



# INDIAN JOURNAL OF PRACTICAL PEDIATRICS



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Executive Editor

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## IAP - IJPP CME 2016

**FEVER IN NEWBORN****\*Shyamala J**

**Abstract:** *Fever in the newborn is defined as a rectal temperature greater than 38°C or 100.4°F. It may occur due to infections, bacterial and non bacterial, from environmental causes and medications. Clinical acumen will not reliably distinguish 'well' from 'sick' neonates. Septic work up is mandatory. Acute phase reactants are a useful adjunct in the diagnosis of infection. In fever beyond 72 hours of life, lumbar puncture and urine culture are recommended. Empiric antibiotic therapy should be given when there is a history suggestive of maternal chorioamnionitis, in toxic neonates with cardiorespiratory, neurologic symptoms and cerebrospinal fluid pleocytosis. Microbiologic cultures (blood, urine, CSF) though the reference standard for diagnosis, have limitations. Less invasive, highly accurate diagnostics with small volume samples - genomic technologies may be the way for the future.*

**Keywords:** *Neonatal sepsis, Neonatal fever, Diagnosis, Investigations.*

Fever in a newborn is defined as a core body temperature greater than 38°C (100.4°F). Core body temperature is best estimated by rectal temperature. Axillary, temporal artery and tympanic membrane temperatures are unreliable in young infants when compared to rectal temperature as the gold standard. These may be used when rectal thermometry is contraindicated, as in patients with neutropenia, bleeding diathesis or necrotizing enterocolitis.<sup>1</sup>

The neonate's temperature at birth reflects maternal temperature and is usually about 0.5°C higher than the mother's. Epidural anesthesia is commonly associated with elevated maternal temperature and the baby is likely to be worked up for sepsis and treated for presumed intra amniotic infection.<sup>2</sup>

Hyperthermia should be distinguished from actual fever. Hyperthermia is a non-interleukin peripherally-mediated elevation of body temperature. Infection, on the other hand, produces fever, that is interleukin-mediated elevation of body temperature. Differentiation between the two is of practical importance.<sup>3</sup> A febrile baby overheated due to the environment tries to lose heat by vasodilation - where the extremities and trunk are at the same temperature. A septic baby is vasoconstricted, with extremities colder than rest of the body. Measuring the temperature difference between abdominal skin and sole of the foot may be useful bedside. Core periphery temperature difference is less than 2°C in an overheated infant while it is over 3°C in a neonate with sepsis. A hyperthermic neonate has flushed skin and an extended posture since he is trying to lose heat in contrast to a septic neonate with mottled skin and flexed posture because of an attempt to conserve heat. Antipyretics, which act upon the central set-point of the hypothalamus, are helpful in fever but ineffective in cases of hyperthermia (here physical measures are more effective).

Fever may be a manifestation of serious bacterial illness like sepsis, meningitis, bacterial gastroenteritis, pneumonia or urinary tract infection (UTI) which have a high potential for adverse outcomes including death. Hence, there must be a low threshold for evaluation and empiric antibiotic therapy in this age group. Infections may present with fever in 50% neonates, normal temperature in 15% and hypothermia in 35%. Term neonates with infections more often present with fever while preterms present with hypothermia.<sup>4</sup>

Incidence of sepsis in term neonates is about 1- 2 per 1000 live births and 4.4 - 6.3 per 1000 live births in late preterm infants according to western data while in the Indian scenario, 38 per 1000 live births as per National Neonatal Perinatal Database (NNPD).<sup>5,6,7</sup> Depending on the age of onset of symptoms, sepsis may be defined as early onset (onset of symptoms within 72 hours of life) or late onset (onset beyond 72 hours of life).

Viral infections may be a common but unrecognized cause of fever in this age group. Possible viral infections include influenza, respiratory syncytial virus, parecho virus,

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enterovirus, cytomegalovirus, herpes simplex and in the appropriate season in our country, dengue fever. The neonate acquires infection through vertical transmission or post-natally from sources such as family members and hospital personnel. Neonates are prone to viral infections partly due to decreased T cell-mediated immunity. Less common infections include spirochetal, parasitic (congenital malaria, toxoplasmosis) and fungal.

**Non-infectious causes of fever**

While investigating for infections as a cause of fever in the neonate, non-infectious causes should not be overlooked (Box 1).

<p><b>Box 1. Non-infectious causes of fever in neonate</b></p> <p>Excessive environmental temperature - Phototherapy, summer</p> <p>CNS insult – Hypoxia, intracranial bleed, CNS malformations</p> <p>Neonatal abstinence syndrome</p> <p>Enclosed bleeds</p> <p>Congenital adrenal hyperplasia and salt wasting</p> <p>Medications - Atropine eye drops, maternal SSRIs (selective serotonin reuptake inhibitors)</p>
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In warm weather, healthy neonates on exclusive breast feeds especially if born by cesarean section, may develop fever upto 10 days of life. Dehydration fever was initially

described by Singh.<sup>8</sup> This phenomenon can occur even in large for gestational age (LGA) infants and especially in late preterms. Insensible water loss coupled with poor lactation or attachment problems, causes dehydration and ‘fever’. This may lead to hypernatremia, renal failure, venous thrombosis and occasionally even mortality.<sup>9</sup>

**Approach**

A systematic work up for fever in the neonate begins with accurate history taking and eliciting risk factors (Table I).<sup>10,11</sup> Subtle clues may be altered sleep patterns, temperature instability or paradoxical irritability.

Cultural practices like oil instillation, nose blowing, applying various substances to the cord stump and expressing witch’s milk are important risk factors for late onset sepsis in our set up.

**Physical examination**

A thorough physical examination should include vital signs, perfusion, skin colour, alertness, rashes and hydration status. Weight gain or loss should be assessed. The examination may be deceptively normal but helps categorize febrile neonates into ‘sick’ and well groups. The sick neonate who needs immediate resuscitation and treatment should be identified. Irritability, inconsolability, poor perfusion, poor tone and lethargy are useful pointers. Pulse oximetry better predicts lung infection than respiratory rate.<sup>12</sup> Evidence of localized infections e.g. omphalitis, arthritis, limb swelling or inflammation, etc, not only help in choice of antibiotics but may also provide a clue regarding

**Table I. Sepsis - Risk factors**

Early onset sepsis <sup>10</sup>	Late onset sepsis <sup>11</sup>
Prematurity (<37 weeks)	Prematurity (<37 weeks)
Low birth weight (<2500 grams)	Low birth weight (<2500grams)
Maternal GBS colonization	NICU admissions
H/o STDs in mother - herpes, gonorrhea, chlamydia	Central venous catheterization
Premature rupture of membranes	Invasive procedures
Prolonged rupture of membranes (>24hours)	CPAP use
Maternal fever >38° C within 2 weeks prior to delivery	Superficial infections (umbilical sepsis)
Chorioamnionitis	Aspiration of feeds
Foul smelling or meconium stained liquor	Cultural practices
Prolonged or difficult labour	
Perinatal asphyxia (Apgar score <4 at 1 min of birth)	

the causative organism. This includes skin or mucous membrane lesions consistent with herpetic etiology; pustules or umbilical focus predictive of a gram positive infection. Symptoms of bacterial meningitis may be minimal or absent. Nuchal rigidity presents only in 27% of infants 0 - 6 months with bacterial meningitis.<sup>13</sup>

## Investigations

The goal of diagnostic tests is to identify and treat all infants with bacterial sepsis and minimize treatment of patients who are not infected. A full diagnostic evaluation includes: (a) Complete blood count (CBC) with differential and platelet count, (b) C-reactive protein (CRP) or procalcitonin (PCT), (c) chest X-ray if respiratory symptoms are present and (d) blood culture  $\pm$  CSF analysis. No single test is sufficient to rule in or exclude serious bacterial infection (SBI) in febrile young infants. In addition, cultures from other potential sites of infection - tracheal aspirates if intubated, purulent eye discharge or pustules are important. WBC count has poor sensitivity and specificity for identifying bacteremia and meningitis in young infants.<sup>14</sup> Decision to perform blood culture or CSF analysis should not depend on WBC counts.

Serum procalcitonin or CRP levels may be a better marker of SBI than WBC count. They are the two most commonly studied acute phase reactants in neonatal sepsis. CRP levels rise within 6-8 hours of infection and peak at 24 hours. Quantitative CRP is more accurate than qualitative CRP. CRP is usually elevated in bacterial rather than in viral infections. CRP has the best predictive value if measured within 24 - 48 hours of infection. An increasing CRP level is a better predictor than individual values. Two negative CRP values have been shown to have a negative predictive value of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis.<sup>15</sup> Repeatedly normal CRP values are evidence against bacterial sepsis and antibiotics can be safely discontinued.

Procalcitonin is the peptide precursor of calcitonin. Physiologic rise in healthy neonates occurs within 24 hours, peaks at 24 hours, returns to normal by day 3. It is produced by monocytes and hepatocytes in response to bacterial endotoxin, rises after 4 hours, peaks at six to eight hours, remains raised for at least 24 hours with a half life of 25-30 hours.<sup>16</sup> With treatment the value declines. In general procalcitonin is more sensitive for earlier detection of sepsis than CRP. The level is more likely to be increased during bacterial infections than viral.<sup>17</sup> There may be false positive elevations in noninfectious conditions like respiratory distress syndrome, hemodynamic instability and infants of diabetic mothers.

In a recent multicenter study from France involving 2047 febrile infants 7 to 91 days of age, done in 15 pediatric emergency departments over a 30-month period, serum PCT value was substantially more accurate than CRP, white blood cell count, or absolute neutrophil count for identifying young infants with invasive bacterial infections. At a threshold of 0.3 ng/mL or more, the serum PCT had a sensitivity of 90%, specificity of 78%, and negative likelihood ratio of 0.1.<sup>18</sup>

**Blood culture:** A positive blood culture would be ideal both for diagnosis and the choice of antibiotics while treating neonatal sepsis. A single blood culture sample drawn by aseptic technique is sufficient and the minimal recommended volume is 1 mL. As per studies, a lower volume may not detect low level bacteremia [4 colony forming units (CFU) or less].<sup>19</sup> Upto 25% of infants with sepsis have low colony count bacteremia (< 4 CFU/ml) and two thirds of infants less than 2 months of age have colony counts less than 10 CFU/mL.<sup>20,21</sup>

**Urine culture:** This will not be required in work up for early onset sepsis but important in late onset sepsis. In neonates, urinary tract is seeded during bacteremia and not by an ascending infection.

**Lumbar puncture:** This is done whenever there are clinical findings suggestive of sepsis (clinical signs of meningitis may be lacking), neonatal seizures or clinically evident invasive infections (cellulitis, abscess, mastitis, omphalitis, osteomyelitis, etc.). Incidence of meningitis may be as high as 23% in bacteremic infants.<sup>22,23</sup> However, blood culture alone cannot be used to guide the decision, since blood cultures can be negative in up to 38% of infants with meningitis.<sup>24,25</sup> LP may be deferred till clinical status is stable in critically ill infants or those with cardiorespiratory compromise.

## Management

Prediction criteria like those of Rochester, Minnesota and Boston are not useful in neonates as also the available guidelines and approach to management of fever in older infants. Hence after drawing appropriate culture samples, empiric antibiotics are recommended regardless of clinical appearance. This is even more important in ill neonates, those with temperature instability, cardiorespiratory or neurologic symptoms, confirmed or suspected maternal chorioamnionitis and CSF pleocytosis (WBC count more than 20 - 30 cells / cu mm).

The choice of antibiotics is dependent on local resistance patterns. The most common infectious organisms

in neonates include *E. coli*, *Klebsiella*, *Staphylococcus aureus*, *Pseudomonas* and rarely, *Enterococcus*. GBS and *Listeria* are not common in India. Intravenous ampicillin and gentamicin are the recommended first line agents for these infections in neonates. Concerns about *E. coli* resistance to ampicillin have led some to recommend a third-generation cephalosporin, such as cefotaxime. However, with units increasingly reporting extended spectrum beta lactamase (ESBL) resistant organisms, ticarcillin-clavulanic acid or piperacillin-tazobactam are suggested agents with caution to avoid cephalosporins. If MRSA is common, vancomycin can be chosen. If cultures are sterile and acute phase reactants are negative, antibiotic can be stopped after 48 hours. A positive blood culture should be treated for 10 days and meningitis for 14 - 21 days. Antibiotic stewardship programs are crucial to reduce the emergence of resistant strains of micro organisms.

Routine use of acyclovir is not indicated in febrile neonates. Herpes simplex infections in neonates is uncommon (25 to 50 cases per 100,000 live births in the USA).<sup>26</sup> Indications for acyclovir are: h/o maternal genital herpes, ill neonates, presence of mucocutaneous vesicles, neonatal seizures, elevated liver enzymes (early indicator of disseminated herpes in neonates <2 weeks), CSF pleocytosis. While awaiting CSF culture, send for HSV DNA PCR which is confirmatory.<sup>27</sup> The recommended dosage is 60 mg/kg/day in 3 divided doses.<sup>28</sup>

Dehydration fever is managed with effective environmental cooling, intravenous fluids if suck is poor, and other supportive and symptomatic therapy. Free water intake is increased, maternal lactation enhanced and hypernatremia if present is corrected over 48-72 hours. Serial monitoring of temperature, weight and serum sodium levels is required.

### Future directions

Culture based approaches and more specifically blood culture, though a reference standard for diagnosis of SBI, have important limitations including 'a noninconsequential number of false-positive and false-negative results and turnaround time of at least 48-72 hours.'<sup>29</sup> The authors cite genomic technologies to be a viable alternative, being less invasive and highly accurate. These not only have 'the potential to detect the molecular signature of the pathogen in small amounts of biologic samples' but could also help measure host response to the pathogen which is termed 'a paradigm shifting approach'.<sup>30,31</sup> These technologies need further validation before they can be clinically implemented.<sup>32</sup>

### Points to Remember

- *Fever in newborn is defined as a rectal temperature greater than 38°C or 100.4°F.*
- *Commonest cause in low risk neonates on exclusive breast feeds is 'dehydration fever'.*
- *Basic work up for sepsis is mandatory in any febrile newborn.*
- *Biomarkers like procalcitonin and CRP have a useful role in diagnosis of bacterial infections.*
- *Microbiologic cultures (blood, urine, CSF) though the reference standard for diagnosis, have limitations.*
- *Empiric antibiotic therapy should be given in the setting of maternal chorioamnionitis, toxic neonates, cardiorespiratory, neurologic symptoms and CSF pleocytosis.*
- *Genomic technologies may facilitate more accurate diagnosis of infections in future.*

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## NEWS AND NOTES

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## IAP-IJPP CME 2016

**FLUID AND ELECTROLYTE MANAGEMENT IN NEONATES****\*Ratnakumari TL**

**Abstract:** *Fluid and electrolyte physiology and fluid management in neonates are very important topics for pediatrician and the practitioner alike. The changes in fluid physiology which take place in fetus from the embryo to the neonate and beyond are phenomenal. Careful attention to finer details of the same and good clinical observation and analysis is the key to successful fluid management. Factors which have helped in this complex manoeuvre in the last three decades are antenatal steroids, appropriate use of surfactant, restricted fluid use, kangaroo mother care and recently delayed clamping of the cord.*

**Keywords:** *Extracellular Fluid, Intracellular Fluid, Total Fluid Requirement, Insensible water loss, Dehydration, Hyponatremia, Hypernatremia, Hypokalemia, Hyperkalemia.*

Fluid and electrolyte management in the neonate is ever an interesting and at times very intriguing proposition. All the same, this complex topic has to be understood by every pediatrician and neonatologist.

**Intrauterine fluid dynamics**

In newborn fluid homeostasis, the base rests on the physiological basics and developmental changes the neonate undergoes from conception to the end of neonatal period. This includes early intrauterine period, labor and delivery and immediate postnatal period of 7 days (designated as perinatal period) and upto 30 days of newborn period. The early gestate fetus has larger composition of total body water (TBW) and less of solids. Higher proportion of this total water remains within the extracellular compartment. The cellular component is added rapidly later on. The process of rapid cellular proliferation, accretion and fat deposition are the reasons responsible for decrease

in the total body water content as the gestation advances.

In a 16 week old fetus the TBW is 94%, two thirds remain in extracellular and one third in intracellular compartment. By the time the fetus develops into a term baby the TBW comes down to 75% with almost 50% in both intracellular and extracellular compartments.<sup>1</sup>

Also during the development of the fetus towards term there is translocation of fluid from the placenta to the fetus. The maternal hormones which play an important role in this translocation are catecholamines, vasopressin and cortisol which physiologically seem to increase when the gestation is nearing its zenith of completion. This in reality increases the pressure within the fetal arteries with simultaneous add on effect by relative hypoxia that ensues with the start of labour. Also there is a hormonal milieu change occurring within the fetus who is ready to assume an extrauterine responsibility of growth.

This results in capillary leak which allows the fluid to be shifted from the vascular compartment into the interstitial compartment. In the immediate postnatal period there is a relative correction of hypoxia and with the action of vasoactive hormones, the fluid which was squeezed out earlier into interstitium gets back into the vascular compartment. It is in fact the deficit of 25% plasma volume that gets restored in the immediate postnatal period. In the normal term infant, this helps in maintaining intravascular volume in the face of minimal availability of feeds - colostrum and breast milk from the mother during the first 2 days after birth. This bountiful and delicate sequence when even slightly distorted as in preterms, hypoxic ischemic encephalopathy (HIE), trauma, or blood loss proves to be devastating. Fluid management in such situations should be carefully planned.

All these sequence of change in body composition and distribution described as translocation, shift and reclamation are very dynamic. Any factor which affects any of these three, can alter the composition and distribution so much so the fluid management in the neonate needs to be modified. If the mother receives drugs like indomethacin or excessive electrolyte free fluid as a vehicle for drug delivery especially during late pregnancy and labor can cause neonatal hyponatremia which is dilutional. Also excessive use of

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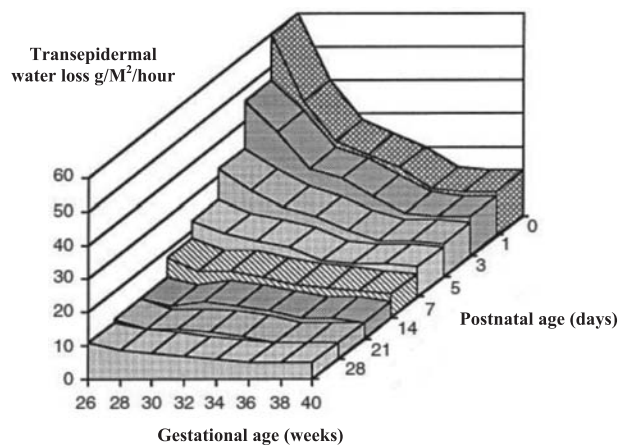
diuretics and placental insufficiency can cause changes in foetal hydration status.

When the blood volume increases postnatally because of movement of extravascular fluid into vascular compartment and with changing hormonal milieu, especially the release of atrial natriuretic peptide (ANP), excretion of both water and sodium gets a boost. This results in physiological postnatal weight loss both in well term neonates and preterm babies. The expected weight loss in term neonates is 5%-10% over 3 to 4 days or 2% to 3% per day, while in preterms it may be even up to 15% cumulative, norm being 10% to 15%. Usually this may ensue over a period of 4 to 7 days postnatally in term neonates and in preterms over a period of 7-10 days which at times can even extend into third week.<sup>1,2,4</sup>

A delicate balance exists between the osmolar set points set by osmoreceptors and baroreceptors in the blood vessels and the heart and the effector organs which are cardiovascular, capillary bed and kidneys. It is to be noted that thirst as a trigger to increase intake is not optimally developed in neonates and it is always mandatory to be decided by the caregivers and hence it assumes greater importance to understand the finer points of fluid and electrolyte needs.<sup>1,2</sup> The humoral arm consists mainly of renin angiotensin system, vasopressin, ANP (brain beta type), bradykinin, catecholamines and prostaglandins, prolactin and cortisol to some extent.

In an ill neonate the above mentioned regulator and effector components act interdependently yet haphazardly depending upon the pathological undertones caused by the disease / disorders which the neonate suffers from. Renal maturity also is an important factor. A neonate is functionally immature when compared to a child or an adult as far as renal functions are concerned.<sup>1,2,5</sup> Both concentrating and diluting ability is at a lower ebb. Base conservation, water and sodium handling are also altered.

As for as skin is concerned, keratinization plays a major role in the protection against evaporative fluid loss. This has a greater implication in the early preterms [extremely low birth weight (ELBW) and very low birth weight (VLBW)] (Fig.1). In a 750 gram preterm neonate ISWL may go upto more than 200 ml/Kg/day also.<sup>1,2</sup> Antenatal steroids and intrauterine stress is said to enhance skin maturity. When there is a sudden and greater loss of water through skin, it leads to severe dehydration with hypertonicity and hypernatremia which in turn can lead on to intracellular loss of fluid dynamics and may prove to be fatal.



