and painful that the child

cannot walk. In about a third of these patients there is a red rash over the involved joint. Sometimes, the sole finding of the disease may be episodes of joint pain and swelling, which is misdiagnosed as acute rheumatic fever, or juvenile idiopathic arthritis. Usually the joint swelling resolves over 5-14 days. In about 5-10% of cases the joint involvement may become chronic. Some children may complain muscle pain in the legs. Rarely, children have recurrent pericarditis, myositis, meningitis and orchitis. Frequent attacks can affect the child's and family's life, including school attendance.

The most severe complication of FMF if untreated is the development of amyloidosis. The most common organ involved is the kidney, but amyloid can deposit in the gut, skin and heart. Eventually amyloid causes a loss of function, especially of the kidneys. Children who are properly treated are safe from the risk of developing this life-threatening complication.

FMF can appear or be active in adults but often the disease is milder and less obvious than in children. The risk of amyloidosis is lower in adult onset disease.

#### ***How to diagnose?***

Diagnosis of FMF is still based on clinical signs. FMF is suspected in children with episodic fever with an ethnic origin typical for FMF and/or with a family history of FMF or unexplained kidney failure. Often children initially have episodes of fever without the other symptoms. so it takes

careful observation (families should write a diary documenting the episodes and describing what happens) until a diagnosis is made. Because not all children have typical episodes it may take a long time to suspect FMF and to make the diagnosis. Examining the child during an episode and obtaining laboratory tests showing signs of inflammation are helpful (like tests for a sedimentation rate or a complete blood cell count). Generally, these tests become positive during an episode and return to normal, or near normal, after the episode ends. A sample of urine is also tested for the presence of protein. Patients with amyloidosis will have high levels of protein in urine tests. This warns the physician to do more tests to see if the protein in the urine is from amyloidosis.

In children suspected of having FMF, a genetic test to look for the gene mutation will be obtained. If these tests are positive (homozygote, which means that the gene defect is found in both gene copies, one from each parent), the diagnosis of FMF is definite. However, it is possible to have FMF with a defect in only one gene copy (called heterozygote) or even without any gene defect. In that case the response to the specific FMF treatment, colchicine, will determine the diagnosis. It is highly probable that children have FMF if they do not have episodes or have a lot fewer episodes when they are being treated with colchicine. Usually a trial of 6 months of treatment is given.

#### ***How is it treated?***

FMF cannot be cured, but it can be well

controlled with life-long use of colchicine. In this way, episodes can usually be prevented (in 60% of patients completely prevented, in 33% partially prevented, and in about 5% colchicine is not effective) and amyloidosis can be prevented in 100% of patients. If the patient stops taking the drug, episodes (often after missing only one dose!) and the risk of amyloidosis may return. Compliance is very important. If colchicine is taken regularly the child can live a normal life with a normal life expectancy. The patient or the parents should not change the medication dose without discussing this first with the doctor. Some children initially need psychological support for a disease that means taking medications for their entire life. Colchicine prevents episodes from starting but does not treat an episode that has already started. Therefore, the dose of colchicine should not be increased during an already active episode.

#### ***What are the side effects?***

Colchicine is a safe drug with minor side effects. The most frequent side effect is diarrhea. Other side effects are nausea, vomiting, and abdominal cramps. Children taking colchicine grow normally, though they should have blood count and urine tests at least twice a year.

#### ***What is the long-term outcome and course of the disease?***

If treated properly with life-long colchicine, children with FMF live a normal life. If there is a delay in diagnosis, or lack of compliance with treatment, the risk of developing

amyloidosis increases. Children who develop amyloidosis may eventually need dialysis or a kidney transplant. There are no restrictions on the child's everyday life.

### **B. Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)**

TRAPS is a genetic disease with an **autosomal dominant** inheritance. Besides episodes of fever, other symptoms include abdominal pain, diarrhea, migratory painful red skin rashes, muscle pain and swelling around the eye. The gene defect was only recently discovered. The former name of this syndrome was Familial Hibernian fever.

#### *How common is it?*

TRAPS is a rare disease but since the gene defect was discovered more patients with different clinical features have been discovered. Thus, the actual frequency is still unknown. It affects males and females equally and the onset seems to be during late childhood, or adulthood. The first cases were reported in patients from Irish-Scottish ancestry; however the disease has also been identified in almost all ethnic groups.