**Fig.1. Gestational age and transepidermal water loss<sup>3</sup>**

### General rules

If the neonate is well, mother's care with good warmth and breastfeeding is sufficient enough for maintaining the fluid balance as stressed in the concept of 'Kangaroo mother care (KMC)'. The question of maintenance fluid arises only for ill neonates either in ICU or level II care. The acceptable maintenance charts are very many but all of them confirm to the afore mentioned fluid dynamics and distribution.<sup>2,6</sup>

Fluid and electrolytes management is the mainstay in the management protocols of any NICU or newborn ward. While guidelines have helped in managing smaller neonates, one should not forget that fluid formulations in any neonate who is ill should always be individualised.

While planning IV fluids the following points of prenatal period need to be taken note of. Drugs like indomethacin, ACE inhibitors and furosemide administered for maternal illness may cause hyponatremia in the neonate. Also if the fluid given as vehicle for drugs is electrolyte free or not has to be looked into. The use of oxytocin to induce labor, antibiotics like aminoglycosides should be noted. History of oligo/polyhydromnios is also essential as it may give a clue to the renal status of the foetus.<sup>1</sup> Birth asphyxia will always play a negative role in fluid dynamics. Increasing fluids inadvertently can cause edema early in the neonate. Checking the urine output by weighing the diaper (immediately after voiding) is a closer and sensitive way of assessing the output.<sup>2</sup>

Fluid modification is needed in the following condition such as birth asphyxia, HIE, high and low ambient humidity, use of open care warmers, neonatal necrotizing enterocolitis (NNEC), peritonitis, paralytic ileus, and prolonged use of paralytic agents in ventilation etc.<sup>1,2</sup>

The primary goal is to maintain the extracellular fluid volume, intracellular fluid osmolality while maintaining the

**Table I. Fluid requirements in relation to body weight<sup>1</sup>**

Birth weight (g)	Fluid requirements (ml/kg/day)			
	Day 1	Day 2	Day 3-6	Beyond day 7
<750	100-140	120-160	140-200	140-160
750-1000	100-120	100-140	130-180	140-160
1000-1500	80-100	100-120	120-160	150
>1500	60-80	80-120	120-160	150

normal intravascular volume and tonicity. Heart rate, urine output and electrolyte monitoring and pH will be the evaluation pointers. In a term neonate the fluids are started as 60 ml/kg body weight and increased by 15-20 ml/kg everyday.<sup>7</sup> In preterms from 1kg to 1.5 kg the fluid requirement is 80-100 ml/kg with an increment of 15-20 ml/kg/day. Below 1kg it is 100-120 ml/kg/day and increments are generally as for term babies (Table I). This fluid charting is preferably for the first 3 days of life, but may need alteration in preterms depending upon whether they are in the prediuretic, diuretic or homeostatic stage of postnatal age as the expected postnatal diuresis is delayed in ill preterms.

In order to give the correct volume of IVF it is essential to closely monitor not only the vital signs but also blood glucose status, urine output and strictly weighing the neonate 12 hourly. In term babies who are in the newborn unit for minor feeding issues investigations are mainly for deciding on the primary illness only. In ELBW, VLBW and in all ill neonates fluids has to be ordered based on investigations like RFT, osmolality and specific gravity of urine, urinary electrolytes and ABG. The factors which are helpful are weighing the neonate 12 hourly, computing urine output hourly and estimating sodium 8 hourly, potassium 12 hourly, creatinine 12 hourly, urea daily and hematocrit daily.<sup>1</sup> Clinical signs like tachycardia, skin turgor etc are also to be monitored though these two cannot be relied upon as they are very non-specific.<sup>8</sup> Urine output is measured by weighing diapers immediately after voiding, using urine bags or by placing urinary catheters if neonate is very ill.

### The concentration of fluids

It is generally accepted that 10% dextrose is the fluid that suits the needs of the neonate who is otherwise well during the first 2 days of life. In less than 1 Kg preterms it is conventional to start 5% dextrose as day 1 fluid. No electrolytes are to be supplemented in this period since this is the period where equilibrium is regained after placental translocation and intravascular reclamation.<sup>1,9</sup> The only

reason where the child would need electrolytes is boluses for shock or very rarely for known electrolyte losers like Bartter syndrome and congenital adrenal hyperplasia. The simple rule is to start electrolytes when there is a weight reduction of 6% of the birth weight. Conventionally waiting to start electrolytes until day 4 is not practiced now.

Because of the fragile calcium kinetics of the neonates, calcium is added to this regimen as 4-8 ml/kg of 10% calcium gluconate. This is essential for preterm, IUGR and low birth weight infants and also ill neonates until they stabilise. This can be given 8<sup>th</sup> hourly through a side port diluted with distilled water in 1:3 dilution as infusion.

On day three, generally sodium is added as 3% NaCl, 3-4 mEq/kg and potassium as KCl 2mEq/kg and calcium continued as before. Severe hyperkalemia had been a menace in ELBW and VLBW before the antenatal steroid era. It is ideal to start potassium after urine output is established especially in preterms.<sup>1,2</sup> Volume increments are as before upto 150 ml in term babies and preterm<sup>7</sup> except in ill polyuric preterms who need more fluids.

Erring on the lower side of the volume is not very harmful in neonates who are not very ill. There are ample evidence to show that restricted fluid management is helpful against risk of patent ductus arteriosus (PDA), insensible water loss (ISWL), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and intraventricular hemorrhage (IVH).<sup>1,2,10</sup> Volume depleting disorders like CAH or Bartter syndrome are in contravention to the above point. If the neonate is not very ill early introduction of feeds along with IV fluids is the key.

Crying and irritability is a sign of inadequate feeds most of the time. Increasing fluids because of low blood sugar values without looking for the cause for hypoglycaemia would not be helpful.

The volume of fluid total fluid requirement (TFR) is the sum of fluid volume to be provided by way of parenteral,

oral, bolus or drugs and their vehicle. It needs meticulous calculation of volume of bolus and drug infusions if they are of large volume. Again if the neonate receives blood or blood products as transfusion, they need to be adjusted as per TFR. Specified hourly fluid volume has to be modified in the above situations and also taking into consideration glucose infusion rates (GIR) so that the child would not go into inadvertent hypoglycemia.<sup>2,8</sup>

The situation wherein one would increase the stipulated volume are if open care bed is the only available system, polyuria and undue weight loss. Phototherapy may not need added allowances if it is light emitting diode (LED).<sup>1</sup>

The situations wherein one would decrease fluids are hypoxic ischemic encephalopathy (HIE) with increased intracranial tension (ICT), congestive heart failure (CHF), undue weight gain (dilutional hyponatremia), acute kidney injury (AKI) and syndrome of inappropriate antidiuretic hormone secretion (SIADH). In CHF reduce fluid volume by not more than 25%. In AKI chart fluids, by taking into account the previous 24 hours' urine output with calculated ISWL. In HIE with ICT, decrease fluid by 25%. In all the above scenarios, one must have a close watch on tissue perfusion by hemodynamic monitoring since decreasing the volume should not be counterproductive to tissue perfusion. It is ideal to compute fluids 8<sup>th</sup> hourly. Essentially weighing the baby with a sensitive electronic scale also helps to fine tune fluid management.<sup>2</sup>

**Renal water loss and growth**

Renal water loss gradually increases when the solute load to be excreted increases. For the requirement of 80-120 kcal/kg/day the solute load generated is 15-20 mOsm/kg/day. To excrete this load, fluid needed is 60-80 ml/kg/day.<sup>1,13</sup> If the baby has the normal acceptable weight gain of 30 g/day then an additional 25 ml of water is needed every day. Rapid changes in weight unless proved otherwise is a clear pointer to weight loss or gain.

Insensible water loss:

A quick way of calculating insensible water loss in neonate is as in the given formula<sup>1</sup>

$$ISWL = \text{Fluid Intake} - \text{Urine output} + \text{weight loss (or)}$$

$$ISWL = \text{Fluid Intake} - \text{Urine output} - \text{weight gain}$$

ISWL is also through lungs. It is much reduced when humidified ventilator circuits are used or ambient humidity is > 80%. Accordingly TFR has to be increased or decreased. ISWL through skin can be prevented by using incubators for ELBW and VLBW and using plastic shields

in open care system. Using mittens and caps can reduce ISWL. Use of oil and emollients also helps.<sup>8</sup> Having decided the volume and concentration, TFR has to be charted as ml/hr and a boxed notation helps the nurses, postgraduates and residents.<sup>1</sup> The factors affecting TFR is given in Table II.

**Table II. Factors which modify total fluid requirement**

Increase TFR	Decrease TFR
Gross weight reduction	CHF
Diuresis	SIADH
Vomiting	Increased ICT
Excessive ISWL in VLBW and ELBW	AKI
Non LED phototherapy and halogen lamp phototherapy	High humidity

The above table is not absolute in terms of either increasing or decreasing TFR and overall assessment of the morbidity is to be accounted for. Lab guidelines for modifying TFR are given in Table III.<sup>8</sup> The lessons to be learnt are initial loss of ECW should be allowed, and constant assessment is needed.

**Table III. Lab guidelines for modifying TFR**

Increasing TFR	Decreasing TFR
Increased weight more than 3%/day	Decreased weight loss <1%/day
Cumulative loss of more than 15%	Cumulative loss < than 5%
Serum Na more than 145 mEq/L	Serum Na less than 130mEq/L despite weight gain
Urine specific gravity > 1020	Urine specific gravity <1005
Urine output <1 ml/Kg/hour	Undue polyuria >6ml/Kg/day

**Electrolyte disturbances**

The common electrolyte disturbances encountered in neonates are hyponatremia, hypernatremia, hyperkalemia and hypokalemia in that order.

**Hyponatremia**

The most common electrolyte abnormality in ill neonates is hyponatremia. The type of hyponatremia varies

from dilutional to true hyponatremia, the former seen in AKI, SIADH, CHF and preterm / ELBW who are not supplemented properly when their need is higher.<sup>2,11</sup>

The clues to the etiology of fluid overload

- Weight gain with hyponatremia and oliguria without edema - SIADH
- Weight gain with edema and good urine output - probably iatrogenic.
- Weight gain with oliguria and edema along with lack of expected postnatal fall in serum creatinine - AKI.

**Management:** i) For SIADH, restriction of fluid by 25%-30% will help in gradual fall of sodium levels. If symptomatic (seizures), it is always prudent to correct upto 120-125 mEq/L of sodium safely by giving 3% NaCl 4-6 ml/kg over one hour. Usually the rise is over 4-6 hours by 6 mEq/L of sodium. Rarely one may have to use a diuretic. Then on, restriction of fluid itself will correct the deficit.

ii) In true deficit, with sodium level above 120 mEq/L, correct either with 1/3<sup>rd</sup> isotonic (50 mEq/L) or 1/2 isotonic (75 mEq/L) solution spread over next 36 hours.

iii) In CHF treating the cause and fluid restriction will correct hyponatremia.

iv) In diuretic excess withdraw diuretic while gradually increasing sodium levels with 1/3 isotonic fluid.

v) In AKI- calculate ISWL plus urine output in the past 24 hours to compute desired volume and infuse as 10% D and 1/4th isotonic fluid (37.5 mEq/L). It is not necessary to use electrolyte free fluids in AKI.<sup>2,5</sup> True hyponatremia is seen in conditions like CAH, Bartter syndrome, infantile hypertrophic pyloric stenosis, NNEC and diarrhea in non breast fed neonates.

To treat hyponatremia with dehydration, follow the 3 steps

a) Calculate % of dehydration with BW as reference point. For e.g. Term BW 3Kg dehydrated, current weight 2.2 kg, serum sodium 118mEq/L.

Fluid loss is  $3 \times 0.7 \times (118/135 - 1)$  ml which is 264 ml where 3 is the body weight, 0.7 (total body water), 118 is the observed serum sodium and 135 is the desired sodium level.

Sodium needed to correct the hyponatremia is calculated by the formula (desired sodium - observed sodium) X 0.7 X 3 i.e. 25mEq (130-118 x 0.7 x 3). It is safe to correct up to 130 to 135 mEq/L of serum sodium with close monitoring).

Correct sodium deficit in steps. Half of 25 mEq i.e. 12 mEq is corrected over 12 hours by adding 3% sodium chloride to half of calculated fluid deficit along with calculated maintenance (modified for 12 hours). Roughly it works around 1/3 isotonic fluid. Rest is corrected over next 24 hours.

Note: If symptomatic correct up to 125mEq/L with 3% sodium chloride over 1hour and then as 1/3 isotonic fluid over next 36 hours. If baby has shock first give isotonic bolus 10ml/Kg. Reduce this volume from total fluid.

## Hypernatremia

It is the most common scenario in ELBW with excessive insensible water loss and in term neonates with lactation inadequacy issues. In lactation inadequacy with hypernatremia<sup>1,2,12</sup> the neonate is irritable, peevish with good skin turgor, doughy feel of skin, good pulses and delayed hemodynamic compromise. If hemodynamically compromised, 10-15 ml/kg of isotonic NaCl (145 mEq/L of sodium) is to be given as bolus over 10-15 minutes. One should keep in mind that in hypernatremia with sodium above 165 mEq/L, normal saline is hypotonic with more than 21% free water and will cause rapid fall of sodium with attendant problems of fluid shift. But most of the time with one or two bolus alone hemodynamic stability is attained. One half of the fluid deficit is corrected over 24 hrs to 36 hours with 1/2 NS safely. Attendant hyperglycemia and uremia will fall gradually without the need for any other measures. Very rarely alteration in concentration of sodium is needed. If the hypernatremia is acute (less than 48 hours), the rate of fall of sodium can be 1 mEq / hour but if chronic (more than 48 hours), it has to be only 0.5 mEq / hour. For ELBW the correction needs to be done over 3 days.

## Hyperkalemia<sup>1,2</sup>

It is the most common electrolyte disturbance if associated with unexplained brady/tachycardia in ELBW. The levels up to 5.5mEq/L are considered normal.

ECG changes occur above 6.5mEq/L. Treatment is needed at level higher than 6 mEq/L. Treatment starts by changing the fluid in use to potassium free fluid. Then the following are given sequentially (i) 10% calcium gluconate 1ml/Kg as bolus diluted 2:1 with distilled water over 2 to 5minutes (ii) Give sodium bicarbonate 1 to 2 mEq/kg over 30 to 60 minutes (iii) Tromethamine 3 to 5 ml/Kg (iv) Insulin 0.05 unit with 2 ml of 10% dextrose IV as a brisk bolus, followed by 0.1 unit with 2 to 4 ml of 10% dextrose as infusion and v) Salbutamol 0.15mg/Kg (150mcg/kg) every 20 minutes by nebulisation (Note: one respule of Salbutamol

2.5 mL=2.5mg=25000 mcg). Ion exchanging resins are used with normal saline instead of sorbitol at times.

If renal functions are normal, furosemide 1mg/kg is given as IV bolus. Treat the cause for hyperkalemia, like hypermetabolic state, CAH, blood transfusions, etc.

### Hypokalemia<sup>2</sup>

Correction is carried out by adding potassium chloride (KCl) to the fluids 1 to 2 mEq /Kg /day along with oral supplements subsequently. Very rarely in ill neonates with ECG changes one may give 0.3 mEq of KCl/ Kg over 2 hours with close ECG monitoring. If there is alkalosis, correcting this first has a priority.<sup>1,2</sup> If there is associated hyponatremia it also has to be corrected early. Intravascular volume has to be replenished meticulously.

### Special issues in fluid management

In ELBW, because of the handicap of being premature by 10 weeks or more, the issues to be sorted out are excessive ISWL, late diuresis, proximal tubular base wasting, hyperkalemia if antenatal steroids are not received and problems related to respiratory distress syndrome, NNEC, PDA and chronic lung disease. Current evidence tilts towards restricted fluids for most of these issues.<sup>10,13</sup>

### Points to Remember

- *Fluid management is pure science and every point is to be remembered.*
- *Only application and guidelines differ based on underlying morbidity.*
- *Restricted fluids over liberal use of fluid are favoured.*
- *It is always more than one issue that has to be tackled in those with fluid and electrolyte disturbances in neonates.*
- *Fluid charting and documentation has to be written clearly.*
- *Allow acceptable weight reduction initially.*
- *Prevention of insensible water loss is more rewarding than treating it.*

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### NEWS AND NOTES

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## IAP - IJPP CME 2016

**PNEUMONIA - TREATMENT GUIDELINES****\*Gowrishankar NC**

**Abstract:** *Pneumonia is a killer disease in children especially in under five. Most of the developing countries look upon the guidelines given by developed nations in order to treat pneumonia effectively and reduce the mortality and decrease the morbidity. In this review, various guidelines for pneumonia treatment and their applicability will be discussed.*

**Keywords:** *Pneumonia, Children, Treatment guidelines.*

Pneumonia and diarrhea are diseases of poverty and deaths are mainly among the poorest. Globally 1.4 million children under 5 died from these two diseases in 2015 accounting for almost one in every four deaths. In a developing country like India there are many risk factors like overcrowding with poor access to clean water, exposure to tobacco smoke along with young maternal age, low birth weight and malnutrition predisposing to increased morbidity and mortality. Deaths due to pneumonia has declined from 1.7 million in 2000 to 920,000 in 2015 but at a slower rate compared to other common childhood diseases like malaria, measles and HIV.<sup>1</sup> Data from India shows that in 2010, 3.6 million (3.3-3.9 million) episodes of severe pneumonia and 0.35 million (0.31-0.40 million) deaths occurred in children under five years.<sup>2</sup>

The diagnosis of pneumonia in the community by the pediatrician is mostly based on clinical features along with chest X-ray (CXR). Interpretation of chest X-ray can have very high level of agreement for alveolar pneumonia (consolidation) and no pneumonia but very poor agreement for non alveolar pneumonia (interstitial infiltrates, linear and patchy densities). This variability in X-ray interpretation is a recognised problem and added to that is the inability to differentiate viral from bacterial etiology. But still CXR is

used as a major tool for treatment decision.<sup>3</sup> Microbiological diagnostic testing in many studies have revealed more viral pathogens than a bacterial pathogen especially in children under five. Point of care microbiological investigations for diagnosing pneumonia done in developed countries is not recommended for the developing world. Most of the available guidelines for community acquired pneumonia utilise only symptoms and signs for the diagnosis of pneumonia. This invariably leads to over diagnosis of pneumonia as virus induced wheeze can mimic pneumonia in many children under five years of age.

In India, the initial roadmap for proper identification and treatment of pneumonia was through the acute respiratory infection (ARI) control programme in 1990 which was integrated into child survival and safe motherhood (CSSM) programme in 1992. The CSSM programme was integrated into reproductive child health (RCH) programme in 1997-98. Integrated management of childhood illness (IMCI) developed by World Health Organisation and the national rural health mission (NRHM) addressed the management of pneumonia. The main roadblocks are diagnosing pneumonia early, initiating the appropriate antibiotics and referring to next higher health facility if the condition warrants.

**India clinical epidemiology network (IndiaCLEN) Task force on pneumonia (2010)<sup>4</sup>.**

As per the initial guidelines, domiciliary treatment of pneumonia consisted of administration of cotrimoxazole followed by a review after 48 hours to decide further treatment based on the response. In 2010 the report of India CLEN task force on rational use of antibiotics for pneumonia was published.<sup>4</sup> This report was able to give a clear guideline to the practicing pediatrician that for non severe pneumonia there was no evidence to change from the guideline of prescribing cotrimoxazole in the dose of 5-7 mg/kg/day of trimethoprim and 25-35mg/kg/day of sulphamethoxazole for duration of 5 days. But it added that amoxicillin at a dose of 30-40 mg/kg/ day for 3-5 days is a suitable alternative drug. Also in a child with severe pneumonia one has to start with ampicillin at 50 mg/kg as IM/IV every 6<sup>th</sup> hourly and if child improves, change over to oral amoxicillin for another 5 days. If there was no

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**Table I. Antibiotics for pneumonia (2010)<sup>4</sup>**

Pneumonia	Drug(s) recommended	Dose and duration
Non severe	Cotrimoxazole (oral)	5-7 mg/kg/day of T + 25-35 mg/kg/day of S for 5 days
	Amoxycillin (oral)	30-40 mg/Kg/day for 3-5 days
Severe	Inj ampicillin	50 mg/kg IM/IV every 6 hours for 7 days
	Add inj gentamycin – if age less than 2 months or fails to respond at 48 hours	7.5 mg/kg IM/IV once a day for 7 days
Very severe	Inj.ampicillin + Inj gentamycin	50 mg/kg IM/IV every 6 hours +7.5 mg/kg IM/IV once a day for 7 -10 days
	Inj.cefotaxime (or ceftriaxone) + inj. cloxacillin - if no improvement at 48 hours or associated septicemia or meningitis	100 mg/kg/day + 200 mg/kg/day given every 6 hours for 7-10 days

improvement, the advice was to add gentamycin (7.5 mg/kg IM/IV once a day) to ampicillin. In infants less than two months of age at presentation or if it was a very severe disease gentamycin has to be added at the outset along with ampicillin. After adding gentamycin if there was improvement in 48 hours, antibiotics for 7 days have to be completed. But if there was no improvement, antibiotics need to be changed to cefotaxime or ceftriaxone. The antibiotics should be given for 7-10 days for very severe disease (Table I).

In a systematic review (2011) on ARI and pneumonia in India it was concluded that though there was adequate data to support the choice of antibiotics recommended in the IAP-IndiaCLEN 2010 guideline, amoxicillin may be prudently used as the first line antibiotic in view of increasing drug resistance for cotrimoxazole but with the suggestion that sensitivity patterns has to be monitored.<sup>1</sup> The review also inferred that all children with acute lower respiratory infection with fast breathing have to be treated with antibiotics paving the way for faster recovery but with the drawback of increased antibiotic resistance if overtreatment is given.

### **British Thoracic Society guidelines update 2011<sup>6</sup>**

The update of the guidelines for the management of community acquired pneumonia in children in October 2011 by British Thoracic Society (BTS) stated that bacterial pneumonia has to be considered in any child presenting with persistent or repetitive fever (>38.5°C) together with chest recession and a raised respiratory rate. But it is necessary to have them reassessed if symptoms persist and they need to be hospitalised if they have saturation

below 92%. It was recommended that chest X-ray should not be done to children with pneumonia who are not admitted. Treatment should be instituted to all those with a clinical diagnosis of pneumonia as it is difficult to differentiate between viral and bacterial pneumonia and added that oral amoxicillin is as effective as parenteral penicillin and is the first choice for treatment of pneumonia. Even for severe pneumonia oral amoxicillin is safe and effective. Macrolides are added at any age only if there is no response to first line empiric therapy. The difference in this guideline from the INCLIN guideline is in the choice of first line empirical treatment is oral amoxicillin rather than oral cotrimoxazole for non-severe pneumonia and injectable ampicillin for severe pneumonia.

### **Infectious Diseases Society of America guidelines 2011<sup>7</sup>**

The clinical practice guidelines by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) for the management of community acquired pneumonia in infants and children older than 3 months of age was released by October 2011, the same time as BTS released the guidelines for pneumonia in UK. There were significant differences in the guideline released by the IDSA. It is stated that all those with moderate to severe pneumonia should be hospitalised. In infants less than 6 months of age even if pneumonia is suspected they need to be hospitalised as benefits are likely to be greater. It concurred with BTS in not recommending chest X-ray routinely in all children with suspected pneumonia who can be treated as outpatient. But it stated that antimicrobials are not routinely needed in preschoolers with pneumonia as etiology is viral in most of them and

whenever antimicrobials have to be started for pneumonia suspected to be of bacterial origin, amoxicillin should be used as the first line drug. If the clinical findings are suggestive of pneumonia caused by atypical pathogens especially in school going children and adolescents then macrolide antibiotics can be given. This is in contrast to BTS which stated that macrolides have to be added to the treatment regimen if there is no improvement to first line antibiotics. Another recommendation is the administration of antivirals in those children with moderate to severe pneumonia having symptoms consistent with influenza viral infection. This was not advised in the British guidelines. Also, IDSA guidelines state that though short course of antibiotic therapy may be effective the standard treatment duration of 10 days antimicrobial treatment regimen is the one which has robust data to support it as far as uncomplicated community acquired pneumonia is concerned.

### **World Health Organization-recommendation update 2012<sup>8</sup>**

The World Health Organization (WHO) after the second consultative meeting based on the evidence by GRADE methodology (*"Grading of Recommendations, Assessment, Development and Evaluation"*) in 2012 updated the recommendations for management of pneumonia in non-HIV infants and children. The main recommendation was that in children with non severe pneumonia with wheeze but without fever antibiotics are not routinely recommended but with a remark that this is applicable only when the health workers are able to assess the wheeze. The main reason for this recommendation is that in children without fever but with fast breathing and wheeze the etiology is most likely to be viral. Also the panel noted that addition of fever improves the diagnostic accuracy of WHO criteria in this group of children. The recommendation for the choice of antibiotics was changed to amoxicillin in the dose of 40 mg/kg/dose twice a day for 3 days with low HIV prevalence and for 5 days in high HIV prevalence. This recommendation was for children with non severe pneumonia without HIV infection. The shortened antibiotic course was found to have equal effectiveness as that of five days course with the added advantage of improved compliance and lower cost.

Children with severe pneumonia (with both fast breathing and chest in drawing) should be treated with amoxicillin for 5 days in a dose of 40 mg/kg/dose twice a day but this guideline is for those without HIV. In children with very severe pneumonia parenteral ampicillin or penicillin along with gentamycin should be the choice of treatment. If they fail to respond, then second line drug to

be used is ceftriaxone. The dosage for ampicillin is 50 mg/kg/dose while that for benzylpenicillin is 50,000 units/kg/dose. Either of these drugs should be given 6<sup>th</sup> hourly by intramuscular (IM) or intravenous (IV) route for five days while gentamycin has to be given in the dose of 7.5 mg/kg as IM/IV once a day for 5 days.<sup>8</sup>

### **Antibiotic guidelines – effectiveness**

In a study on short course antibiotic treatment from Israel published in 2014 with amoxicillin in a dose of 80 mg/kg/day as the drug of choice for ambulatory children between 6 and 59 months with CAP it was found that a 5 day treatment regimen was not inferior to a 10 day course. Also the study revealed that a 3 day antibiotic course may be associated with a unacceptable failure rate.<sup>9</sup> This study throws a question on the recommendation of WHO which had stated in 2012 that children residing in low HIV prevalence region with non severe pneumonia be treated with amoxicillin with 40 mg/kg/day for 3 days.<sup>8</sup>

Queen, et al., in 2014 compared the effectiveness of empiric antibiotics for community acquired pneumonia among hospitalised children with CAP in a multicenter retrospective study in US and found that the use of the narrow-spectrum therapy (ampicillin, amoxicillin) was not inferior to broad-spectrum antibiotics (second or third generation cephalosporins with or without macrolides) in all measured outcomes including length of stay, duration of oxygen, duration of fever, daily standardized pharmacy and overall costs, or readmission rates within 7 days. Even though this study was from a developed country it is reassuring to note that hospitalised children with CAP improved with narrow spectrum antibiotics.<sup>10</sup>

### **WHO revision 2014<sup>11</sup>**

The WHO revision in 2014 involved both redefining the severity of pneumonia and also the choice of antibiotic. In the revised severity classification only two categories of pneumonia are to be identified (i) pneumonia defined by fast breathing with or without chest indrawing requiring home therapy with oral amoxicillin and (ii) severe pneumonia where any general danger sign is present (not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition) requiring referral and injectable therapy. The advantages with the modifications were that oral amoxicillin can be used to treat pneumonia with both fast breathing and chest indrawing. Also the ease of administration of dispersible antibiotic at home improves the compliance thus ensuring completion of the course and reducing the need for referral to higher centres.

The dose of amoxicillin for children aged 2-59 months with pneumonia is 80 mg/kg/day in two divided doses for 5 days. Severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamycin as a first-line treatment. Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment. Studies have shown that the serum levels of the drug should be above the minimum inhibitory concentration for more than 40% of the time during treatment to get a bacteriological cure rate of about 85-100% during treatment. For penicillin resistant strains only amoxicillin provided levels above MIC for more than 40% of the dosing interval. Moreover American Academy of Pediatrics recommend amoxicillin in a dose of 75-100 mg/kg /day for treatment of CAP based on the extrapolation from microbiological studies from acute otitis media. Amoxicillin given in a twice-daily dosage regimen is as effective as regimens of three or four-times daily, provided that the total daily dosage of amoxicillin is the same. In view of the concern of increasing resistance to penicillin by the causative organisms in CAP, the dose of amoxicillin has been modified to 80 mg/kg/day in two divided doses.<sup>11</sup>

### Canadian pneumonia guidelines 2015<sup>12</sup>

The recent guideline by Canadian pediatric society has also advised to treat children with uncomplicated pneumonia - both lobar and bronchopneumonia with amoxicillin stating that the aim has to be to give good coverage against *Streptococcus pneumoniae* as it has been shown to be the predominant pathogen. They have also advised to treat with antiviral -oseltamivir or zanamivir if influenza is strongly suspected. It also states that empirical intravenous ampicillin should be given to those who are admitted with pneumonia but without a life threatening illness as it leads to good clinical outcome in almost all cases of CAP. But children with life threatening illness needs to be treated with third generation cephalosporin. Vancomycin should be added to the treatment regimen if there is rapid progression of multilobar disease or pneumatoceles to provide cover for methicillin resistant staphylococcus aureus (MRSA) till bacteriological support in the form of culture results are available.<sup>12</sup>

### Compliance with guidelines

In an audit by BTS of the 3123 prescriptions for oral antibiotics in 2482 children with CAP, the prescriptions were 35.2% for macrolide, 34.2% for co-amoxiclav and only 24.2% for amoxicillin. In the same audit, among the 1704 prescriptions for IV antibiotics for 1469 children it was for co-amoxiclav in 39.6%, cefuroxime in 17.8%, amoxicillin in 7.6% and cefotaxime in 6.3%.<sup>13</sup> This indicates that

though guidelines are given after careful review of available data with the advice to use amoxicillin as first line drug in CAP there is still hesitation in using the drug as first line even in a developed country with very good health system in place.

### Conclusion

Most of the guidelines give a uniform message that most of the pneumonia episodes in the community can be treated as outpatient with a simple drug like amoxicillin. Once treatment is started it is necessary to review them in 48-72 hours to assess the response to treatment. Following the 2014 WHO guidelines, where the classification of pneumonia has been simplified, domiciliary treatment with oral amoxicillin would go a long way to reduce morbidity and mortality.

### Points to Remember

- *Diagnosis is based on fast breathing, chest indrawing and general danger signs and classified as either pneumonia or severe pneumonia.*
- *For children between 2-59 months of age, domiciliary treatment of pneumonia, amoxicillin is the drug of choice in the dose of 80mg/kg/day in two divided doses for 5 days.*
- *Children between 2-59 months of age with severe pneumonia should be treated with IM/IV ampicillin or benzyl penicillin along with gentamycin for atleast five days.*
- *Ceftriaxone should be used as second line drug in those with severe pneumonia not responding to first line drugs.*
- *Reassessment at 48-72 hours is always necessary after initiating or changing treatment.*

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### CLIPPINGS

#### ***Association of acute toxic encephalopathy with litchi consumption in an outbreak in Muzaffarpur, India, 2014: a case-control study.***

Outbreaks of unexplained illness frequently remain under-investigated. In India, outbreaks of an acute neurological illness with high mortality among children occur annually in Muzaffarpur, the country's largest litchi cultivation region. In 2014, we aimed to investigate the cause and risk factors for this illness.

Between May 26, and July 17, 2014, 390 patients meeting the case definition were admitted to the two referral hospitals in Muzaffarpur, of whom 122 (31%) died. On admission, 204 (62%) of 327 had blood glucose concentration of 70 mg/dL or less. 104 cases were compared with 104 age-matched hospital controls. Litchi consumption (matched odds ratio [mOR] 9.6 [95% CI 3.6 – 24]) and absence of an evening meal (2.2 [1.2–4.3]) in the 24 h preceding illness onset were associated with illness. The absence of an evening meal significantly modified the effect of eating litchis on illness (odds ratio [OR] 7.8 [95% CI 3.3–18.8], without evening meal; OR 3.6 [1.1-11.1] with an evening meal). Tests for infectious agents and pesticides were negative. Metabolites of hypoglycin A, MCPG, or both were detected in 48 [66%] of 73 urine specimens from case-patients and none from 15 controls; 72 (90%) of 80 case-patient specimens had abnormal plasma acylcarnitine profiles, consistent with severe disruption of fatty acid metabolism. In 36 litchi arils tested from Muzaffarpur, hypoglycin A concentrations ranged from 12.4 µg/g to 152.0 µg/g and MCPG ranged from 44.9 µg/g to 220.0 µg/g.

Our investigation suggests an outbreak of acute encephalopathy in Muzaffarpur associated with both hypoglycin A and MCPG toxicity. To prevent illness and reduce mortality in the region, we recommended minimising litchi consumption, ensuring receipt of an evening meal and implementing rapid glucose correction for suspected illness. A comprehensive investigative approach in Muzaffarpur led to timely public health recommendations, underscoring the importance of using systematic methods in other unexplained illness outbreaks.

***Shrivastava A, Kumar A, Thomas JD, Laserson KF, Bhushan G, Carter MD, et al. Association of acute toxic encephalopathy with litchi consumption in an outbreak in Muzaffarpur, India, 2014: a case-control study. Lancet Glob Health 2017; 5: e458–66.***

## IAP - IJPP CME 2016

**ATYPICAL MANIFESTATIONS OF DENGUE****\*Shrishu R Kamath**

**Abstract:** *Dengue, caused by a flavivirus, spread by Aedes aegypti mosquito, is common in tropical countries following rains. Atypical manifestations are increasingly reported. A high index of suspicion is needed to identify them as complications of dengue. This review highlights the importance of recognition of atypical complications for early treatment that be life-saving.*

**Keywords:** *Dengue, Atypical manifestations.*

Dengue is caused by a flavivirus, which has four different serological types (DEN-1, DEN-2, DEN-3 and DEN-4). Although the serotypes are antigenically similar, they do not offer cross protection. Infection with any one serotype confers lifelong immunity to only that virus serotype. Dengue virus is spread by the bite of vector viz. *Aedes aegypti* mosquito also called the tiger mosquito because of striae on the wings. *Aedes aegypti* larvae flourish in clean stagnant water which is likely to occur following rains. Dengue infection is more common in well nourished children especially in infants and young children. The case fatality rate of dengue is around 5% and most fatal cases are among children. The most favoured pathogenesis accepted is that the virus strains enhance antibodies and memory T-cells in a secondary infection resulting in "Cytokine tsunami" which target vascular endothelium, platelets and various organs leading to vasculopathy and coagulopathy responsible for the development of hemorrhage and shock. Shock and bleeding manifestations are hallmarks of dengue.

**Classification and diagnosis of dengue**

Dengue is classified by WHO into following types:<sup>1</sup>

1. Probable dengue (without warning signs)
2. Dengue with warning signs
3. Severe dengue

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The clinical course of illness passes through the following three phases: a) febrile phase, b) critical phase and c) convalescent phase. Diagnosis of dengue is usually clinical and laboratory investigations will only aid in the diagnosis. Hemoconcentration and thrombocytopenia are hall marks of dengue. ELISA based NS1 antigen test along with IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) are diagnostic of dengue.

**Management of dengue**

Management of dengue is largely supportive. Fluid management titrated to urine output and targeting a fall in the hemocrit (reversing the hemoconcentration) will largely help (WHO protocol).<sup>1</sup> Colloids are indicated especially in children with hypotension. There is no role of platelet transfusion unless there is severe thrombocytopenia associated with bleeding. Correction of shock and acidosis takes priority. Transfusion of PRBC/ whole blood is the cornerstone in management of shock associated with bleeding manifestations.

**Atypical manifestations**

All children with shock, multi-organ dysfunction and atypical manifestations are usually classified as severe dengue. The following write-up will focus only on atypical manifestations of dengue in various organ systems and importance of their recognition. The various atypical manifestations seen in dengue infection are summarized in Box 1.

**Manifestations in circulatory system**

Shock is the major manifestation of dengue and occurs due to plasma leakage exceeding fluid replacement. Whenever the shock becomes refractory to fluids and inotropes then other causes of refractory shock should be looked for. Both systolic as well as diastolic dysfunction of the heart has been described in a series of patients with severe dengue (shock).<sup>2</sup> Diastolic dysfunction is a unique manifestation and requires an expert in ECHO for diagnosis. Identification of diastolic dysfunction is of paramount importance because unlike systolic dysfunction, diastolic dysfunction requires a decrease in the vasoactive adrenergic agents (adrenaline, dopamine) and use of lusitropic agents like milrinone. Cardiac rhythm disorders, attributed to

dengue viral infection of myocardium may manifest as atrio-ventricular blocks, atrial fibrillation, sinus node dysfunction and ectopic ventricular beats. Most are asymptomatic and have a benign self limiting course with resolution of infection and no other attributable cause can be found.<sup>3,4,5</sup> Pericardial involvement occurs in the form of mild pericardial effusion. This resolves during recovery phase and there is no evidence that it causes tamponade.<sup>6</sup>

### Box 1. Atypical manifestations in dengue

#### 1. Circulatory

- Cardiogenic shock\*
- Cardiac rhythm disturbances
- Pericardial effusion

#### 2. Abdominal

- Abdominal compartment syndrome\*
- Ischemic hepatitis\*
- Acalculous cholecystitis\*

#### 3. Renal

- Acute renal failure due to multi-organ dysfunction, acute tubular necrosis, hemolytic uremic syndrome

#### 4. Respiratory

- ARDS\*

#### 5. Hematological

- Hemophagocytic lymphohistiocytosis\*

#### 6. CNS

- Encephalopathy and Encephalitis\*
- Myelitis
- ADEM
- Guillain Barre Syndrome
- Myositis
- Cerebellitis
- Hypokalemic periodic paralysis

\* frequently encountered atypical manifestation

### Abdominal manifestations

**a) Abdominal compartment syndrome:** The third spacing and ascites due to fluid leak are temporary phenomena and resolve during the recovery phase. But occasionally the leak may be large and the ascites can cause abdominal compartment syndrome (ACS). Abdominal compartment syndrome is an atypical

complication of dengue. It needs high index of suspicion as it can cause multi-system derangement. Any child with severe dengue who has gross ascites, persistence of shock (despite adequate resuscitation) along with decreased urine output and metabolic acidosis should make one suspect ACS. It is diagnosed by measurement of bladder pressure using urinary catheter. If the bladder pressure is more than 10mmHg along with above mentioned features (shock, metabolic acidosis, >2 organ dysfunction) it is suggestive of abdominal hypertension. Serial measurements may be helpful at bedside. Initial conservative measures with fluid restriction and diuretics can be tried but if complications are more release of the abdominal fluid by tapping or by peritoneal dialysis may help. In a study of 109 children admitted in pediatric intensive care unit in a referral childrens' hospital in South India, compartment syndrome was seen in 3 children and contributed to refractory shock. Improvement in cardio-respiratory function occurred in 2 children following controlled release of the intra-abdominal pressure by peritoneal dialysis while the third child failed to improve and expired.<sup>2</sup>

**b) Ischemic hepatitis:** The presence of jaundice in dengue is multifactorial. It can be due to hepatic involvement caused by the dengue virus and ? or hypoxia and tissue ischemia in cases of shock. Jaundice occurs in 12-62% of patients with dengue shock syndrome.<sup>7</sup> There is a greater elevation in aspartate transaminase (AST) than alanine transaminase (ALT) levels, which may be explained by AST being released from the damaged monocytes.<sup>8</sup> This information may be useful in differential diagnosis of acute hepatitis especially in dengue endemic areas. Severe hemorrhage, shock, metabolic acidosis and disseminated intravascular coagulation may also contribute to severe changes in liver.<sup>8,9</sup> Acute liver failure is a severe complicating factor in dengue infection predisposing to life threatening complications. Several cases of fulminant hepatitis with high mortality have been reported. The increase in aminotransferases has been associated with increased disease severity and might serve as an early indicator of dengue infection.

**c) Acalculous cholecystitis:** Cholecystitis is rare in dengue fever and patients present with right upper quadrant abdominal pain, fever, positive Murphy sign, abnormal liver function tests and thickened gall bladder wall without stones on abdominal ultrasonography.<sup>10</sup> The exact pathogenesis of acalculous cholecystitis is not known; it could be due to increased vascular permeability causing plasma leakage. There is a significant association between thickening of gall bladder wall and severity as well as progression of dengue fever. It is usually self-limiting. Surgical intervention is reserved for patients with diffuse peritonitis.

## Renal manifestations

Acute renal failure is rare in dengue fever and it is due to shock induced acute tubular necrosis. Acute renal failure and multiple organ failure can also be a manifestation of rhabdomyolysis.

Renal failure because of hemolytic uremic syndrome has been described in an isolated case report. Another cause of renal failure could be compartment syndrome which in turn causes shock leading to acute tubular necrosis.