#### *What causes TRAPS?*

TRAPS is due to a gene defect in a protein called **Tumor Necrosis Factor Receptor (TNFR)**, which leads to an increase of the patient's normal inflammatory response. The protein that causes inflammation, called tumor necrosis factor (TNF), overacts, since the receptor (TNFR) that usually binds to TNF is not present to control its activity. Infection,

trauma or psychological stress may trigger episodes. However, not every person that has a gene defect will have the clinical signs of TRAPS.

#### *What are the main symptoms?*

The main symptoms are recurrent episodes of fever typically lasting two or three weeks, associated with chills and intense muscle pain involving the trunk and the upper limbs. The typical rash is red and painful, representing underlying inflammation of the skin and muscle. The rash moves from one place to another on the body, usually from the arms and legs to the trunk. Most patients feel cramping muscle pain at the onset of attacks that gradually increases in strength and also moves from one part of the body to another. Abdominal pain with nausea and vomiting are common. Inflammation of conjunctiva, and/or swelling around the eye is common. Other less common features include chest pain, due pleuritis or pericarditis. Like FMF, amyloidosis is the most severe late complication of TRAPS and often results in large amounts of proteins in the urine and kidney failure.

#### *How is it diagnosed?*

TRAPS is suspected based on the clinical symptoms, the physical examination and from taking a family medical history. Blood tests will show signs of inflammation during an episode. The diagnosis is confirmed only by genetic tests showing a genetic defect in the TNFR gene. Other types of periodic fever syndromes should be tested and excluded

### ***What are the treatments?***

There is still no proven definitive treatment to prevent or cure the disease. Non-specific anti-inflammatory agents, including steroid use, help to relieve symptoms, but long-term steroid use leads to serious side effects. Giving a medicine that is similar to the TNF receptor called Enbrel (etanercept, a medicine used to treat juvenile idiopathic arthritis) has been shown to be an effective treatment in some patients when given at the beginning of an attack or even as preventive medicine.

### ***How long will the disease last?***

Patients with TRAPS will have episodes of symptoms throughout their life.

### ***What is the long-term outcome and course of TRAPS?***

It is hard to predict the outcome in any one patient since amyloidosis appears in only a minority of patients. This risk is dependent in part on the genetic defect and on other unclear environmental factors.

### **C. Hyperimmunoglobulin D syndrome (HIDS), also called Mevalonate Kinase Associated Periodic Fever Syndrome**

HIDS is an **autosomal recessive** disease that results in episodic high fever with skin rash, swelling of lymph nodes in the neck, abdominal pain, vomiting and diarrhea. The disease starts early in infancy. The name of this disease comes from the fact that most patients have very high amounts of immunoglobulin D. The most severe form of this disease starts at birth and is called mevalonic aciduria. These patients also have

neurologic disease and suffer from poor growth. More mild form of this disease form starts with episodes of fever.

### ***How common is it?***

HIDS is a very rare disease. The disease is mostly found in Western Europe, especially in the Netherlands and in France but has been described in all ethnic groups. Boys and girls are equally affected. Symptoms usually start in early childhood, most commonly in the first year of life.

### ***What are the causes HIDS?***

HIDS is a genetic disease. The gene defect is in a protein called mevalonic kinase (MVK). MVK is a protein that facilitates a chemical reaction in the body involved in the process of making cholesterol. In HIDS the MVK enzyme is active in only 1-10% of the normal enzyme activity. It is still not known why the gene defect causes fever. Episodes can be triggered by infection, stress, and vaccination or without any obvious trigger. HIDS is inherited in an **autosomal recessive** way.

### ***What are the main symptoms?***

Fever episodes are the major symptom, lasting three to seven days and recurring every 2-12 weeks. The attacks begin suddenly, often with shaking chills. Headache, abdominal pain, loss of appetite and flu-like symptoms are common. Most patients experience nausea, vomiting or diarrhea. Skin rashes, painful ulcers in the mouth and joint pain all occur, but the most striking feature is swelling of the lymph nodes in the neck, or other parts of the body.

### *How is it diagnosed?*

The disease is diagnosed based on clinical symptoms. Blood tests showing signs of inflammation during an episode are usually seen. Most, but not all, especially very young patients have elevated levels of immunoglobulin D. During episodes, a urine test for organic acid will show high levels of mevalonic acid. The diagnosis will be confirmed by a genetic test finding the genetic defect in the MVK protein.

### *What is the treatment?*

HIDS cannot be cured. An effective treatment to prevent attacks is not available. Research is being done to search for effective treatments. During an episode non-steroidal anti-inflammatory drugs (like ibuprofen, naproxen) or steroids may be partially helpful.

### *How long will the disease last and what is the outcome?*

HIDS is a lifelong disorder but episodes usually get milder and less frequent over time, often resolving later in life. Some patients develop arthritis. Except for amyloidosis in very rare cases, HIDS does not lead to severe organ damage.

### **D. Neonatal Onset Multisystem Inflammatory Disease (NOMID), in Europe called Chronic Inflammatory Neurological Cutaneous Articular (CINCA) syndrome and related diseases**

NOMID is a rare genetic disease causing episodes of fever. The symptoms start at birth, or are observed within the first weeks of life. The first symptoms are usually a skin

rash and fever. Infants also have neurologic symptoms, such as chronic meningitis, hearing and vision loss. About 50% of the children later develop severe joint involvement and have significant growth abnormalities. Two other less severe diseases that are caused by defects on the same gene of NOMID are called Muckle-Wells syndrome (MWS) and familial cold auto inflammatory – also called familial cold urticaria - syndrome (FCAS). These diseases start later in life. The entire group of these diseases are now called the **cryopyrin- associated auto inflammatory diseases**.

### *How common is it?*

NOMID is a very rare condition. MWS and FCAS are probably seen more frequently but are still rare.

### *What are the causes of the disease?*

NOMID is a genetic disease inherited as an **autosomal dominant**. A genetic defect is found in only 50% of patients. The gene defect is in a protein called **cryopyrin**, which has the important task of controlling inflammation in the body. NOMID occurs equally in males and females. It has been observed in all populations, Caucasian, black or Asiatic. There is no seasonal influence.

### *What are the main symptoms?*

Some of the infants with NOMID are born prematurely. The babies often have signs of infection (fever, rash) at birth but no infection is found. The rash resembles urticaria but is not itchy. The rash increases in intensity with fever. Patients have neurologic problems

from chronic meningitis. This can result in vision difficulties, hearing loss and other neurologic problems. The eyes often appear as bulging and children often have episodes of vomiting. The skull is often slightly increased in size. In some children, there is delayed closure of the anterior fontanel. Usually after 1 year of age, patients develop joint pain and swelling. In severe cases an overgrowth of cartilage and of the bone epiphysis especially at the knee may occur, resulting in joint deformity. These bone changes are seen in X-rays. There is a delay in growth and the children with NOMID are often very short. Not all children have all these symptoms.

#### ***How is it diagnosed?***

NOMID is suspected by the clinical features. The diagnosis is confirmed by the genetic test. However, 50% of the children do not have a genetic mutation.

#### ***How is it treated?***

Until recently there was no effective treatment. Patients were treated with medications to reduce symptoms like nonsteroidal anti-inflammatory drugs, steroids or methotrexate. Exciting recent research has shown that medications that target specific molecules involved in the inflammatory process that may be increased in NOMID due to the genetic defect may be very effective for treating NOMID. Initial studies have shown that most NOMID patients respond dramatically to treatment with Kineret (anakinra , a medication approved for the treatment of

rheumatoid arthritis, is effective in stopping the progression of organ damage in people with NOMID). However this treatment must continue indefinitely as there is no known cure to NOMID.

Physical therapy, splints and other aids are necessary to treat joint deformities if they occur. Splints and walking aids might be necessary. Surgery is occasionally needed to correct these deformities. Hearing aids are needed for children with deafness.

#### ***What is the long-term outcome of the disease?***

The outcome of NOMID used to be poor, with severe growth disturbances. Many patients developed severe joint deformities and neurologic damage, mainly to the ears and eyes. There were also cases of death from brain damage. New treatment may have changed this poor outcome. Future studies are planned to answer this question.