## Respiratory manifestations

One of the common respiratory complications is pleural effusion which usually resolves during the recovery phase. Severe dengue can result in acute respiratory distress syndrome (ARDS). Increased permeability of the alveolar-capillary membrane results in the edema in the alveoli and interstitial spaces which leads to pulmonary dysfunction. Dengue shock syndrome is reported to be third leading cause of ARDS in the pediatric intensive care setting in a dengue endemic area. Early restoration of adequate tissue perfusion is critical to prevent progression of dengue shock syndrome to ARDS. However, equal care must be exercised to avoid excessive fluid infusion after adequate volume replacement because fluid overload may result in ARDS.<sup>11</sup> The use of lung-protective strategies in ARDS usually has a good outcome. Pulmonary hemorrhage with or without hemoptysis has also been reported.<sup>12</sup>

## Hematological manifestations

Hematological complications include thrombocytopenia and deranged coagulation profile leading to bleeding tendencies in children with Dengue. The tourniquet test (Hess test) in dengue is due to capillary fragility. Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory disorder related to macrophage activation and usually presents as prolonged fever and a sepsis-like syndrome. Dengue virus can cause HLH and presents with nonspecific clinical signs such as fever, cachexia, hepatosplenomegaly and lymphadenopathy. Typical laboratory findings include bicytopenia or pancytopenia, hepatic impairment with coagulopathy, hypofibrinogenemia, elevation of serum LDH and triglyceride levels, and ferritinemia. The diagnosis and treatment is based on HLH 2004 protocol proposed by the histiocyte society. This type of HLH is classified as "Infection associated HLH" and prognosis is usually good. The treatment includes IVIG and steroids and rarely the HLH protocol 2004 is required. Dengue was found to be the leading cause accounting for 5 among 43 cases of HLH.<sup>14</sup> In a series of 52 pediatric patients with HLH

15 were infection associated out of which 3 were caused by dengue.<sup>15</sup> There was also a comprehensive report of six cases of dengue associated HLH in adults.<sup>13,14,15</sup>

## CNS manifestations

**a) Encephalopathy and encephalitis:** Encephalopathy is the most common neurological manifestation of dengue infection. Encephalopathy is used to describe a clinical picture of reduced consciousness. When there is presence of focal neurological deficits on clinical examination, focal abnormalities in neuroimaging or focal EEG abnormalities it is usually suggestive of encephalitis. Encephalopathy can be due to various indirect effects of dengue infection rather than direct viral invasion which results in encephalitis.<sup>16</sup> Ideally it would be best if dengue is confirmed in CSF but majority of the times it is not possible though it is confirmed in the serum. The reason for this mismatch remained unexplained. Low viral load/titre of antibodies in the CSF may be a possible explanation.<sup>17</sup> Magnetic resonance imaging (MRI) is the preferred neuro-imaging modality. There are no specific MRI features which characterize dengue encephalitis. MRI may be normal in many cases especially in the early part of the disease or it may show scattered focal abnormality, hemorrhage and edema. The majority of the studies have shown good recovery and better prognosis in patients of dengue encephalitis; however the study by Misra et al. reported a poor outcome and suggested encephalitis as the most severe complication of dengue infection. In this study, 3 patients died and 3 patients had partial recovery. Verma et al., had reported a case of dengue encephalitis leading to epilepsy partialis continua.<sup>18-21</sup>

**b) Myelitis:** Involvement of spinal cord (myelitis) is rare in dengue and MRI is the investigation of choice for confirmation. It is probably caused by direct viral invasion. There are reports of spinal cord involvement in dengue infection, presenting as post-infectious myelopathy, acute disseminated encephalomyelitis or transverse myelitis. Intrathecal synthesis of dengue IgG antibodies may indicate viral neurotropism for the spinal cord and may be contributing to the pathogenesis of the myelitis. A rare case was reported where spinal cord involvement was limited to the grey matter of the spinal cord, preferentially to the anterior horn only, similar to poliomyelitis.<sup>22</sup> Anti-dengue virus antibodies for dengue virus type 1 were detected in the CSF in this patient.<sup>22</sup>

**c) Acute disseminated encephalomyelitis (ADEM):** Acute disseminated encephalomyelitis is an immune mediated illness, usually caused by viral infections or vaccination. Rarely dengue infection can cause acute

disseminated encephalomyelitis. MRI features are similar to the findings seen in patients with ADEM due to other etiologies. Foci of hemorrhages within demyelinating lesions, signal changes in white matter lesions in the centrum semiovale, corona radiata and thalamus are also evident on MRI. In a series of 109 children admitted in PICU, 2 children had ADEM. MRI findings along with CSF confirmed the diagnosis in this series.<sup>2</sup>

**d) Guillain-Barré syndrome (GBS):** There are a few cases of GBS following dengue infection, reported in literature. GBS is reported during the recovery phase of illness and is a post-infectious illness. It is due to an aberrant immune response which causes nerve damage. Dengue infection may trigger an abnormal immune response, which can cross-react with the peripheral nerve via molecular mimicry. However, in patients presenting with Guillain-Barré syndrome without any usual antecedent infections, screening for dengue virus infection may help in identifying it as a rare cause.<sup>23,24</sup>

**e) Myositis:** Though myalgia is very common in dengue infection, myositis and muscle weakness are distinctly uncommon. A few cases are reported which relate dengue infection with myositis. In a case series of dengue infection weakness developed within 3-5 days of illness.<sup>25</sup> The weakness was of severe grade in 4 patients and one patient also required ventilator support. The CPK levels were elevated in all patients. The nerve conduction studies were normal in all patients and EMG was myopathic in one patient. Six patients recovered completely and one who needed ventilator support had poor recovery. Muscle biopsy studies have not demonstrated direct invasion by dengue virus, however, mild lymphocytic infiltration to foci of severe myonecrosis has been shown in dengue infection. Even rhabdomyolysis and myocarditis following dengue infection have been reported. Recently infection of heart tissues in vivo and of striated muscle in vitro by dengue virus has been demonstrated.<sup>26</sup> Early respiratory muscle involvement and very high CPK levels suggest a severe form of dengue myositis with poor prognosis.<sup>26</sup>

**f) Hypokalemic paralysis:** Hypokalaemic paralysis following dengue infection is reported in literature but extremely rare. Jha et al. reported 3 patients of confirmed dengue infection who presented with acute onset pure motor quadriparesis with hypokalaemia.<sup>27</sup> Despite small number of cases getting reported during every epidemic, the prognosis is good with almost all recovering within 12 hours of potassium correction with complete recovery in a few days.

**g) Dengue cerebellitis:** Dengue cerebellitis is a rare atypical manifestations and it is reported in a case series of

8 patients which was basically a MRI-based series.<sup>28</sup> Two distinct imaging features - presence of cerebellar signal abnormalities and presence of micro-hemorrhages within parenchymal lesions were observed in this series. This is in contrast with previous studies which have concluded that changes are nonspecific. Proposed criteria for the diagnosis of dengue encephalitis are the presence of dengue virus RNA, IgM, or NS1 antigen in CSF and CSF pleocytosis without other neuro-invasive pathogens.

**h) Other neurological manifestations:** Various post viral neuropathies such as isolated phrenic neuropathy leading to diaphragmatic palsy, long thoracic neuropathy and ophthalmoplegia due to the involvement of the oculomotor nerve are also reported in dengue infection. There are few cases of dengue infection thought to have led to brachial neuritis. In a retrospective study out of 26 patients in a tertiary care centre, 10 patients had brachial neuritis. There were also 2 cases of opsoclonus myoclonus syndrome associated with dengue seropositivity.<sup>29</sup>

## Conclusion

Critically ill children with dengue may have protean multi-system manifestations. The atypical manifestations described here might be unrecognized and under-reported. However, it is imperative to know all these manifestations for clinical diagnosis and appropriate management, so that early life saving management may be instituted.

## Points to Remember

- *Atypical manifestations in dengue are becoming common.*
- *Frequently encountered atypical manifestations are cardiogenic shock, abdominal compartment syndrome, encephalopathy, ARDS and HLH.*
- *Recognition is of paramount importance as management strategy may change if identified early and may be life saving.*

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### NEWS AND NOTES

**WPC - 14th World Pediatrics Conference  
Los Angeles, United States - 11<sup>th</sup> – 13<sup>th</sup> September, 2017**

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## IAP - IJPP CME 2016

**UPDATE ON CHILDHOOD TUBERCULOSIS****\*Kalpana S**

**Abstract:** *The burden of childhood tuberculosis remains high in India. The diagnosis is challenging because tuberculosis in children is generally paucibacillary. Indian guidelines including Indian Academy of Pediatrics - Revised National Tuberculosis Control Program (IAP RNTCP) consensus guidelines 2015 and the most recently released RNTCP guidelines 2016 have described not only diagnostic techniques involving molecular biology, but also modifications in the standard treatment and new antituberculous drug - bedaquiline. However, the diagnosis continues to be based on clinical features, imaging studies and epidemiological factors. This article will discuss the recent updates in the management of childhood tuberculosis.*

**Keywords:** *Tuberculosis, Children, Management updates, RNTCP*

India is the country with the highest burden of TB. The World Health Organisation (WHO) statistics for 2015 gives an estimated incidence of 2.2 million cases of TB for India out of a global incidence of 9.6 million.<sup>1</sup> The diagnosis is challenging because tuberculosis in children is generally paucibacillary. Further the management of TB in children is replete with challenges. The updates will be discussed under clinical diagnosis, investigations and treatment.

**Clinical diagnosis**

The current WHO guidelines suggest that symptom-based screening is adequate, at least in older children and the complete absence of suggestive symptoms is sufficient to rule out active tuberculosis in that group. Early case detection is vital to interrupt the transmission of TB. The symptom characterisation for suspecting tuberculosis remains the same (Box 1).

**Box 1. Symptoms to suspect TB**

- i. Persistent and unexplained fever (more than 38°C) for more than 2 weeks reported by guardian or objectively recorded at least once.
- ii. Unremitting and persistent cough for more than 2 weeks.
- iii. Definite weight loss / failure to thrive: A weight loss of more than 5% of the last documented weight in the past 3 months with no other apparent cause should prompt further investigations for TB.

“Soft signs” such as loss of appetite, not growing well, chronic cough or low grade fever for prolonged duration are not considered as adequate TB symptoms. Intermittent or episodic cough reported by parents is more likely to be due to recurrent post viral upper respiratory tract infection or due to asthma and is unlikely to be due to TB.

**Investigations**

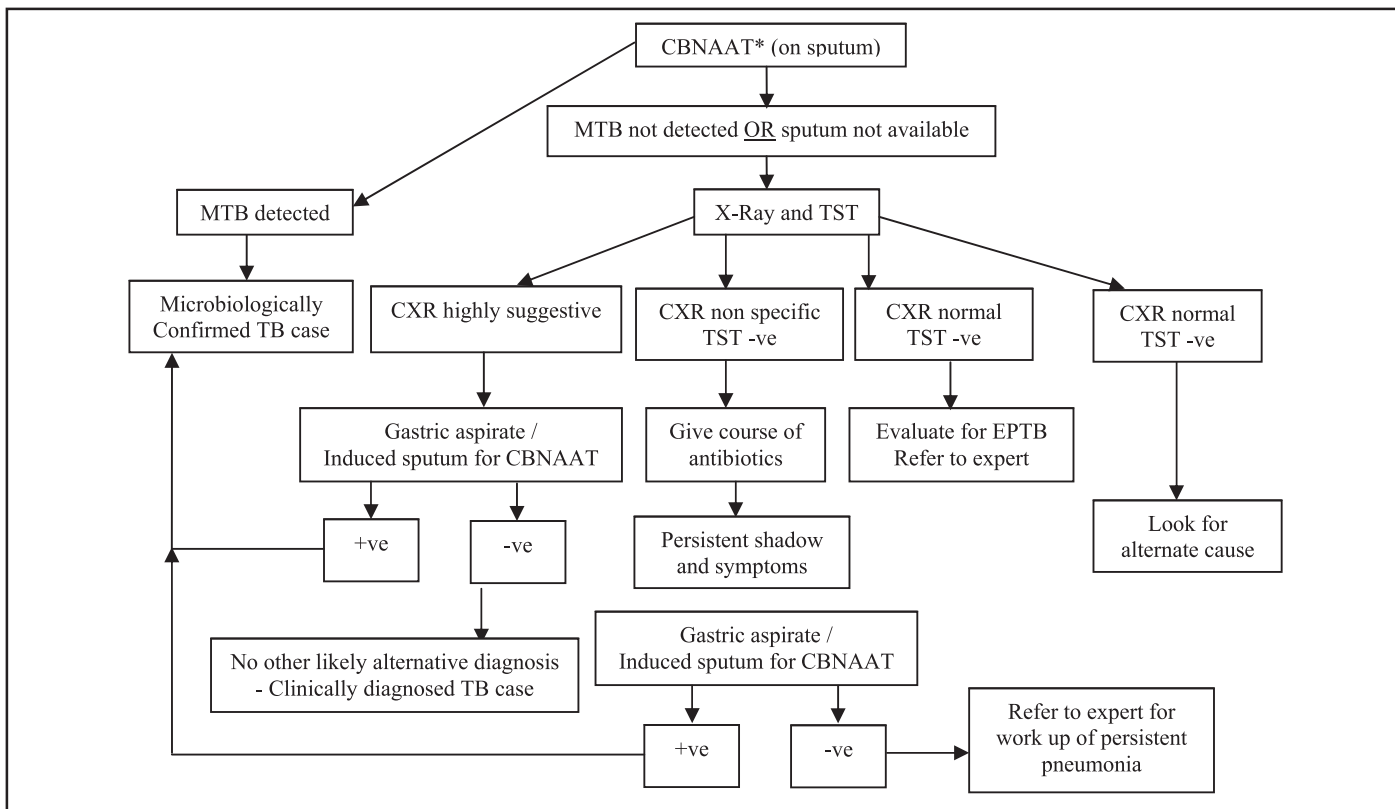
The 2016 RNTCP guideline gives a diagnostic algorithm for pediatric TB. Xpert MTB/RIF is recommended as the initial test in all children suspected to have TB rather than smear or culture (Fig 1).<sup>2</sup> This is in accordance with the 2014 WHO guidelines.<sup>3</sup> So it comes first in the algorithm in children who can expectorate sputum. In the rest, which is the usual case, the guidelines recommend further investigations with chest X-ray and mantoux

**Chest X-ray:** It remains the first and an important investigation despite high inter and intra observer variations that can occur in reading X-rays. Radiological findings of TB are recorded as either “highly suggestive” or “non-specific radiology”. The highly suggestive findings are hilar lymph nodes, chronic fibrocavitary disease and miliary pattern. When these are present, proceed to gastric lavage or induced sputum for GeneXpert. When children present with non-specific radiological signs such as - consolidation, non-homogenous opacities, ground glass opacities or thin walled cavities, a course of antibiotics is given before further evaluation.

Emphasis is given to the lateral chest X-ray. It gives better delineation of retro cardiac lesions and the hilum.

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**Fig 1. Diagnostic algorithm for TB diagnosis in children**

*\*If CBNAAT is not readily available smear microscopy should be performed*

*MTB – Mycobacterium tuberculosis; CBNAAT - Cartridge based nucleic acid amplification test (e.g. GeneXpert TB); TST - Tuberculin skin test; CXR - Chest Xray; EPTB - Extra-pulmonary TB*

The ‘dough nut sign’ visualised on a lateral X-ray—the upper half is seen in normal individuals as an upside down horse shoe is made up of RPA, LPA and aortic arch. Presence of lymph nodes posterior to the bronchus intermedius produces lobular densities that completes the inferior portion of the dough nut.

**Mantoux:** The current recommendation remains unchanged - 2 TU PPD RT 23 is considered the most appropriate for routine diagnostics. The major limitation is the availability. 5TU may be used if 2TU is unavailable.

**Microbiology:** The yield of a sample in detecting TB bacilli is highly dependent on accuracy and adequacy of the technique of sampling - whatever be the diagnostic test. Gastric lavage after overnight fasting or ambulatory or induced sputum should be tried in all cases. Samples should be processed for culture by Mycobacterial growth indicator tube (MGIT) or GeneXpert rather than AFB smear. Samples can be pooled to increase the yield when sent for GeneXpert.

**GeneXpert:** All children will preferentially get an upfront GeneXpert as per the new approved algorithm for pediatric TB.<sup>2</sup> All samples can be sent except blood including lymph nodes, body fluids and biopsy specimens including bone. As GeneXpert can pick up even DNA of dead bacilli it is not recommended for monitoring therapy. Samples can be stored in room temperature for 3 days before processing. Children suspected of having pulmonary TB but who have had a single negative result by Xpert MTB/RIF should undergo further diagnostic testing, and a child for whom there is a high clinical suspicion of TB should be treated even if Xpert MTB/RIF result is negative.

**Rifampicin (RIF) resistance by GeneXpert:** Any RIF resistance reported should be confirmed again by repeat testing with either GeneXpert or line probe assay (LPA) if available before deciding on alternate drug regimen. If there are discordant results between the 1<sup>st</sup> and 2<sup>nd</sup> molecular testing i.e the second testing shows RIF sensitive, it is essential to do drug resistance testing by liquid culture while proceeding to treat the case with first line drugs, if RIF

resistance is reported by Genxpert, the new guidelines recommend to continue INH in standard dose in the MDR treatment regimen till results of LPA or liquid culture drug sensitivity test (DST) are known.

**Line probe assay (LPA):** LPA in RNTCP and WHO endorsed molecular testing which are available in both private and public sectors. It detects resistance to both INH and RIF using the INHa, KATg and RPOb gene mutations. The WHO recommended the use of LPA for smear-positive pulmonary specimens in a 2008 policy statement.<sup>4</sup> In addition to rifampicin resistance (rpoB gene), MTBDR plus assay aids in the detection of high level and low level resistance to isoniazid (INH) via the katG gene and inhA gene, respectively. In cases of low level resistance to INH, INH is added in higher doses.

### Treatment

The programme is now introducing daily regimen for treatment of drug sensitive TB among people living with HIV infection (PLHIV), pediatric TB patients in the entire country and for all TB patients in 104 districts initially. Rest of the country will follow intermittent regimen as per existing guidelines until daily regimen is scaled up in the entire country. The major changes are: a) daily dosing rather than intermittent, b) increasing the doses of the individual TB drugs, c) including ethambutol in the continuation phase and d) using fixed drug combination.

The reasons cited for change from intermittent Directly Observed Treatment Shortcourse (DOTS) to daily regimen are as follows:

High relapse rate of 11% - 13% has been reported in patients treated by DOTS in RNTCP in India over the last several years.<sup>5</sup> Also in India, INH resistance is 11% in untreated TB patients and 37% in previously treated cases and the prevalence of HIV co-infection is 5%. With a background of high INH resistance and/or HIV co-infection it can result in higher rates of treatment failure and relapse with intermittent dosing schedules. In countries where INH resistance is prevalent a full 6 months course of rifampicin is recommended by WHO with a third drug, ethambutol, added to the 4 months of continuation phase.<sup>6</sup>

### IAP RNTCP guidelines

Treatment for new and retreatment cases are shown in Table I. Drug dosage of first line anti TB drugs is given in Table II.

Table III gives the proposed weight bands as well as the drug schedule for the fixed drug combinations (FDC) that will be available in a phased manner under RNTCP.

**Table I. Treatment categories for pediatric TB**

Category of treatment	Regimens*
New cases	2HRZE + 4HRE
Retreatment cases	2HRZES + 1HRZE + 5HRE

\*H- INH; R- Rifampicin; Z- Pyrazinamide; E – Ethambutol; S- Streptomycin; Prefix number denotes number of months.

**Table II. Daily dosage of first line anti TB drugs**

Drug	Dosage (mg/kg)
Isoniazid	10
Rifampicin	15
Pyrazinamide	30
Ethambutol	20
Streptomycin	15

**IAP and RNTCP recommendations for preventive therapy:** Monotherapy with INH 10mg/kg daily for 6 months (maximum dose of 300mg) is indicated for the following.

- (i) All asymptomatic children less than 6 years of age with positive TB contact
- (ii) All HIV infected children more than 1 year of age without active TB disease even without a contact as part of comprehensive package of HIV prevention and care services
- (iii) All mantoux positive children who are receiving immunosuppressive therapy
- (iv) Infants born to mothers treated for TB in antenatal period after ruling out active disease

Prophylactic therapy for children in contact with drug resistant TB is controversial. The guidelines do not recommend any chemoprophylaxis. But the children should be in close follow up for 2 years till the index case becomes noninfective. All children diagnosed with active TB should be offered HIV testing.

**Recommendations for anti tuberculous drug induced liver injury (DILI):** Presence of atleast one of the following characterise DILI and ATT should be stopped in case of non-serious forms of TB.