#### **E. Muckle-Wells syndrome and Familial Cold auto inflammatory syndrome**

These syndromes are related to gene defects on the same cryopyrin protein gene causing NOMID. As in NOMID, no gene defect is found in about 50% of the patients. In familial cold auto inflammatory syndrome, cold, and perhaps other environmental triggers, causes a urticaria like rash to occur.

In Muckle-Wells syndrome patients also develop episodic fever and deafness. In both syndromes untreated patients often develop amyloidosis.

## **F. Periodic fever, Aphthous-stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome**

This syndrome includes recurrent episodes of fever with aphthous-stomatitis, pharyngitis, sometimes with exudate - like that seen in a throat with streptococcal infection. PFAPA affects children in early childhood, usually starting at age two to four years. Episodes usually decrease in frequency and resolve after the age of 10 years. This disease was recognized for the first time in 1987 and was called Marshall's.

### ***How common is it?***

The frequency of PFAPA is not known, but the disease appears to be more common than generally appreciated.

### ***What causes PFAPA?***

The answer to this question is not yet known. **No gene defect has yet to be found** in PFAPA, although in some cases more than one family member has the disease. It is clear that the inflammatory process is activated during episodes but it is not clear why it is triggered.

### ***What are the main symptoms?***

The main symptoms are episodic fevers, accompanied by a sore throat, mouth ulcers, or enlarged cervical lymph nodes. The episodes of fever start abruptly and last for three to seven days. During episodes, the child looks very ill and complains about at least one of the three symptoms mentioned above. The episodes of fever recur every few weeks and often families know the exact day when

an attack will start. On the day the fever starts the child will feel a little ill before the attack and the family knows an attack is about to start. Not all children have all symptoms, especially mouth sores. Some children have other symptoms like joint pain, abdominal pain, headache, vomiting or diarrhea.

### ***How is PFAPA diagnosed?***

There are no laboratory tests, or imaging procedures, specific for diagnosing PFAPA. The disease will be diagnosed based on the results of a physical examination and other symptoms. Inflammatory blood tests like the white blood cell count, erythrocyte sedimentation rate and the C-reactive protein are increased during attacks. Before the diagnosis is confirmed, it is important to exclude all other diseases that may present with similar symptoms especially a streptococcal throat.

### ***How is PFAPA treated?***

There is no specific treatment to cure PFAPA. The aim of treatment is to control symptoms during the episodes of fever, to shorten the duration of episodes, and in some children to prevent attacks from occurring. In most children, the disease will resolve by itself without treatment, usually after the age of 10 years. The fever does not usually respond well to Paracetamol or nonsteroidal anti-inflammatory drugs. A single dose of steroids (usually prednisone), given when symptoms first appear, has been shown to shorten an episode and sometimes even end the episode. However, the interval between episodes may

also be shortened with this treatment, and the next episode may occur earlier than expected. In some patients using cimetidine may prevents attacks from occurring. In patients with very frequent attacks, a tonsillectomy may be considered.

***What is the outcome and course of PFAPA?***

The disease may last for several years. Over time, the intervals between the episodes will increase and usually after the age of 10 years resolve by itself. Children with PFAPA continue to grow and develop normally.

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## The Restless Leg Syndrome

Saheli Misra

Assistant Professor, Institute of Child Health, Kolkata

The restless leg syndrome is a common neurological disorder in adults. Studies over recent years have shown that majority of these adults had their symptoms since childhood or adolescent.<sup>1,2</sup> Although Ekbom reported RLS symptomatology in childhood as early as the 1940s, it was not until the mid-1990s that detailed pediatric case reports with polysomnography appeared in the literature. A population-based data suggest that restless legs syndrome is prevalent and troublesome in children and adolescents, occurring more commonly than epilepsy or diabetes<sup>3</sup>.

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by the prototypic complaint of a strong, nearly irresistible urge to move the legs. Consensus criteria for the diagnosis of RLS in children and adolescents were published in 2003 after a workshop at the National Institutes of Health (Table 1). Typically, RLS follows a circadian pattern, usually occurring in the evening or night but, rarely, at other times during the day. Pain” is a term commonly used to describe the uncomfortable sensations in children with RLS. But the more pain the child complains

of, the less likely it is RLS. RLS-related pain in children typically occurs from both knees down and especially involves the calves, although thigh pain may also appear. These

**Table 1: Criteria for making the diagnosis of definite RLS in children.<sup>6</sup>**

- 
1. The child meets all four essential adult criteria for RLS (the urge to move the legs, is worse during rest, relieved by movement and worse during the evening and at night) and
  2. The child relates a description in his or her own words that is consistent with leg discomfort (the child may use terms such as oowies, tickle, spiders, boo-boos, want to run and a lot of energy in my legs to describe the symptoms. Age-appropriate descriptors are encouraged)

Or

1. The child meets all four essential adult criteria for RLS and
2. Two of the three following supportive criteria are present.