**Table III. Weight bands and dosage schedule of FDC**

Weight bands	Number of tablets (dispersible FDCs)		
	Intensive phase		Continuation phase
	HRZ	E	HRE
	50/75/150	100	50/75/100
4-7 Kg	1	1	1
8 -11 Kg	2	2	2
12 -15 Kg	3	3	3
16 -24 Kg	4	4	4
25 -29 Kg	3 + 1A*	3	3 + 1A*
30 -39Kg	2 +2 A*	2	2+ 2A*

A\* - Adult fixed dose tablet containing (INH 75 RMP 150 PYZ 400)

- In asymptomatic rise of > 5 times the upper limit of normal levels of ALT/AST
- In symptomatic rise of > 3 times the upper limit of normal levels of ALT/AST
- Serum bilirubin >1.5mg/dL

In case the child has serious forms of TB, start daily ethambutol, ofloxacin and streptomycin. Repeat liver enzymes after a week. When enzymes are less than twice the upper limit of normal, rifampicin is started and LFT repeated after a week. If normal, INH is added in full dose with repeat LFT after a week. If normal, pyrazinamide is added in full dose, ofloxacin and streptomycin are withdrawn with a repeat LFT after a week to check if liver enzymes are within the accepted range.

**Management of BCG adenitis:** In case of non suppurative BCG adenitis, masterly inactivity is the management of choice. If the node suppurates, needle aspiration is done to prevent spontaneous rupture and sinus formation. Excision of the node is recommended if needle aspiration fails and also in matted or multiloculated node.

**Tuberculosis and HIV infection:** The treatment regimen is 2HRZE+4HRE+6H. Children started on first line ATT should be given 6 months of INH preventive therapy for sterilising latent infection following the 6 months of ATT. Start ATT first. Start antiretroviral therapy (ART) after 2-8 weeks of ATT.

**Bedaquiline:** Bedaquiline (BDQ) is the new drug approved to treat drug resistant TB. It is a diarylquinoline and is the first drug with a novel mechanism of action against *M. tuberculosis* that has been approved by FDA since 1971. In 2013, the WHO has published interim policy guidance for the use of BDQ. It uses adenosine 5'-triphosphate (ATP) synthase inhibition as its mechanism of action, an enzyme essential to supply energy to the mycobacteria and has bactericidal and sterilizing activity against MTB. No cross-resistance has been found between bedaquiline and first and second line TB drugs.

Bedaquiline may be used on a case-by-case basis in children, HIV-infected persons, pregnant women, persons with extrapulmonary MDR TB and patients with co-morbid conditions on concomitant medications when an effective treatment regimen cannot be provided otherwise. Now BDQ is approved for use in those above 18 years of age with pulmonary MDR TB. As more data become available regarding the dosing, efficacy and safety of bedaquiline in children, this novel drug will soon be included in the armamentarium against drug resistant TB in children.<sup>7</sup>

#### Points to Remember

- *GeneXpert MTB/RIF is recommended as the initial microbiological investigation of choice in all children with suspected tuberculosis.*
- *Mantoux (2TU) testing is the preferred investigation for detecting TB infection.*

- *Daily ATT with increased doses of individual TB drugs is advised as per the newer guidelines.*
- *Ethambutol is now added for the entire course of treatment.*

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## CLIPPINGS

### *Acute Kidney Injury in Children With Type 1 Diabetes Hospitalized for Diabetic Ketoacidosis*

Acute kidney injury (AKI) in children is associated with poor short-term and long-term health outcomes; however, the frequency of AKI in children hospitalized for diabetic ketoacidosis (DKA) has not been previously examined.

The study was done to determine the proportion of children hospitalized for DKA who develop AKI and to identify the associated clinical and biochemical markers of AKI.

The records of all DKA admissions from September 1, 2008, through December 31, 2013, at British Columbia Children's Hospital, the tertiary pediatric hospital in British Columbia, Canada was reviewed. Children aged 18 years or younger with type 1 diabetes and DKA and with complete medical records available for data analysis were included (n=165).

Acute kidney injury was defined using Kidney Disease/Improving Global Outcomes serum creatinine criteria. Multinomial logistic regression was used to identify potential factors associated with AKI. Of the 165 children hospitalized for DKA, 106 (64.2%) developed AKI (AKI stage 1, 37 [34.9%]; AKI stage 2, 48 [45.3%]; and AKI stage 3, 21 [19.8%]). Two children required hemodialysis.

In the adjusted multinomial logistic regression model, a serum bicarbonate level less than 10 mEq/L (compared with  $e^{-10}$  mEq/L) was associated with a 5-fold increase in the odds of severe (stage 2 or 3) AKI (adjusted odds ratio [aOR], 5.22; 95% CI, 1.35-20.22). Each increase of 5 beats/min in initial heart rate was associated with a 22% increase in the odds of severe AKI (aOR, 1.22; 95% CI, 1.07-1.39). Initial corrected sodium level of 145 mEq/L or greater (compared with 135-144 mEq/L) was associated with a 3-fold increase in the odds of mild (stage 1) AKI (aOR, 3.29; 95% CI, 1.25-8.66). There were no cases of mortality in patients with or without AKI.

This study is the first to date to document that a high proportion of children hospitalized for DKA develop AKI. Acute kidney injury was associated with markers of volume depletion and severe acidosis. Acute kidney injury is concerning because it is associated with increased morbidity and mortality as well as increased risk of chronic renal disease, a finding that is especially relevant among children who are already at risk for diabetic nephropathy. Strategies are needed to improve the diagnosis, management, and follow-up of AKI in children with type 1 diabetes.

**Hursh BE, Ronsley R, Islam N, Mammen C, Panagiotopoulos C. Acute Kidney Injury in Children With Type 1 Diabetes Hospitalized for Diabetic Ketoacidosis. *JAMA Pediatr*. Published online March 13, 2017:e170020. doi:10.1001/jamapediatrics.2017.0020**

## IAP - IJPP CME 2016

**TROUBLE SHOOTING IN VENTILATION****\*Shanthi S**

**Abstract:** *Many critically ill children need ventilation. These children need very close monitoring of not only their physiologic status but also the ventilator settings for early identification of any problem in the patient ventilator system. A step wise approach is used to manage a child who deteriorates acutely. Proper setting of alarms and ventilator parameters are essential. Knowledge of ventilator graphics helps the physician to identify any change in the pulmonary physiology early. This article discusses the early identification of these problems and their management.*

**Keywords:** *Trouble shooting, Ventilation, Alarms*

Ventilation is a life saving intervention in critically ill children. However, it is important to understand that ventilating a child is fraught with many complications. It is prudent to anticipate these problems and prevent them by closely monitoring the child.

Trouble shooting is defined as systematic identification and resolution of potentially dangerous situations in the patient ventilator system.<sup>1</sup> The most effective method to identify problems in a ventilated child is to perform meticulous and frequent cardiopulmonary cerebral assessment (CPCA). Meticulous clinical monitoring by a trained physician or nurse is the best method to detect any derangement in the physiologic status of the patient. It is the best practice to have CPCA chart and ventilator chart at the bed side of every ventilated child to identify trouble shooting early.

Whenever a child on ventilator deteriorates or when there is a ventilator alarm the first step is to examine the patient and not attend to the ventilator. Airway, breathing and circulation (ABC) should take precedence. A CPCA is performed to determine the physiologic status. It is advisable not to sedate an agitated child before ruling out hypoxia or shock.

**Procedure to be followed when any child on ventilator deteriorates and is hemodynamically unstable****Step 1**

The child has to be disconnected from the ventilator and manually ventilated with ambu bag. Displacement and obstruction of the endotracheal tube, pneumothorax and equipment failure (DOPE) are the most common causes of deterioration in a ventilated child. If child improves on manual ventilation it indicates that there is an equipment failure.

**Equipment failure:** This may include a disconnection or kinking of the circuit, electrical failure, low gas/oxygen supply. Electrical supply and plugs are to be checked. A mistaken disconnection may have occurred especially if the plugs are not marked. Ventilator function is checked with a test lung and the ventilator is reconnected after rectifying the problem.

Inappropriate ventilator settings can also result in trouble shooting. They are - alarm limits kept low, inappropriate inspiratory flow setting, inappropriate trigger sensitivity or inappropriate mode.

**Step 2**

When the child is being bagged, the resistance to bagging is assessed. If there is increase in resistance it may indicate obstruction, pneumothorax or displacement of tube into a main bronchus, usually the right. Obstruction due to secretions, kinking or biting of endotracheal tube is the most common cause of sudden deterioration of a ventilated child. Suction is applied after preoxygenating with 100% oxygen. Appropriate size suction catheter (endotracheal tube size×2) is used and suction is applied for not more than 10 seconds. Sometimes if the secretions are dried up it may appear as if there is no block but the child will have respiratory distress. In such situations instilling a small quantity of normal saline and applying suction would help. Once the secretions are cleared the resistance to bagging decreases and it will be easy to bag. However, if child is gasping or struggling to breathe with fall in saturations it is safer to remove the endotracheal tube and manually ventilate with bag and mask followed by

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reinsertion of the tube. Tube block can be prevented to a great extent by frequent monitoring, postural changes and physiotherapy. Appropriate humidification is important to prevent drying up of secretions.

### Step 3

If the child does not improve after suctioning and air entry is decreased on the left side consider right main bronchus intubation. If a cuffed tube is used the cuff is deflated. The tube is pulled out and fixed in the appropriate position. The depth of insertion is generally endotracheal tube (ET) size $\times 3$  in centimetres. A five point auscultation (epigastrium, both infraclavicular and axillary) is done to confirm tube position.

Displacement of endotracheal tube into the stomach often presents as an emergency. The child may rapidly deteriorate with fall in saturation, cyanosis and bradycardia. End tidal carbon dioxide monitor may show sudden fall in the reading. The tube is removed, the child manually ventilated with ambu bag and then reintubated.

It is important to document the tube position at the lip every time the ET is manipulated or changed. This will help to identify any inadvertent movement of the ET. Flexion and extension of the neck will cause the tube to migrate in or out. Before taking an X-ray to confirm the tube position the head has to be in the neutral position.

### Step 4

If obstruction and displacement are ruled out and if the child still does not improve and air entry is diminished pneumothorax has to be considered. The affected side may be resonant to percussion. An emergency needle thoracocentesis is done on the side of decreased air entry. A gush of air confirms pneumothorax. An intercostal drainage tube should then be introduced.

### Ventilator alarms

Most modern ventilators have alarms which get activated whenever there is any problem in ventilation. The common alarms which are present in the ventilator are high and low pressure alarms, high and low tidal volume/minute volume alarms, low  $FiO_2$ , low oxygen/air pressure, apnea, high exhaled tidal volume alarms and circuit disconnect alarms. There are visual and auditory alarms. Red display alarms indicate a more serious problem. Once the problem gets corrected yellow display is seen. For example, if the child on the ventilator coughs, immediately the high pressure alarm will get activated and display in red. Once the cough settles and the peak pressure

reaches normal the audible alarm will stop automatically and the red display will change into yellow. Green color will be displayed once the reset button is pressed.

Ventilator alarms should never be ignored. Silencing the alarm before the problem is attended to may endanger the life of the patient. The ventilator also displays the value of various variables of the patient namely inspiratory tidal volume (V<sub>ti</sub>), expiratory tidal volume (V<sub>te</sub>), minute volume (VE), respiratory rate, peak inspiratory pressure (PIP). The newer ventilators have graphics - both scalar and loops. They depict any change in the pulmonary physiology very clearly and help to identify trouble shooting early.

### Hemodynamically stable child but with alarms on ventilator

First attend to the patient and not the alarm. A focused history and clinical examination will help identify the problem. It is necessary to review the indication for intubation, size of the tube, depth of ETT, previous ventilator settings, recent procedures like central line placement, any manipulation of ETT, transport and change of position of the patient.

The ventilator circuit is checked for any leak, water or disconnection and ET tube for kinking or deep placement. The pilot balloon in the cuffed tube is checked. Always listen and feel if there is an airleak, feel for subcutaneous crepitus which may indicate an underlying pneumomediastinum and airleak. A cardiopulmonary cerebral assessment (CPCA) has to be performed. Airway may have to be positioned properly. It is necessary to look for unequal chest rise, listen for equal air entry over the lung fields and for presence of crackles and wheeze.

### Check if the alarms are set correctly

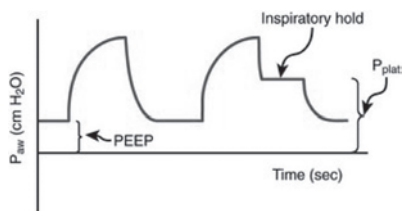
High pressure alarm may indicate deterioration in lung compliance, increase in airway resistance, an equipment problem that needs to be addressed, increased intrathoracic pressure with potential hemodynamic consequence. High airway pressures may cause barotrauma. Most ventilators are set to terminate the inspiratory flow if the upper pressure limit is reached. This leads to markedly reduced inspiratory volume and therefore low tidal volume and minute volume.<sup>2</sup> High pressure alarm may be due to problems in the machine or in the patient (Table I).

In the stable patient alveolar pressure is checked. This is determined by pressing the inspiratory hold. The flow is terminated and the pressure measured is known as plateau pressure which reflects the alveolar pressure (Fig.1a). To prevent lung injury, alveolar pressure should

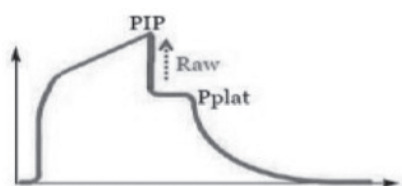


**Table I. High pressure alarm - Causes**

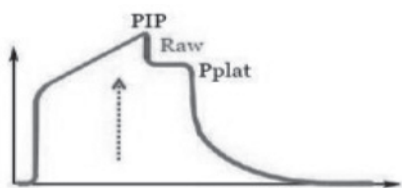
Machine	Patient
Circuit - There may be water in the circuit due to pooling of condensed water vapor; wet filters can cause increased airway resistance; kinking of the circuit can increase the airway pressure.	Increased airway resistance: Asthma, bronchiolitis, mucous plugging.
Ventilator- Improper ventilator settings like alarm limits being set low, excessive tidal volume or flow, excessively short inspiratory time.	Decreased compliance: Acute respiratory distress syndrome (ARDS), pulmonary edema, pneumonia, collapse, pneumothorax, effusion, abdominal distension.
Endotracheal tube (ETT)- Displacement of ETT into the bronchus, kinking of the tube or biting of the tube, obstruction.	Coughing, crying.



**Fig.1a. Plateau pressure**



**Fig.1b. Increased airway resistance**



**Fig.1c. Decreased compliance**

(PEEP: Positive end-expiratory pressure, PIP: Peak inspiratory pressure, Raw: Airway resistance, Pplat- Plateau pressure)

be kept below 30 cmH<sub>2</sub>O. If PIP is high but plateau pressure is normal it indicates there is increased airway resistance (Fig.1b). If peak inspiratory pressure (PIP) and plateau pressure are both high it indicates there is decreased compliance (Fig.1c).

Low pressure alarm is triggered when circuit pressure drops below the preset low pressure limit. It is usually associated with low volume alarms. Conditions causing low pressure/low volume alarms are depicted in Table II.<sup>3</sup>

**Box 1. Patient ventilator asynchrony**

**Equipment factors**

- Inappropriate sensitivity settings
- Inappropriate mode of ventilation
- Inadequate FiO<sub>2</sub>
- Inspiratory flow settings
- System leak
- Response time of ventilator

**Patient factors**

- Disease process of the patient
- Intrinsic PEEP
- Tube block
- Airway problems
- Pain
- Presence of airway leak

High respiratory rate alarms often indicate the patients' need to increase ventilation. It can also result from an inappropriate sensitivity setting. When this control is set excessively sensitive to the patients inspiratory effort, any movement or even water in the circuit can initiate breaths and increase the total respiratory rate.

Apnea alarm is commonly due to disconnection of the ventilator circuit from the patient's endotracheal tube. Other triggers are respiratory muscle fatigue, patient on muscle relaxants.

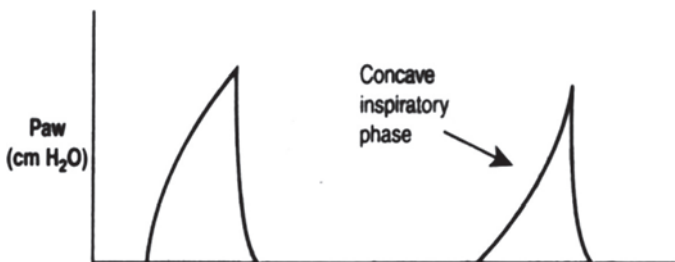
Patient ventilator asynchrony can occur due to equipment factors or due to patient factors (Box 1). It can cause many adverse effects like increased work of

**Table II. Low pressure/low volume alarms – causes**

Loss of circuit pressure	Loss of system pressure	Premature termination of inspiratory phase	Inappropriate ventilator settings
Circuit disconnection Exhalation valve disconnection	Power failure Gas failure/disconnection	Excessive peak flow Insufficient inspiratory time	Excessive rate with insufficient peak flow
Insufficient ETT cuff volume Loose circuit connection Loose humidifier connection	Air compressor failure	Excessive expiratory time	Low pressure limit set too high Low tidal volume set too high

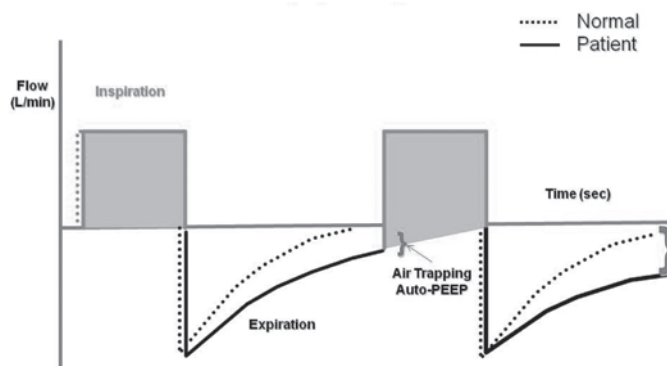
breathing, impaired gas exchange, increased requirement for sedation and prolonged weaning from mechanical ventilation.<sup>4</sup> It can present clinically as agitation, diaphoresis, altered level of consciousness, tachycardia followed by bradycardia and increased work of breathing. DOPE has to be ruled out as mentioned earlier. Most problems can be identified at the bed side by careful observation of the respiratory effort and ventilator cycling.<sup>5</sup>

The ventilator waveforms - scalars and loops assist in detecting the problem early. However, if the child's condition has clinically improved it may indicate that the child is ready to be weaned from the ventilator. Flow asynchrony occurs whenever the ventilator flow does not match the patients flow need (Fig.4). This results in excessive work of breathing. Such patients may require a decelerating inspiratory flow pattern, in which a higher flow is provided in the beginning of inspiration and less toward the end as the lungs fill up. Expiratory asynchrony occurs due to a shortened or prolonged expiratory time or due to patients' efforts during expiration. Newer ventilators have active exhalation valves that continue to sense the patients' effort during expiration and respond to their effort.<sup>6</sup>



**Fig.4. Flow asynchrony**  
(Paw: Peak airway pressure)

Patient ventilator asynchrony is managed by addressing the underlying problem. In certain situations if the asynchrony is causing unacceptable derangement of gas exchange and ventilator-induced lung injury, sedation and analgesia may be necessary to facilitate ventilation and to



**Fig.5. Auto PEEP**

**Auto PEEP/intrinsic PEEP**

reduce the work of breathing. Benzodiazepines and opiates are commonly employed. In certain situations neuromuscular paralysis with a non-depolarizing agent like vecuronium may be needed. Deep sedation is mandatory in any paralyzed child to prevent pain and anxiety.<sup>7</sup> Long term use of sedatives has many adverse effects like drug dependence and withdrawal symptoms. Hence judicious use of these drugs is recommended.

**Auto PEEP/intrinsic PEEP**

Shorter expiratory time leads to air trapping and dynamic hyperinflation (auto PEEP) when a new inspiratory breath is begun before the previous expiratory flow has ended (Fig.5). This is commonly seen in bronchospasm, mucus plugging and bronchiolitis. It is clinically evident as forceful contraction of abdominal muscles during expiration. Intrinsic PEEP may cause triggering difficulties during inspiration. Very high auto PEEP may cause sudden cardiorespiratory collapse in asthma, bronchiolitis. Disconnecting the ventilator for 20-30 seconds and a brief manual squeezing of the chest may help.<sup>1</sup>

Auto PEEP is measured by pressing the expiratory hold. It may be reduced by prolonging the expiratory time

either by reducing the respiratory rate or by decreasing the tidal volume. Use of bronchodilators to reduce bronchospasm will help in asthmatics. Adequate sedation to facilitate ventilation will reduce auto PEEP. In the spontaneously breathing patient setting the PEEP at 2/3 rd of the measured auto PEEP will facilitate triggering and reduce the work of breathing. Anticipating problems in a child who is on a ventilator and a knowledge about the ventilator graphics help in trouble shooting.