Sleep disturbance for age

A biologic parent or sibling has definite RLS

The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep.

---

pains can be symmetric or asymmetric. Partial or complete resolution by movement is a key feature when diagnosing RLS in children with pain complaints. The RLS sensations are partially or completely resolved with motor movements or actions involving the lower extremities like walking or running, rubbing, stretching, or kicking the legs.

### **Etiology**

Primary RLS is believed to be inherited, and evidence indicates that it may be an autosomal dominant disorder. Some RLS-susceptibility loci have been found, and it is believed that other loci may be involved. Central dopaminergic systems are involved to some extent in the pathogenesis of RLS<sup>6</sup>.

The most common cause of secondary RLS in children appears to be iron deficiency. Iron is integral for the biosynthesis of dopamine; it is necessary for tyrosine hydroxylation, which is a rate-limiting step for dopamine production. The levels of serum ferritin in children that are considered normal vary according to age and sex<sup>7</sup>. Kotagal and Silber found that serum ferritin levels in children with RLS were low in a large percentage of subjects who fulfilled the strict criteria of children with definite and/or probable RLS. They found that 33% of children with RLS had serum ferritin below the 5th percentile, 75% below the median (23 micrograms (mcg)/L in males and 17 mcg/L in females), and 83% below 50 mcg/L. The 50 mcg/L level was selected because of its association with greater severity of RLS. Research has

not yet determined whether this iron deficiency is associated with diet or a genetic predisposition, but a combination of both may be the most likely explanation. Other causes of secondary RLS include peripheral neuropathy and uremia. Medications, such as antidepressants (eg, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]), sedating antihistamines, and dopamine receptor antagonists, may worsen or precipitate cases of RLS<sup>8</sup>.

### **Differential diagnosis (Table 2)**

Growing pain, motor tics are sometimes difficult to differentiate from RLS.

**Table 2: Differential diagnosis of RLS**

---

Motor Tics
Growing pains
Attention deficit hyperactivity disorder
Muscle Pain
Leg Cramps
Osgood-Schlatter's Disease
Chondromalacia Patella
Arthalgias
Periodic limb movement disorder

---

### **Management**

The best initial form of treatment is to reduce factors or conditions that may worsen or precipitate RLS. Iron deficiency should be considered in a child with RLS. Measuring serum ferritin is recommended, but it should not be tested in ill children; it can be falsely elevated because ferritin is an acute-phase reactant.

Children with low-iron stores as defined by

low-serum ferritin levels may benefit from iron therapy. Several studies have suggested the benefit of raising serum ferritin above 50 ng/ml.<sup>9,10</sup> The dose of iron therapy is 3 mg of elemental iron/kg/ day. The duration of treatment was 3 months followed by slow tapering of the dose for a period of one year<sup>5</sup>. The preliminary long-term follow-up of these children treated with iron therapy showed consistent evidence of sustained clinical improvements 1–2 years after iron therapy, with serum iron and ferritin remaining at adequate levels<sup>7,11</sup>. Iron therapy seems to lead to long lasting improvement in clinical symptoms, can be considered as the initial

option, when serum ferritin levels are <50 ng/ml.

Good sleep hygiene practices can be helpful for children with RLS. These include enforcing a regular sleep-wake schedule; avoiding heavy meals, fluids, or exercise within a few hours of bedtime; and discouraging non-sleep-inducing activities such as watching television or playing games near bedtime.

There is limited experience regarding the use of dopaminergic medications in children. Although ropinirole and pramipexole are FDA approved medications in adults with RLS and PLMD, there is no approved medication for the pediatric population

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## Case Scenerio

### Case Presentation

**Arunaloke Bhattacharya**

*Associate Professor, Institute of Child Health, Kolkata*

A 4 year old boy presented with insidious onset of fever which was moderate grade intermittent, for 11 days, dry cough and cold for 4 days, there was no respiratory distress. Dull aching pain in upper abdomen for 1 day

#### Examination

Pallor-, Icterus+, Temp-100°F, LN-NP

Chest- movement less on right side vesicular breath sound. Left side, absent breath sound- Rt side middle and lower zone. Dull note on percussion on Right side.

Liver is palpable 3cm below RCM with a span of 12.5cm and was firm and tender.

Spleen was not palpable and fluid thrill could not be appreciated.

#### Investigation

Hb - 12.9 gm%, TC - 9100 / cmm, DC - P49L38M11E2,

Plt-3.68lakh/cmm, ESR-40mm

Serum Bili-5.4mg/dl(c-2.8,uc-2.6), TP-5.7gm/dl (albumin-2.9,globulin-2.8), SGOT-426u/l, SGPT-1039u/l

Serum Lipase- Serum Amylase- Serum LDH-

238u/l, CRP-1.5mg/l

HBSAg-VE, TT(5TU)-VE, Anti HAV IgM- Reactive. Chest Xray is shown in Fig 1.



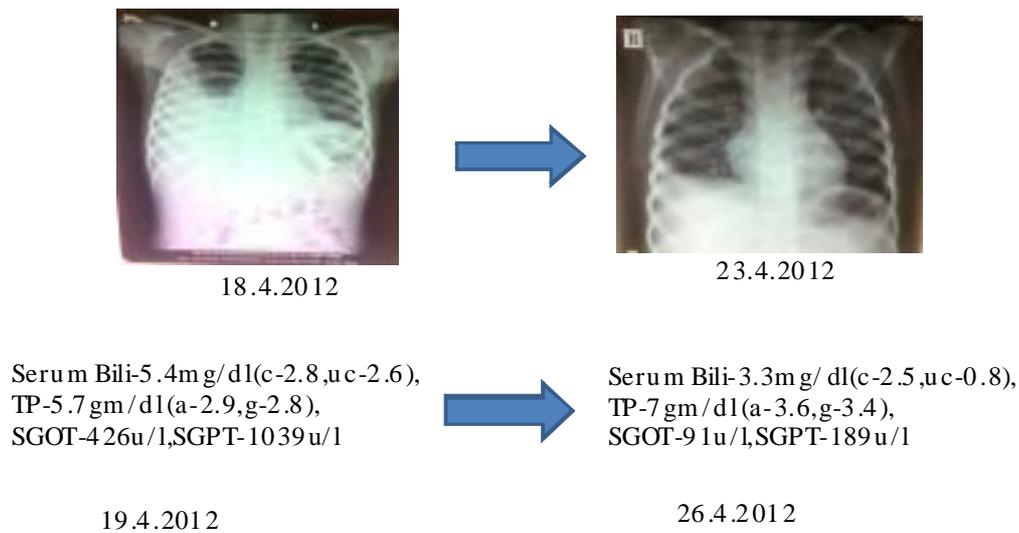
**Fig 1. Chest X-ray PA view on**

Pleural fluid examination revealed-Slight yellow hazy fluid with cell-165/cmm-Mostly lymphocytes (N-18%,L-82%), Protein-2.5gm%,sugar-105mg/dl, ADA-25.2u/L, LDH-120u/L

USG Abdomen-Enlarged liver with heterogenous parenchyma,small thick walled Gall Bladder,ascites with bilateral Pleural effusion, prominent mesenteric lymph nodes

Treatment-Supportive

The outcome of the patient is depicted in Fig.2



**Fig 2. Outcome of the patient**

### Discussion

Pleural effusion is a rare complication of acute viral hepatitis. The first case was reported in 1971, and thereafter 14 additional cases were reported. Among those, 5 were associated with hepatitis B and 2 had hepatitis A infection. The exact mechanism is unknown, though immune complexes have been cited as possible etiological factor<sup>1</sup>. Pleural effusion is a possible benign and early complication of acute hepatitis A infection that resolves spontaneously regardless of illness outcome<sup>2</sup>.

HAV infection may present also with rare complications such as acalculous cholecystitis, pleural effusion and ascites.