### Points to Remember

- *Cardiopulmonary cerebral assessment is the most effective method to identify problems in a ventilated child.*
- *If a child on ventilator suddenly deteriorates rule out displacement and obstruction of ET tube, pneumothorax and equipment failure.*
- *Patient ventilator asynchrony may be due to problems either in patient or ventilator.*
- *Always first attend to the patient and not the alarm.*

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## CLIPPINGS

### *How Good Is an Oral Provocation Challenge to Confirm Amoxicillin Allergies in Children?*

An oral provocation challenge to confirm either an immediate or nonimmediate allergic reaction to amoxicillin was found to be safe and more accurate than skin testing.

Some children who develop a rash while taking amoxicillin are labeled as "allergic" to the antibiotic with no further evaluation. In an observational study, researchers offered a graded oral provocation test to all children referred to an allergy clinic in Montreal with suspected allergy to amoxicillin. Children were given 10% of the therapeutic dose of amoxicillin, observed for 20 minutes, then given 90% of the therapeutic dose and observed for at least 1 hour. Parents were instructed to report reactions that occurred the next week.

Of 818 participants (mean age, 1.7 years), 94% tolerated the provocation test and therefore were not allergic to amoxicillin. Of the others, 2% had immediate reactions (within 1 hour of the last dose) - all mild urticaria that resolved with antihistamines - and 4% had nonimmediate reactions (median of 12 hours after the last dose) - all mild maculopapular rash. Only 1 of the 17 children with immediate reactions tested positive on skin prick and intradermal testing 2 to 3 months later.

History of a rash lasting longer than 7 days and parental history of drug allergy were associated with nonimmediate reactions on the provocation test (adjusted odds ratios, 5 and 3, respectively); history of allergic reaction within 5 minutes was associated with immediate reactions (AOR, 10). During 3-year follow-up of children who tolerated the test, 55 received a subsequent full course of amoxicillin and 6 (11%) had nonimmediate reactions. All patients with reactions to amoxicillin tolerated cefixime.

*Louis M. Bell, Mill C, et al. How Good Is an Oral Provocation Challenge to Confirm Amoxicillin Allergies in Children? JAMA Pediatr 2016 Apr 4.*

## IAP - IJPP CME 2016

**ACUTE PANCREATITIS - MANAGEMENT****\*Sumathi B**

**Abstract:** *Acute pancreatitis is not an uncommon condition and should be considered as one of the differential diagnosis in children and adolescents with acute abdominal pain. Severe acute pancreatitis may be life threatening; early diagnosis and appropriate treatment help to reduce disease related morbidity and mortality. A thorough clinical examination, biochemical tests and imaging studies aid in diagnosis. Supportive measures include adequate fluid replacement, pain relief and nutritional care. Early enteral nutrition is likely to reduce infection related complications. Acute recurrent pancreatitis needs investigations to rule out structural, metabolic and genetic causes.*

**Keywords:** *Acute pancreatitis, Children, Acute abdominal pain.*

Acute pancreatitis (AP) is characterized by the presence of inflammation of the pancreatic parenchyma resulting in interstitial edema, infiltration with inflammatory cells, variable degrees of cellular apoptosis, necrosis and hemorrhage that may result in organ failure or fibrosis. On most occasions, it is a one-time attack with recovery but some may progress to acute recurrent pancreatitis or chronic pancreatitis.<sup>1</sup>

According to the Atlanta criteria and the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) definition, a diagnosis of AP is made if 2 of the following 3 are present.<sup>2-5</sup>

(a) Clinical symptoms which include abdominal pain, nausea, vomiting, or back pain, (b) Elevated serum levels of pancreatic amylase and/or lipase three times the upper limit of normal and (c) Radiographic evidence of AP including pancreatic edema on ultrasound (US) or computed tomography (CT).

Acute recurrent pancreatitis (ARP) is defined as at least two distinct episodes of pancreatitis with complete resolution of pain with more than a month of pain-free interval between the diagnoses of AP or complete normalization of serum pancreatic enzyme levels before the subsequent episode of AP is diagnosed, along with complete resolution of pain symptoms, irrespective of specific time interval between AP episodes.<sup>2</sup>

Two studies, one from Pittsburg children's hospital, USA and another from Royal Children's Hospital, Melbourne, Australia have revealed an incidence of 13.2 cases per 100,000 children per year (about 1 in 7500/year) and 3.6 cases in 100,000/year, (about 1 in 28,000/year) respectively, while a study from Chennai has shown that AP accounted for 48 (0.06 %) of the 80,157 admissions over eight years [6-7 cases/year] in children.<sup>6-8</sup> Table I shows causes of acute pancreatitis.<sup>1,9</sup>

**Pathophysiology<sup>10</sup>**

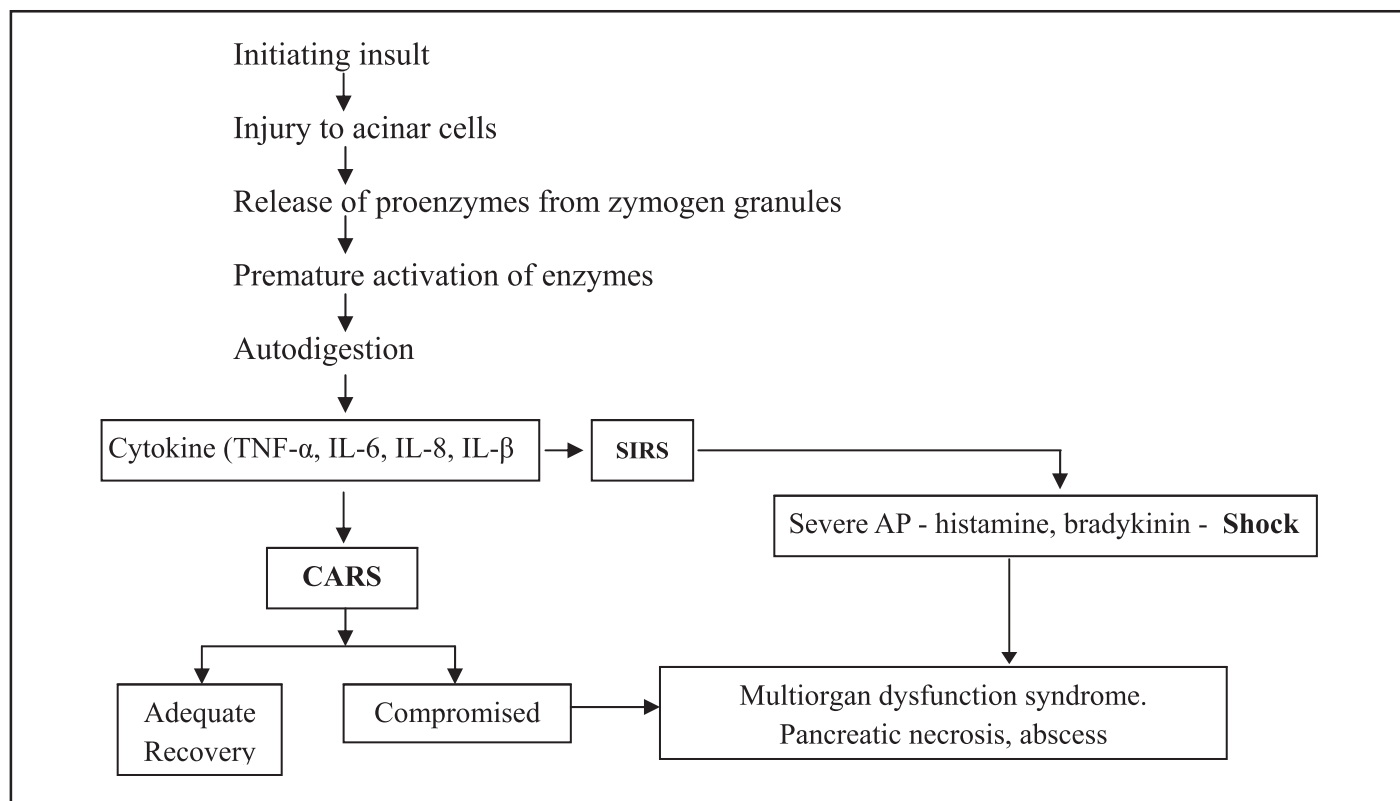
The pathophysiology of AP remains obscure and whatever be the cause, inflammation appears to be the result of a common pathway. Generation of aberrant non-physiological calcium signals within the pancreatic acinar cells occur as an initial event and is followed by the premature activation of intra-acinar pancreatic proenzymes, or zymogens, within the acinar cells. Activated zymogens, in particular the protease trypsin, mediate pancreatic acinar cell injury, with production of cytokines such as tumor necrosis factor- $\alpha$  (TNF  $\alpha$ ), responsible for acute inflammatory response and also the varying degrees of extra pancreatic inflammation. Pancreatic ischemia secondary to the ensuing inflammation may cause pancreatitis. Several protective mechanisms within the pancreas limit the development of pancreatitis and these include compartmentalization of pancreatic enzymes, endogenous trypsin inhibitors such as SPINK1 and auto-degradation of trypsin. In severe pancreatitis, vasoactive substances like histamine and bradykinin are released resulting in hypovolemia and shock. Biological defence response includes production of cytokine antagonists called compensatory anti-inflammatory response syndrome (CARS). In compromised CARS, this compensatory mechanism inhibits new cytokine production with increased

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**Table I. Acute pancreatitis - Causes**

Category	Conditions
Biliary tract	Common bile duct stone, biliary ascariasis, stricture
Drugs	L-asparaginase, steroids, sodium valproate
Trauma - Abdomen	Blunt injury abdomen, road traffic accidents, cycle bar injury
Anatomical malformation	Choledochal cyst, pancreatic divisum, abnormal pancreatic bile duct junction
Metabolic	Hypertriglyceridemia, hypercalcemia
Infections	Mumps, HIV, coxsackie B, mycoplasma infection, hepatitis A & B, salmonella, gram negative infections, leptospirosis.
Idiopathic	
Genetic mutations	Cationic trypsinogen (PRSS1), serine protease inhibitor Kazal type 1 (SPINK1), cystic fibrosis transmembrane regulator (CFTR), chymotrypsin C (CTRC), calcium-sensing receptor (CASR) genes
Systemic	Systemic lupus erythematosus (SLE), hemolytic uremic syndrome
Malignancy (rare)	Lymphoma, solid papillary tumour
Nutritional	Malnutrition, vitamin A and D deficiency

**Fig.1. Pathogenesis of pancreatitis**

(SIRS-Systemic inflammatory response syndrome, CARS- compensatory anti-inflammatory response syndrome, MOF-multi organ failure)

susceptibility to infection, endotoxemia mediated tissue injury and remote organ failure. Fig.1 shows the pathogenesis of pancreatitis.

### Clinical features

The symptoms and signs are variable based on the severity. A detailed history including abdominal pain, blunt abdominal injury (cycle handle bar), drug intake, viral prodromal illness, fever, jaundice, and family history is to be recorded. Abdominal pain is often localized to upper abdomen which is deep, boring and penetrating in nature, aggravated by food with nocturnal awakening. In older children, stooping forward while walking is well observed. Young infants present with non specific symptoms like poor feeding, vomiting, lethargy and incessant cry. The clinical signs include fever, tachycardia, hypotension, icterus, abdominal guarding, rebound tenderness and decreased bowel sounds. Table II shows the classification of AP based on severity. The following clinical features were observed in children with acute pancreatitis in descending order of frequency as abdominal pain (80-95%), vomiting (40-80%) and abdominal distension (30%).<sup>8</sup> Presence of abdominal pain, fever, jaundice, high coloured urine and pale stools indicate biliary cause for pancreatitis.

### Assessment of severity

To select the appropriate initial treatment and predict the prognosis, rapid and precise assessment of severity is necessary. The clinical assessment of severity is based on the presence of abdominal distension, absence of bowel sounds, tachycardia, hypotension and cutaneous bleeds. If all these are present, it points to a severe form of illness. There is no validated scoring system to predict severity in children. Ranson criteria,<sup>11</sup> the modified Glasgow scale,<sup>12</sup> and the Apache II index<sup>13</sup> that are used to predict severity of adult AP have limitations when applied to pediatrics.<sup>14,15</sup> A single retrospective study in pediatric patients found

**Table II. Classification of AP based on the severity**

Classification	Features
Mild AP	No organ failure, no local/systemic complications
Moderately severe AP	Organ failure that resolves within 48 hours and/or local or systemic complications, without persistent organ failure
Severe AP	Single or multiple persistent organ failure for >48 hours

elevated lipase more than seven times the upper limit of normal within the first 24 hours had 85% sensitivity and 54% specificity for predicting severe AP.<sup>16</sup> In 2002, the first scoring system to predict the severity of childhood acute pancreatitis was introduced by De Banto, et al., Recently, a new severity assessment pediatric Japanese (JPN) scoring system (Box.1) is found to be useful for Asian children.<sup>15</sup>

Recently, CT severity index is found to be superior to a clinical scoring system to identify acute pancreatitis in children at risk to develop serious complications.<sup>17</sup>

### Diagnosis

Diagnosis is made by history, clinical findings, lab investigations, imaging studies. Genetic studies is usually reserved for acute recurrent pancreatitis.

### Lab investigations

Literature has shown that serum lipase has a sensitivity and specificity of 96.6% and 99.4%, respectively, whereas serum amylase had a sensitivity and specificity of 78.6% and 99.1%, respectively. Serum amylase has a shorter half-life, rises earlier than serum lipase, generally within hours of pancreatic injury,<sup>18</sup> returns to normal by 3-5 days. In about 20% of cases and in hypertriglyceridemia amylase may be normal.<sup>19,20</sup> Other investigations include calcium, triglycerides, transaminases, bilirubin, white blood cell count, blood urea nitrogen and serum albumin.<sup>21</sup> An increase in bilirubin, amino transferases, alkaline phosphatase and gamma glutamyl transpeptidase (GGTP) is indicative of biliary pancreatitis. An elevated creatinine and thrombocytopenia points to hemolytic uremic syndrome. During the recovery phase, fasting lipid profile and plasma calcium should be estimated to exclude metabolic cause.

### Imaging

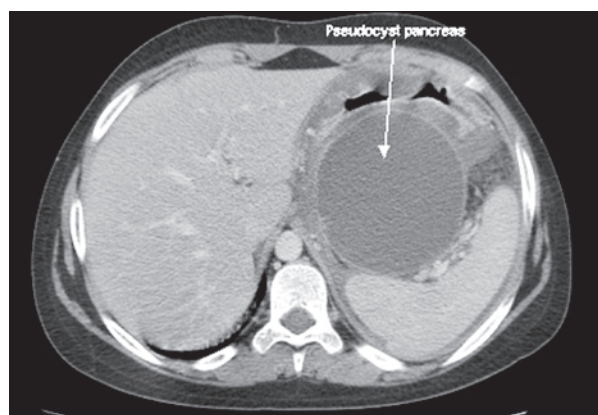
There is no specific X-ray finding in acute pancreatitis. The findings vary from normal to mild ileus, presence of sentinel loop, colon cut off sign, retroperitoneal gas and rarely calcified gall stones. Presence of pancreatic calcification is suggestive of underlying chronic pancreatitis presenting as an acute episode. Chest X-ray may be normal or reveal pleural effusion or findings suggestive of ARDS.

USG abdomen is a useful tool and aid in clinical diagnosis of AP with 70% sensitivity as against >90% sensitivity with CT abdomen. It helps to identify etiologies like biliary sludge, common bile duct calculi, ascariasis and choledochal cyst.<sup>22</sup> Abdominal CT is the second most common imaging modality used to diagnose and identify etiologies and complications of pancreatitis (Fig.2).<sup>18</sup>

**Box 1. Pediatric JPN scores<sup>§</sup>**

1. Base excess  $\leq -3$  mEq or shock (systolic blood pressure cutoffs according to the age group)
2.  $\text{PaO}_2 \leq 60$  mmHg (room air) or respiratory failure
3. Blood urea nitrogen  $\geq 40$  mg/dL [or creatinine (Cr)  $\geq 2.0$  mg/dL] or oliguria ( $< 0.5$  mL/kg per hour)
4. Lactate dehydrogenase  $\geq 2 \times$  the value of the upper limits
5. Platelet count  $\leq 1 \times 10^5/\text{mm}^3$
6. Calcium  $\leq 7.5$  mg/dL
7. C-reactive protein  $\geq 15$  mg/dL
8. Number of positive measures in pediatric systemic inflammatory response syndrome (SIRS) score  $\geq 3$
9. Age  $< 7$  years old or/and weight  $< 23$  kg

<sup>§</sup>Presence of any three of the above criteria indicates severe pancreatitis



**Fig.2. CT abdomen - Pseudocyst of pancreas**

Magnetic resonance cholangiopancreatography (MRCP) is seldom required for first attack of AP but is especially needed in the evaluation of pancreaticobiliary abnormalities such as intrahepatic and pancreatic ductal abnormalities, common bile duct abnormalities, choledocholithiasis, strictures, pancreatic divisum, long common channel and pancreatic and biliary tumors and<sup>23</sup> when recurrence occur. The added advantages are lack of ionizing radiation, high-quality multiplanar images of the pancreatic and biliary ductal systems (Fig.3) and is slowly replacing diagnostic endoscopic retrograde cholangiopancreatography (ERCP).<sup>24</sup>

Endoscopic USG (EUS) is yet another imaging study that can be considered in AP when no other cause is identified by other modalities.<sup>25</sup> EUS guided pseudocyst drainage can be done where facilities are available.

**Genetic mutation studies<sup>10</sup>**

These are required in those children with acute recurrent pancreatitis with no identifiable structural defects or metabolic cause. The most common genes involved in

**Box 2. Acute recurrent pancreatitis evaluation**

General Examination - Obesity, offending drugs

Level 1 - Investigations - LFT, lipid profile, serum Ca, USG abdomen.

Level 2 - IgG subclass, MRCP, ERCP, EUS

Level 3 - Genetic studies

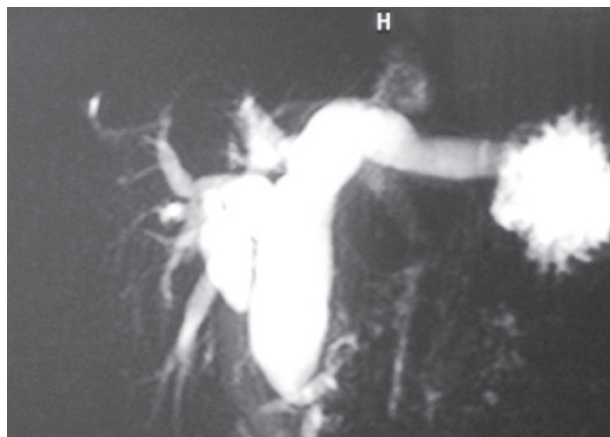
pancreatitis are cationic trypsinogen (PRSS1), serine protease inhibitor Kazal type 1 (SPINK1), cystic fibrosis transmembrane regulator (CFTR), chymotrypsin C (CTRC) and calcium-sensing receptor (CASR) genes. Acute recurrent pancreatitis (ARP) in a child needs evaluation as outlined in Box 2.

**Management**

Supportive care irrespective of etiology is the mainstay of therapy and includes hydration, analgesia and nutritional care. In children with severe AP, ICU care is necessary.

**Intravenous fluid management**

Fluid resuscitation is an integral part of management.<sup>26-27</sup> Recent randomized controlled trial in adults with AP has shown that lactated Ringer's solution is better than normal saline by reducing the systemic inflammatory response syndrome presumably secondary to the greater pH-buffering capacity.<sup>28</sup> There is supportive evidence for early, aggressive fluid resuscitation.<sup>29,30</sup> "Early resuscitation" has been defined as receiving greater than one-third of the total 72-hour intravenous fluid volume within the first 24 hours of presenting to the emergency department.<sup>29</sup>



**Fig.3. MRCP - Choledochal cyst**

### **Pain management**

Alleviating pain is an important step, but requires a balance between adequate control and over sedation, though there is no single superior drug. Tramadol can be used at 1 mg/kg/dose up to four times a day, diluted in saline solution with minimum infusion duration of 20 minutes. Narcotic sparing drugs like intravenous acetaminophen and ketorolac that are used in post operative pain control need study in children with AP.<sup>31</sup> Morphine (0.05mg/kg Q 2-4 hourly) and IV fentanyl (0.5-1µg/kg/Q 1-2 hourly) can be used. Other pain control measures like celiac and thoracic epidural analgesia that are used in adults have not been studied in children with AP.