The exact pathogenesis of the effusion is

unknown but it seems likely to be related with inflammation of the liver, immune complexes or secondary to ascites<sup>3,4</sup>.

In all cases pleural effusion resolved spontaneously except the case reported by Tesovic et al which resulted in death<sup>5</sup>.

With this case, we want to emphasize that even though pleural effusion is rarely seen during the course of hepatitis A, it should be considered in differential diagnosis in the patients who are admitted for pleural effusions. Pleural effusion accompanying hepatitis A infection tends to resolve spontaneously. No unnecessary investigation as well as aggressive management is not indicated.

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Journal Scan

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**1. Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus. Silbergleit R et al. N Engl J Med 2012; 366:591-600**

*Something is always better than nothing and can sometime even be equal.*

Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes but intravascular access is always a problem particularly in the peripheries and in office practice. This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam was noninferior to intravenous lorazepam by a margin of 10 percentage

points. At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the intramuscular-midazolam group and in 282 of 445 (63.4%) in the intravenous-lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0 to 16.1;  $P < 0.001$  for both noninferiority and superiority). Hence the study concluded that for subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for pre-hospital seizure cessation.

**2. School children's backpacks, back pain and back pathologies. Rodríguez-Oviedo P et al. Arch Dis Child. 2012 Mar 10**

*Are we training our children to be mules and at what cost to their health?*

All of us must have felt sorry whenever we see school going children carrying heavy back packs. This study done in Spain investigated whether backpack weight is associated with back pain and back pathology in school children. In total they analyzed 1403 school children (aged 12–17) for their backpack weight along with body mass index, age and

gender. They found 61.4% had backpacks exceeding 10% of their body weight. Those carrying the heaviest backpacks had a 50% higher risk of back pain (OR 1.50 CI 95% 1.06 to 2.12) and a 42% higher risk of back pathology, although this last result was not statistically significant (OR 1.42 CI 95% 0.86 to 2.32). Girls presented a higher risk of back pain compared with boys. In conclusion carrying backpacks increases the risk of back pain and possibly the risk of back pathology. A study from India has also implicated backpacks of significant weights to alter postural angles (Ramprasad et al Indian Pediatrics, 2010, July 47 (7) 575 -580). It will be interesting to see the result of a similar study in our school children.

**3. Reliability of resting blood pressure measurement and classification using an oscillometric device in children with chronic kidney disease. Flynn JT et al. J Pediatr. 2012 Mar;160(3):434-440.e1.**

*Old still remains the gold.*

Availability of automated blood pressure measuring devices has lead to increasing reliability on it and often we are forgetting that the gold standard remains manual auscultation. This was again reconfirmed in a cohort of children suffering from chronic kidney disease. The oscillometric BP readings were higher than auscultatory readings, with a median paired difference of 9 mm Hg for systolic BP (SBP) and 6 mm Hg for diastolic BP (DBP). Correlation for mean SBP was 0.624 and for mean DBP was 0.491. The bias

for oscillometric BP measurement was 8.7 mm Hg for SBP ( $P < .01$ ) and 5.7 mm Hg for DBP ( $P < .01$ ). In conclusion compared with auscultation, the oscillometric device significantly overestimated both SBP and DBP, leading to frequent misclassification of BP status.

**4. ADHD drugs and serious cardiovascular events in children and young adults. Cooper WO et al. N Engl J Med. 2011 Nov 17;365(20):1896-904.**

*It is always good to be reassured about safety of any medications.*

Reported adverse-event raised concern that the use of drugs for attention deficit-hyperactivity disorder (ADHD) increases the risk of serious cardiovascular events. Most of these reports have come from trials that have been small and hence inconclusive. This current trial reviewed a retrospective cohort of 1,200,438 children and young adults between the ages of 2 and 24 years with 2,579,104 person-years of follow-up, including 373,667 person-years of current use of ADHD drugs. Cohort members had only 81 serious cardiovascular events (3.1 per 100,000 person-years). Current users of ADHD drugs were not at increased risk for serious cardiovascular events (adjusted hazard ratio, 0.75; 95% confidence interval [CI], 0.31 to 1.85). In conclusion this large study showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events, although the upper limit of the 95% confidence interval

indicated that a doubling of the risk could not be ruled out. However, the absolute magnitude of such an increased risk would be low.

**5. Electrocardiogram Screening for Disorders That Cause Sudden Cardiac Death in Asymptomatic Children: A Meta-analysis. Rodday AM et al. Pediatrics. 2012 Apr;129(4):e999-e1010. Epub 2012 Mar 5.**

*Another screening opportunity ???*

Pediatric sudden cardiac death (SCD) occurs in an estimated 0.8 to 6.2 per 100,000 children annually. Screening for cardiac disorders causing SCD in asymptomatic children has public appeal because of its apparent potential to avert tragedy; however, performance of the electrocardiogram (ECG) as a screening tool is unknown. A systematic review of literature on hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Wolff-Parkinson-White syndrome, the 3 most common disorders associated with SCD and detectable by ECG were performed. Phenotypic prevalence per 100,000 asymptomatic children were 45 (95% confidence interval [CI]: 10-79) for HCM, 7 (95% CI: 0-14) for LQTS, and 136 (95% CI: 55-218) for Wolff-Parkinson-White. The areas under the receiver operating characteristic curves for ECG were 0.91 for detecting HCM and 0.92 for LQTS. The negative predictive value of detecting either HCM or LQTS by using ECG was high; however, the positive predictive value varied by different

sensitivity and specificity cut-points and the true prevalence of the conditions. In conclusion ECG was a sensitive test for mass screening and negative predictive value was high, but positive predictive value and false-positive rates varied.

**6. Randomized trial of oral versus sequential IV/oral antibiotic for acute pyelonephritis in children. Bocquet N et al. Pediatrics. 2012 Feb;129(2):e269-75. Epub 2012 Jan 30.**

*Is this going to change an age old concept?*

Oral antibiotic for acute pyelonephritis sounds adventurous. This particular study tried to examine this very question of whether oral antibiotic treatment is as efficacious as sequential intravenous/oral antibiotic treatment in the prevention of renal scarring in children with acute pyelonephritis and scintigraphy-documented acute lesions. In a prospective multicenter trial, children aged 1 to 36 months with their first case of acute pyelonephritis, a serum procalcitonin concentration  $\leq 0.5$  ng/mL, no known uropathy, and a normal ultrasound exam were randomized into 2 treatment groups. They received either oral cefixime for 10 days or intravenous ceftriaxone for 4 days followed by oral cefixime for 6 days. The study included 171 infants and children. Initial scintigraphy results were abnormal for 119 children. Ninety-six children were measured for renal scarring at the follow-up scintigraphy (per protocol analysis population). The incidence of renal scarring was 30.8% in the

oral treatment group and 27.3% for children who received the sequential treatment. Before introducing any change in our practice it has to be remembered that they had excluded any atypical findings such as abnormal USS or any known uropathy.

**7. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. Messina AF et al. *Pediatr Infect Dis J.* 2011 Dec;30(12):1019-21.**

**Are we ignoring cheaper alternatives?**

The emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has complicated the conventional management of osteomyelitis. The excellent oral bioavailability, susceptibility profile, favorable palatability, and low cost of trimethoprim-sulfamethoxazole (TMP-SMX) make this drug an attractive option for treating osteomyelitis, yet its clinical efficacy for osteomyelitis has not been established. This

study reviewed 20 children who received a TMP-SMX-containing regimen for acute osteomyelitis and their cases reviewed for clinical outcome and drug safety. Causative pathogens were found in 8 (40%) cases of which 5 were CA-MRSA and 3 were methicillin-susceptible *Staphylococcus aureus*. Eleven patients (55%) received TMP-SMX as their primary therapy. The median dose of TMP-SMX was 16.4 mg/kg/d. During TMP-SMX therapy, 8 patients (40%) experienced adverse events; all were considered mild. Duration of total therapy was 26 to 59 days, with a median of 40 days. All 20 patients were considered cured of their infection at the end of therapy. In conclusion orally administered TMP-SMX appears to be a useful and well-tolerated therapy for treatment of acute osteomyelitis in children. Obviously it will be hard to adopt this immediately before larger prospective comparative studies are available.

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## *Neurodevelopmental Clinic*

Neurodevelopment clinic is held every **Friday 12 noon** onwards. All types of developmental delay, cerebral palsy, speech delay, poor scholastic performance, autism, ADHD are dealt in this clinic.

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