### **Nutrition**

AP is a hypermetabolic, hyperdynamic state and the magnitude of the systemic inflammatory response generated creates a highly catabolic state of organic stress. Total parenteral nutrition (TPN) impairs humoral and cellular immune responses, increases the magnitude of pro inflammatory response, the bacterial translocation, thereby increasing infection related complications. Early introduction of enteral nutrition prevents mucosal atrophy, maintains the integrity of the intestinal mucosa and the associated lymphoid tissue, the normal intestinal bacterial flora, limits the translocation of bacteria to the portal and systemic circulation and the consequent sepsis.<sup>32,33</sup> There are no published studies on the optimal timing, and mode of nutrition in pediatric pancreatitis. Oral feeding is ideal. If unable to take orally, feeding can be given via nasogastric or nasoenteric tubes. Early introduction of enteral feeds within 48 hours after diagnosis is recommended if child's condition and intestinal transit permit. Progression of the diet must be slower, based on tolerance.<sup>34,35</sup> TPN is reserved for those who are intolerant of enteral nutrition. Literature has

shown there is not much of difference in outcomes between polymeric and elemental formula usage. There is no supporting evidence for immune enhanced nutrients or probiotics.

### **Drugs**

Octreotide is useful in ductal disruption and fluid collections. Prophylactic use of antibiotics is not recommended. In those children with organised pancreatic necrosis and infected pseudocyst, antibiotics with good tissue distribution are useful.<sup>10</sup>

### **Endoscopic retrograde cholangiopancreatography (ERCP)**

ERCP has a therapeutic role in gallstone pancreatitis for relief of obstructive stones or sludge.<sup>36</sup> According to the American Gastroenterology Association recommendations, urgent ERCP (within 24 hours) should be performed in gallstone pancreatitis with cholangitis and early ERCP (within 72 hours) should be performed in patients who present with a high suspicion of a persistent common bile duct stone.<sup>37</sup> Other uses of ERCP include stent placement and also to define pancreatic ductal disruption.

### **Surgery**

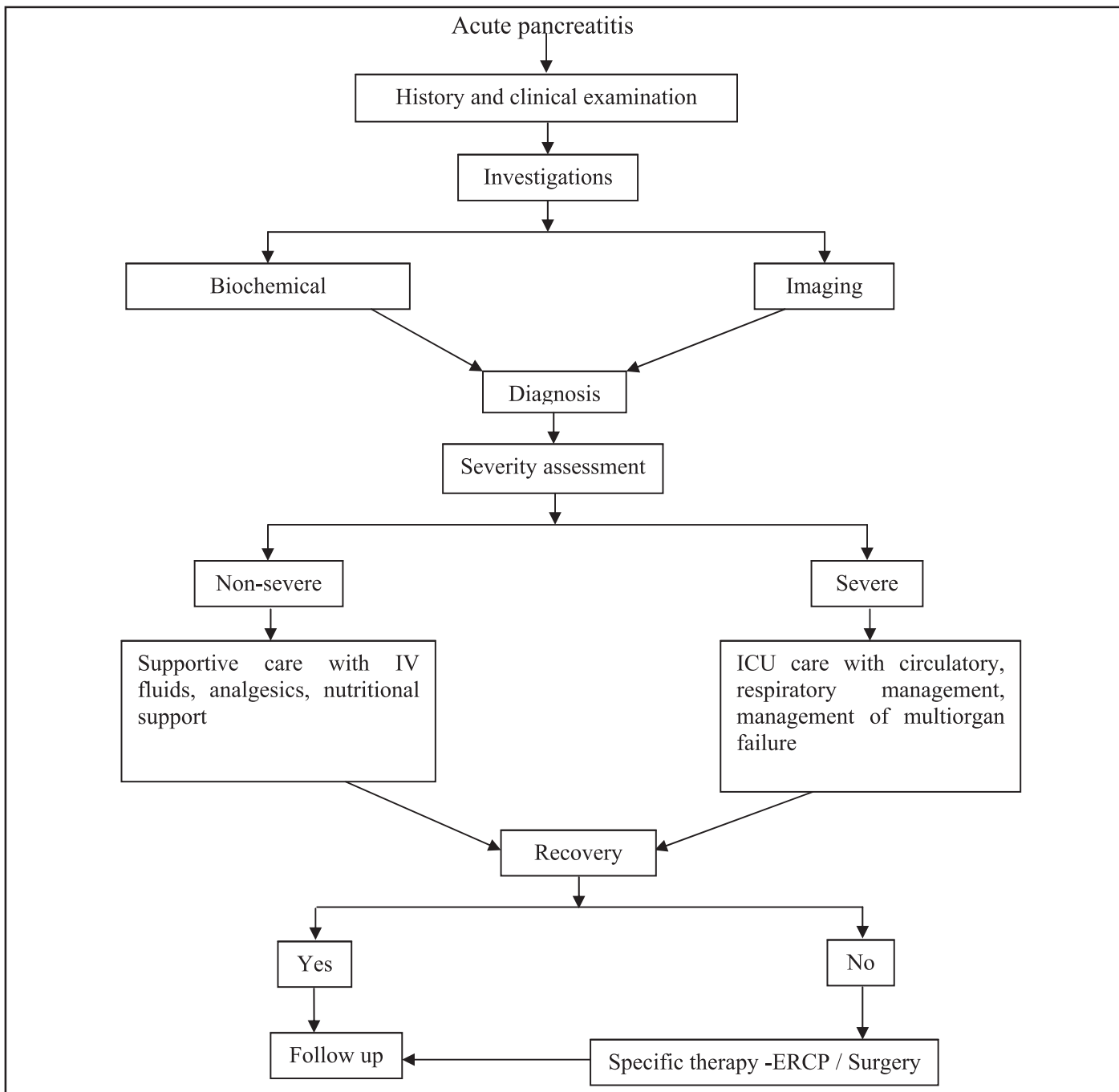
Gallstone pancreatitis usually needs to be managed by cholecystectomy or an ERCP before cholecystectomy.<sup>38,39</sup> Other role for surgery include necrosectomy and failed interventional procedures. Choledochal cyst needs surgical excision.

An approach to acute pancreatitis is shown in Fig.4.

### **Complications**

These can be divided into early and late onset. Early-onset complications primarily include multi-organ dysfunction or shock and late-onset complications are mainly pancreatic necrosis and pseudocyst formation.<sup>40</sup> Pseudocyst is a homogenous collection of amylase rich pancreatic fluid that lacks an epithelial lining, and can be complicated by infection, intracystic hemorrhage or rupture leading to pancreatic ascites. Walled-off necrosis (WON) is a collection of necrotic debris within a fluid filled cavity lined by fibrous tissue. Recurrent gastrointestinal bleed due to pseudoaneurysm is a rare complication. Recurrence of pancreatitis is known to occur in about 15% to 35% of children and this is seen in patients with biliary anomalies, metabolic disorders, particularly hypertriglyceridemia, idiopathic and hereditary pancreatitis.<sup>41</sup> Mortality of AP in children can go up to 11%.<sup>5</sup>





**Fig.4. Approach to management of AP**

**Points to Remember**

- *The incidence of acute pancreatitis is increasing in children and has diverse etiology.*
- *Good history and physical examination are essential steps.*
- *Imaging plays an important role in the diagnosis, identification of complications and possibly predicts the course of the disease.*
- *Early diagnosis with appropriate management of hemodynamic status and early enteral nutrition is*

*essential to prevent morbidity and mortality.*

- *Acute recurrent pancreatitis needs further evaluation including MRCP, metabolic work up and rarely genetic mutation studies.*
- *ERCP has a role in biliary pancreatitis.*

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### CLIPPINGS

#### ***Invasive pneumococcal disease in children aged younger than 5 years in India: a surveillance study.***

Invasive pneumococcal disease continues to be a major cause of morbidity and mortality among children younger than 5 years of age in India. The aim was to provide nationally representative data for the pattern of disease due to *Streptococcus pneumoniae*, trends in the serotype of invasive pneumococci, and invasive pneumococci antimicrobial resistance patterns, in India.

In this prospective hospital-based and retrospective laboratory-based surveillance study, children aged younger than 5 years with suspected or proven invasive pneumococcal disease were prospectively enrolled from 18 hospitals or institutional centres and retrospectively included laboratory-confirmed pneumococcal isolates from ten sentinel laboratories (together representing 11 states in India). Eligibility criteria were fever higher than 38°C without localising symptoms, clinical presentation of suspected meningitis or pneumonia, and evidence of radiographic pneumonia. Blood and other normally sterile body fluids were cultured, reconfirmed and serotyped pneumococcal isolates, and established antimicrobial susceptibility using standard study protocols.

Between Jan 1, 2011, and June 30, 2015, 4377 patients were enrolled. Among 361 (8%) patients with culture-proven pneumococcal disease, all clinical data were known for 226 (63%); among these patients, 132 (58%) presented with pneumonia, 78 (35%) presented with meningitis, and 16 (7%) had other clinical conditions. 131 (3%) died overall and 29 (8%) patients with invasive pneumococcal disease died. Serotypes 14 (52 [14%] of 361), 1 (49 [14%]), 5 (37 [10%]), and 19F (33 [9%]) were the most common. Penicillin non-susceptibility occurred in isolates from 29 (8%) patients, co-trimoxazole resistance occurred in 239 (66%), erythromycin resistance occurred in 132 (37%), and chloramphenicol resistance occurred in 33 (9%). Multidrug resistance was found in 33 (9%) of 361 patients.

The proportion of positive blood cultures, number of isolates, geographical representation, and data generated over the 4.5 years of the study are representative of data for most of India. Continued surveillance is warranted as the decision to introduce protein conjugated vaccine in India is made.

***Manoharan A, Manchanda V, Balasubramanian S, Lalwani S, Modak M, Bai S, et al. Invasive pneumococcal disease in children aged younger than 5 years in India: a surveillance study. The Lancet Infectious Diseases 2016 Dec 10.***

## IAP - IJPP CME 2016

**RESEARCH AND PAPER WRITING FOR CLINICIANS****\*Sridevi A Naaraayan**

**Abstract:** *Clinical research forms the basis of updating science and is a clinician's prerogative. It starts with a research idea which has to be converted into a research question after a thorough literature search, followed by framing the objective. The objective forms the basis of choosing the study design and detailed methodology has to be worked out 'a priori'. Ethics committee approval and involvement of a biostatistician throughout the study, starting from the conception stage are essential components for performing research. On completion of the study, manuscript for original articles has to be prepared in Introduction, Methods, Results, and Discussion (IMRAD) format and other articles according to the instruction to the authors of the journal for publication. Systematic review and meta-analysis are considered highest in level of evidence; the understanding of these are essential to practice evidence based medicine. It is high time the clinicians of our country move forward from practicing evidence based medicine to creating evidence.*

**Keywords:** *Clinical research, Biostatistics, Systematic review, Meta-analysis.*

Oxford dictionary defines research as the systematic investigation into and study of materials and sources in order to establish facts and reach new conclusions.<sup>1</sup> Clinical research is nothing but methodical observation of patients and systematic analysis of the recorded data which helps us gain insight into health and diseases.

**Importance**

Medicine is an ever changing field. Management protocol of most of the diseases has changed drastically over years and is still continuing to change year after year. Further, textbooks are revised with newer editions

periodically. The reason behind these is accumulation of new evidence arising out of research. Thus ongoing research is essential for updating science.

Research on basic sciences is largely conducted by full time research scholars and by research organizations. In contrast, clinical research is best performed by a person, who has basic knowledge about the disease process/drugs, who is in constant touch with patients and is the end user, i.e., one who is going to apply these results on the patients. Thus, clinical research is a clinician's prerogative.

A study done by Peters et al in 2002 revealed that while people largely turned to government health sector for preventive services like immunization, private sector was sought more for curative services.<sup>2</sup> Thus private health sector comprising of hospitals as well as private clinics play a major role in addition to the government health sector in delivering health care in our country. Hence, clinical research assumes equal importance in academic institutions as well as office practice.

**Objectives**

Clinical research is done to study various aspects of disease like etiology, risk factors, burden of the disease, natural history and prognosis of a disease and to evaluate the usefulness of diagnostic and therapeutic modalities.<sup>3</sup>

**Steps**

The starting point of research is a "research idea" which may sometimes stem from a casual observation, experience or intuition. Then, the ideal way to get started is to do a thorough literature search on the topic of interest and identify the gaps in knowledge which should form the basis of research idea.<sup>4</sup> Since research is primarily done to contribute some new piece of information about disease, the ones which will have a significant impact like decreasing the burden of illness will be given more priority for funding and publishing. Study topics chosen should be relevant, interesting and feasible, besides having some amount of novelty.

The research idea has to be converted to a "research question" as the next step. A research question is nothing but a question which is going to be answered by your

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**Table I. Objectives of clinical research and their appropriate study design(s)**

Objective	Study design(s) used
To determine the disease burden	Descriptive cross sectional study(survey)
To determine causative/risk factors	Randomized controlled trial / Analytical cohort study/ Case control study/Analytical cross sectional study*
To determine natural history/prognosis of a disease	Descriptive cohort study
To evaluate a diagnostic test	Descriptive study
To evaluate therapeutic/preventive measures	Randomized controlled trial / other trials*

*\*in the order of preference*

research. The next step is framing the “objective”. An objective is a specific and measurable statement of what one wishes to do. After framing the objective, the next step will be to choose a study design appropriate to the objective (Table I).

After choosing the appropriate study design, the next step is to work on the methodological issues in detail. Characteristics of study population namely, the inclusion/exclusion criteria and the sample size have to be determined. Sample size is calculated based on the objective and the existing literature. Sample size calculation is ideally done with the help of a biostatistician who should be involved in the study at the conception stage and not after complete data collection. The methods used for making clinical observations or laboratory estimation should be of acceptable standard and on par with those used in previous studies. The outcome variable, i.e. the characteristic of interest should be decided ‘a priori’ (before starting the study) and has to be objective, rather than subjective. A complete ‘data collection form’ incorporating all the details to be collected has to be prepared. Information on proposed plan of statistical analysis must be obtained from the biostatistician.

Ethical considerations are next aspect of a study. Bioethics is study of principles that guide human conduct. The important component of ethics is ‘Respect for autonomy’; participation in research has to be intentional and informed.<sup>5</sup>Hence for all types of research including observational studies, patient information sheet which provides the participant/parent all the details about the research and a written informed consent / assent form are necessary. These have to be prepared in triplicate one each for the participant, the principal investigator and the institution. Similarly ethics committee (institutional review board) approval is mandatory for conducting a research as

well as for a research article to be published in most journals. Hence, clinicians must obtain approval from the ethics committee of their institution before commencing the study. In order to obtain ethics committee approval, a study proposal, which is a written document describing the research study has to be submitted. It consists of introduction/scientific background, review of literature, study justification, objectives and detailed methodology, including all the details mentioned above. Researchers outside an institution can submit their research proposals to an ethics committee near their place.

The study has to be commenced after obtaining ethics committee approval. The methodology described in the proposal has to be strictly adhered to while recruiting the patients and collecting the data. If due to any unavoidable reason there is a deviation from the approved protocol, proposal has to resubmitted with modifications and the reason(s) for the same and ethics committee approval has to be obtained for the modified protocol. The collected data has to be presented to the biostatistician for analysis and the results obtained from him/her.

### **Understanding biostatistics jargons**

While summarizing numerical data, both measures of central tendency and measures of dispersion are described. Commonly used measures of central tendency are mean, median and mode. Commonly used measures of dispersion are range, standard deviation, interquartile range (IQR) and percentile. While data following normal/Gaussian distribution are summarized as mean and standard deviation, skewed data/non Gaussian (the one which is not normally distributed) is summarized as median and IQR.<sup>6</sup>

While performing a study to determine the prevalence/natural history of a disease, the result is expressed in proportion/percentage. For example, one may conclude that

the prevalence of refractory errors in school going children is 18% or the mortality of AKI is 20%. But these values give the proportion in the sample studied and not the whole population. If the same study is repeated by another person using the same methodology in a different sample, the percentage will not be the same. Using the percentage obtained in the study, if we are able to derive a range/interval inside which the value will fall when the study is repeated many times it will be really useful. This interval is called the 'confidence limits'.<sup>7</sup> Commonly used confidence limits/interval is 95%, while 90% and 99% confidence intervals can also be used. 95% confidence interval is the range within which the value is expected to fall 95 out of 100 times when the study is repeated in different samples using the same method.

While performing a study to determine risk factors and compare two different treatments, hypothesis is framed after framing the research question. A hypothesis is nothing but the research question written in a statement format. For example if the research question is 'Is frequent junk food intake a risk factor for childhood obesity?' the hypothesis is 'Frequent junk food intake is a risk factor for childhood obesity'. Hypothesis is a postulate made to be proved or disproved. In order to prove the hypothesis, tests of hypothesis (certain statistical tests) are employed. The choice of test depends on the type of data, its distribution, sample size and the number of groups. When a difference is observed between two groups, (those who develop obesity in junk food group and those who develop obesity in non-junk food group) one needs to be sure whether this difference is real or has occurred by chance. This is indicated by the 'p' value which is nothing but the probability of the difference occurring by chance.<sup>8</sup> A 'p' value of 0.05 means the probability of the difference occurring by chance is 5%, which is reasonably low. In practice significance level of 'p' value is usually set at 0.05, though it can be set at other levels like 0.01 or 0.001. Since this 'p' value tells us how true our hypothesis is, it has to be calculated and reported only for the objective(s) which is/are based on the hypothesis and not for comparison of all the data collected which then becomes meaningless.

## **Paper writing**

The main purpose of identifying the gaps in knowledge and performing research is to make it known to the scientific community. Though this is commonly done by presenting in scientific forums, publication is the best option. Most standard journals accept manuscripts prepared in accordance with International Committee of Medical Journal Editors (ICMJE) recommendations. Introduction, Methods, Results and Discussion (IMRAD) format is

generally followed while drafting an original article.<sup>9</sup> Word count, font and size vary from journal to journal.

In a manuscript, the purpose of introduction is to introduce the topic and engage the reader. It should move from known to unknown and should end with the objective. Material and methods section should give detailed description of how the study was actually done to the extent that it provides enough information for the study to be replicated exactly by the reader. Ideally, it has to be the lengthiest section of the paper. It should include the following details - study design, setting and period, ethical considerations, study population-inclusion and exclusion criteria and sample size, maneuver (measurements made, in chronological order), definition of terminologies used, outcome assessment and statistical analysis.

The purpose of results section is to present the main data collected and its inference while the explanation/comparison is reserved for the discussion section. It should contain all end points listed in methods section in the same order. Results section should start with summarizing the descriptive data followed by the main results; sub group analysis, if any has to be presented at the end. Results can be presented as text, tables and figures. Duplication has to be avoided. Text is preferred for the main result, tables for too much data that is difficult to be expressed in words and figures for depicting relations. Results section should give a clear indication whether the results were statistically significant.

Purpose of discussion section is to discuss how results answer the research question and to compare and contrast the results with other studies in the field. It is the most difficult part of the manuscript. It should contain synopsis of findings, explanation and novelty of findings, comparison with other studies, for and against, with explanations, strengths and limitations, potential significance of findings and future research directions.

Abstract is a mini version of the entire paper. It is the most read part of the paper next to the title. It has to be a stand-alone text and not a supplement to the full manuscript. It can be structured or unstructured. It usually has a word limit that varies for different journals. Key words are used for indexing and cross indexing. It should reflect the purpose of the study and should ensure easy access on online search. It is ideal to use MeSH (Medical Subject Heading) terms as keywords in order to ensure visibility on PubMed search.

## **Secondary research**

Secondary research (also known as desk research)

involves the summary, collation and/or synthesis of existing research rather than primary research, in which data are collected from participants. Systematic reviews and meta-analysis are examples of secondary research.

**Systematic reviews**

Traditional narrative reviews discuss the literature available in books, published and electronic articles on a specific topic and give a concise up to date knowledge from a theoretical point of view. In contrast, systematic reviews, as the name implies, typically involve a detailed and comprehensive plan and search strategy derived a priori, with the goal of reducing bias by identifying, appraising and synthesizing all relevant studies on a particular topic.<sup>10</sup> The steps of conducting a systematic review are given in Box 1.<sup>11</sup>

**Box.1 Steps of systematic review**

Step 1: Framing questions for a review

Step 2: Identifying relevant work/Developing the search strategy

Step 3: Assessing the quality of studies

Step 4: Summarizing the evidence

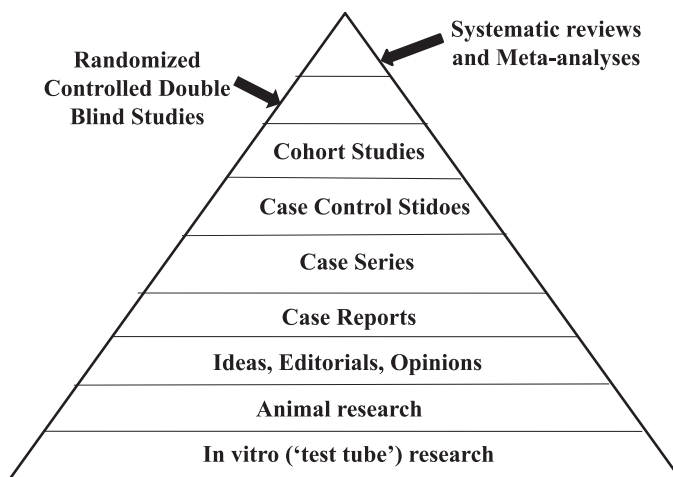
Step 5: Interpreting the findings

**Meta-analysis**

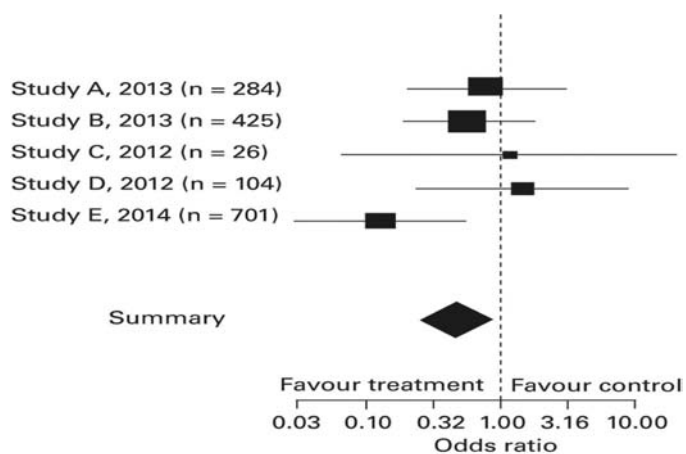
Meta-analysis is a statistical procedure that integrates the results of several independent yet similar studies and produces a more precise estimate of the effect of treatment or risk factor for disease, or other outcomes, than any individual study contributing to the pooled analysis.<sup>12</sup> In the hierarchy of evidence (Fig.1), where clinical evidence is ranked according to the strength of the freedom from various biases that beset medical research, meta-analyses are in the top.

Meta analyses are generally performed on randomized controlled trials and diagnostic tests rather than observational studies. The statistical output of meta-analysis is expressed as forest plot. A forest plot, also known as a blobbogram, is a graphical display of estimated results from a number of scientific studies addressing the same question, along with the overall results (Fig.2).

Systematic reviews and meta-analysis can be done together or independently. For example a systematic review can be done without performing a meta-analysis and a meta-analysis can be done out of systematic review. In such cases, they are not considered as the best level of



**Fig.1. Levels of evidence**



**Fig.2. Forest plot**

evidence. Only when a systematic review is followed by a meta-analysis, it is considered the highest level of evidence.

**Cochrane collaboration**

Cochrane collaboration is a widely recognized and respected international and not-for-profit organization that promotes supports and disseminates systematic reviews and meta-analyses on the efficacy of interventions in the health care field.<sup>13</sup>

**Critical appraisal**

It is a systematic process used to identify the strengths and weaknesses of a research article in order to assess the usefulness and validity of research findings. It consists of a checklist of questions which has to applied to the research article in order to evaluate its quality. Separate tool/checklist exists for different study designs which are listed in Table II.

**Table II. Critical appraisal tools**

Study design	Critical appraisal tool
Systematic review and meta-analysis	PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
Randomized controlled trial	CONSORT (CONsolidated Standards Of Reporting Trials)
Diagnostic test	STARD (STAndards for the Reporting of Diagnostic accuracy)
Observational studies	STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)
Case report / series	CARE (CAseREports)

To conclude, practicing evidence based medicine is undoubtedly the norm. At the same time, there is a need for clinicians of our country to create our own evidence instead of following the western evidence, which may not be suitable to our population in all circumstances. Thus research too is a prime responsibility of a clinician in addition to patient care.

### Points to Remember

- *Clinical research should be done by clinicians rather than research scholars/institutions to fill the gaps in knowledge about diseases.*
- *Study design is chosen on the basis of objective.*
- *Involvement of a biostatistician right from an early stage till manuscript revision and ethical clearance are mandatory for all types of study.*
- *Research articles are written in IMRAD format.*
- *Understanding systematic reviews and meta-analysis is essential to practice evidence based medicine.*

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### NEWS AND NOTES

**CIP2017 - 6<sup>th</sup> Global Congress for Consensus in Paediatrics and Child Health**  
**Colombo, Sri Lanka - 12<sup>th</sup> – 15<sup>th</sup> November, 2017**

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## IAP - IJPP CME 2016

**COMMON ISSUES IN OFFICE PRACTICE****\*Selvan R**

**Abstract:** *Pediatricians face a vast array of congenital as well as acquired conditions, in their day to day office practice. They have to identify the abnormal from the normal variation and treat them if needed. They need to arm themselves with evidence based recommendations for many childhood health issues. This article addresses some day to day childhood problems and their management.*

**Keywords:** *Common health issues, Office practice.*

**Plagiocephaly**

Plagiocephaly is a condition that affects the skull, making the back or side of a baby's head appears flattened. Positional plagiocephaly is much more common. It affects boys and girls equally, especially premature babies. Positional plagiocephaly is produced by pressure from the outside on part of the skull while in the womb or after delivery due to moulding. The main cause of pressure on the skull is the baby's sleeping position. A firm mattress on which the baby sleeps can be a contributory factor too. If a baby lies flat on back, any positional moulding is likely to be evenly spread across the back of the head. Some babies have a tendency to turn their heads in one side and that side will be affected.

There are no symptoms associated with plagiocephaly other than the flattened appearance of the back of the head - either evenly across the back or more on one side. It does not cause any pressure on the baby's brain. Development will not be affected by it in later life. Its importance is entirely cosmetic. Diagnosis is by physical examination.

Mild plagiocephaly does not require any active treatment and can improve over time. There are several ways of encouraging natural improvement in the shape of the head. The earlier the recognition of plagiocephaly and younger the child when it is recognised, the better the chances of improving it.

**Tummy time:** More the time babies spend on their tummies, the better chance of stopping the plagiocephaly from worsening and allowing natural correction to begin. It is advisable to play with them on their tummy as babies like to lift their heads and look around them.

**Supervised sleeping pattern:** The baby's sleeping position is adjusted so that everything exciting is in the direction that encourages them to turn their head the other way (e.g. altering the position of toys). A rolled up towel under the mattress also can help the child sleep with less pressure on the flattest part of the head.

**Physiotherapy:** For those children with difficulty turning the head in one direction, physiotherapy can be very helpful. The sooner the head turns as easily one way as the other, the sooner natural correction of head shape can begin.

**Helmets and bands:** The benefit of these remains controversial. They often have to be worn for several months and for 23 out of 24 hours preferably before six months of age.

Mild positional plagiocephaly may have corrected itself by the time a child is a year or so old. Severe cases improve with time, although a degree of flattening usually remains. Positional plagiocephaly does not affect child's development.<sup>1</sup>

**Kids and Technology - Tips for parents in the digital age**

In a world where children are "growing up digital," it's important to help them learn healthy concepts of digital use and citizenship. Parents play an important role in teaching these skills.

**Treat media as you would any other environment in your child's life:** The same parenting guidelines apply in both real and virtual environments. Limits should be set as kids need and expect them. It is essential to know their friends, both online and off, what platforms, software and apps are being used, where they are surfing on the web, and what they are doing online.

**Set limits and encourage playtime:** Tech use, like all other activities, should have reasonable limits. Unstructured and offline play stimulates creativity. Make unplugged playtime

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a daily priority, especially for very young children. Parents should join their children in unplugged play whenever possible.

Families who play together, learn together: Family participation is also great for media activities as it encourages social interactions, bonding, and learning. Playing a video game with kids demonstrates good sportsmanship and gaming etiquette. Parents can introduce and share their own life experiences and perspectives and guidance as they play with kids.

Be a good role model: Teach and model kindness and good manners online. And, because children are great mimics, parents should limit media use. In fact, parents will be available for and connected with the kids if interacting, hugging and playing with them rather than simply staring at a screen.

Know the value of face-to-face communication: Very young children learn best through two-way communication. Engaging in back-and-forth “talk time” is critical for language development. Conversations can be face-to-face or, if necessary, by video chat, with a traveling parent or far-away grandparent. Research has shown that it’s that “back-and-forth conversation” that improves language skills much more so than “passive” listening or one-way interaction with a screen.

Create tech-free zones: Keep family mealtimes and other family and social gatherings tech-free. Recharge devices overnight outside kids bedroom to help children avoid the temptation to use them when they should be sleeping. These changes encourage more family time, healthier eating habits, and better sleep, all critical for children’s wellness.

Don’t use technology as an emotional pacifier: Media can be very effective in keeping kids calm and quiet, but it should not be the only way they learn to calm down. Children need to be taught how to identify and handle strong emotions, come up with activities to manage boredom, or calm down through breathing, talking about ways to solve the problem, and finding other strategies for channeling emotions.

Apps for kids: More than 80,000 apps are labeled as educational, but little research has demonstrated their actual quality. Products pitched as “interactive” should require more than “pushing and swiping.” Look to organizations like Common Sense Media for reviews about age-appropriate apps, games and programs to guide you in making the best choices for your children.

Online for teen: Online relationships are part of typical adolescent development. Social media can support teens

as they explore and discover more about themselves and their place in the grown-up world. Just be sure your teen is behaving appropriately in both the real and online worlds. Many teens need to be reminded that a platform’s privacy settings do not make things actually “private” and that images, thoughts and behaviors teens share online will instantly become a part of their digital footprint indefinitely. Keep lines of communication open and let them know you’re there if they have questions or concerns.

Remember: Kids will make mistakes using media. Try to handle errors with empathy and turn a mistake into a teachable moment. But some indiscretions, such as texting, bullying, or posting self-harm images, may be a red flag that hints at trouble ahead. Parents should take a closer look at child’s behaviors and, if needed, enlist supportive professional help from a pediatrician.<sup>2</sup>

Media and digital devices are an integral part of the world today. The benefits of these devices, if used moderately and appropriately, can be great. But, research has shown that face-to-face time with family, friends, and teachers, plays a pivotal and even more important role in promoting children’s learning and healthy development. Keep the face-to-face up front, and don’t let it get lost behind a stream of media and tech.

## **Red reflex**

Red reflex testing is vital for early detection of vision and potentially life-threatening abnormalities such as cataracts, glaucoma, retinoblastoma, retinal abnormalities, systemic diseases with ocular manifestations and high refractive errors. The American Academy of Pediatrics currently recommends red reflex assessment as a component of the eye evaluation in the neonatal period and during all subsequent routine health supervision visits. The red reflex test uses transmission of light from an ophthalmoscope through all the normally transparent parts of a subject’s eye, including the tear film, cornea, aqueous humor, crystalline lens and vitreous humor. This light reflects off the ocular fundus, is transmitted back through the optical media and through the aperture of the ophthalmoscope, and is imaged in the eye of the examiner. Any factor that impedes or blocks this optical pathway will result in an abnormality of the red reflex. An abnormal red reflex can result from mucus or other foreign bodies in the tear film, corneal opacities, aqueous opacities, iris abnormalities affecting the pupillary aperture (pupil), cataracts, vitreous opacities, and retinal abnormalities including tumors or chorioretinal colobomata. Unequal or high refractive errors (need for glasses) and strabismus (eye misalignment) may also produce abnormalities or asymmetry of the red reflex.

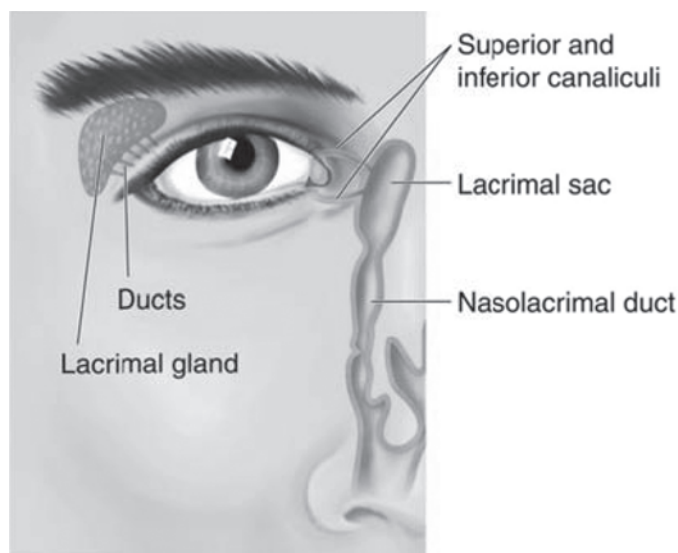
There may be significant variation in the red reflex in children from different racial or ethnic groups resulting from their differing levels of pigmentation of the ocular fundus.

The red reflex test is properly performed by holding a direct ophthalmoscope close to the examiner's eye with the ophthalmoscope lens power set at "0", in a darkened room, the ophthalmoscope light should then be projected onto both eyes of the child simultaneously from approximately 18 inches away. To be considered normal, a red reflex should emanate from both eyes and be symmetric in character. Dark spots in the red reflex, a markedly diminished reflex, the presence of a white reflex or asymmetry of the reflexes (Bruckner reflex) are all indications for referral to an ophthalmologist. All infants with positive family history of retinoblastoma, congenital, infantile or juvenile cataract, glaucoma or retinal abnormalities need referral.<sup>3</sup>

### **Congenital nasolacrimal duct obstruction**

The lower end of the nasolacrimal duct (Fig.1), in the region of the valve of Hasner, is the last portion of the lacrimal drainage system to canalize, with complete patency most commonly occurring soon after birth. Epiphora is seen in at least 20% of neonates, but spontaneous resolution occurs in over 95% within the first year. It has been suggested that early epiphora with resolution may be regarded as a normal variant.

**Treatment:** Massage of the lacrimal sac has been suggested as a means of rupturing a membranous obstruction by hydrostatic pressure. The index finger is initially placed over the common canaliculus to block reflux, and then rolled over the sac, massaging downwards (Fig.2).



**Fig.1. Nasolacrimal duct system**



**Fig.2. Lacrimal sac massage**

The likelihood of success and the optimal regimen is undetermined.<sup>4</sup>

### **Tongue tie**

Ankyloglossia (Tongue tie) is a congenital anomaly characterized by an abnormally short lingual frenulum which might restrict mobility of tongue and occurs in 4% of newborns. It varies from a mild form in which tongue is bound only by a thin mucus membrane, to a severe form in which tongue is completely fused to the floor of mouth. Many tongue tie are asymptomatic and cause no problem. Breastfeeding difficulties such as latching onto breast and poor weight gain can occur.<sup>5</sup>

The effect on speech is not clearly established. It does not prevent vocalization or delay onset of speech. Frenula that extend to the tip of the tongue and prevent the tongue to reach upper dental alveolus is significant as it may affect sibilant and lingual sounds.<sup>6</sup> Hence speech evaluation is a must. Mechanical problems include difficulty with oral hygiene, local discomfort, diastasis between lower incisors etc. Others include periodontal disease and psychosocial issues.

**Management:** If feeding difficulties are present a lactation consultant advice is sought. Speech pathologist opinion is obtained in a child with articulation problem and the decision on surgery (release of frenulum) is taken after discussing about potential risks and benefits with the parents.<sup>6</sup>

### **Topical mosquito repellent use**

It is likely that people have been using repellents to prevent insect bites since prehistory.<sup>7</sup> Topical insect repellents protect users from mosquito bites as people go about their daily activities and therefore offer a potential tool against outdoor-biting mosquitoes. Early repellents were largely plant derived and include some repellents that are still in use today, such as citronella (oil derived from plants

of the *Cymbopogon* genus), neem (leaves from *Azadirachta indica*) and lemon eucalyptus (*Eucalyptus maculata citriodon*). *N,N*-diethyl-m-toluamide (DEET), developed in the 1950s, is the most effective repellent available.<sup>8</sup> Topical insect repellents are very successful at reducing outdoor biting at any time of the day from a wide range of insects, but this protection is short-lived. For example, the current 'gold standard' repellent, DEET, applied topically will provide approximately six hours of protection under field conditions, although this is dependent on the formulation.<sup>9,10</sup>

Insect repellents work by masking human scent, or by using a scent which insects naturally avoid. For protection against mosquitos, recommendation equals DEET, picaridin, oil of lemon eucalyptus and IR 3535 for skin. 40% oil of lemon eucalyptus and Citronella oil, Nochi, are also effective. Permethrin, a contact insecticide, is recommended for clothing gear or bed net.

### Stammering management

There are many different treatments available for stammering, depending on a person's age and their individual circumstances.

Indirect therapy: In pre-school children, indirect therapy is the method commonly used.

This is often based on the 'demands and capacities model', which is based on the concept that children start to stammer when the demands on their speech are greater than what they are able to produce. These 'demands' are often made by the child, as they put pressure on themselves to communicate in a way they can't yet manage.

The goal of indirect therapy is to create an environment in which a child feels more relaxed and confident about their use of language. This involves: (i) speaking slowly and calmly to the child, (ii) developing a positive parent-child interaction, (iii) avoid criticising the child and (iv) making the family environment relaxing and calm.

Direct therapy: With school-age children, an speech and language therapist (SLT) may more likely choose direct therapy, (v) helping to improve fluency, (vi) helping the person understand more about stammering, (vii) sharing experiences with others who stammer, (viii) working on feelings associated with stammering, such as fear and anxiety, (ix) improving communication skills and (x) developing self-confidence and positive attitudes.

A widely used type of direct behavioural therapy in the treatment of young children is the Lidcombe Programme. This is designed to be carried out by the parents of the child under guidance from an SLT and is based on the principle of providing consistent feedback to the child about their speech in a friendly, non-judgemental and supportive way.<sup>11</sup>

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<b>GENERAL ARTICLE</b>
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## **MEDIA AND CHILDREN: CONCERN AND THE NEEDS**

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**Abstract:** *Media plays a major role in children's lives. Despite the increasing percentage of hours of media exposure among young children, there are few rules around their media use. Though there is a concern about potential harmful effects of media, important positive and prosocial effects should also be recognized. Years of research has shown that even youngest babies know more and learn more than we have thought. Reduction of TV viewing has been identified as a fitness objective. A healthy approach to child's media use should minimize potential health risks and foster appropriate and positive media use.*

**Keywords:** *Media, Consequences, Educational media, Recommendations, Children*

Children today live in a world where many of their experience is mediated by screen technologies.<sup>1</sup> From built-in DVD players to smart cell phones they have more access to electronic media than any of previous generation.<sup>2</sup> Media's presence is large and growing among children. Industry has also targeted 0 to 2 year age group (and their parents) as key consumers of electronic media. Educational DVDs/videos, television (TV) programs and even entire cable networks are geared for this age group.<sup>2</sup> However, scientific research and policy statements lag behind pace of digital innovations.<sup>3</sup> Though media are not the leading cause of any major health problem, the evidence is now clear that they can and do contribute substantially to many different risks and health problems.<sup>4</sup>

### **Definitions**

**Media:** The word media is defined as "one of the means or channels of general communication, information or

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entertainment in society". New media is a term used to define all that is related to the internet including cell phones, i-pads, social media and the interplay between technology, images and sound.<sup>4,5</sup>

**Foreground media:** Media which is intended for viewing of the child.<sup>2</sup>

**Background media:** Media exposure in children due to their presence in the room which is intended for adult viewing.<sup>2</sup>

**Media literacy:** Ability to use, understand and create media and communication in a variety of contexts.<sup>6</sup>

### **Incidence**

'Common sense media' survey showed an increase in mobile use among less than 8 years to 72%, while Pew research had revealed 75% of 13-17 year old have smartphones and 24% use phone constantly.<sup>3</sup> 90% of parents report that their children younger than 2 years watch some form of electronic media.<sup>2</sup> By 3 years, almost one third of children have a television in their bedroom.<sup>2</sup> More children are using portable devices to watch TV.<sup>6</sup> Mobile phone is used to play games, watch video, communicate, take pictures, for social media and music.<sup>3</sup> Electronic media use in different age group is shown in Table I.

### **Normal development**

Prenatal period and first year of life provides platform for remarkable growth and development and neural plasticity which is shaped by both positive and negative experience is at its peak. Total brain volume doubles in first year of life and increases by additional 15% over second year.<sup>7</sup>

Children develop their emotional and social capabilities through a complex process. To participate effectively in their culture, they must acquire the norms, rules and values that will enable them to form connections and function in families, peer groups and the broader society.<sup>6</sup> They learn about emotions and about relationships from parents, friends, teachers, and siblings. They also bring their own personalities, temperaments and cognitive abilities to each social situation.<sup>1</sup> It remains clear that infants learn language

**Table I. Summary of electronic media use by age:<sup>6</sup>**

	3-4yrs	5-7yrs	8-11yrs	12-15 yrs
Texting				25% (F>M),135hrs / week
Online			11.1hrs/wk	18.9 hrs/wk
Internet access			91%	96%
TV watching			14.8hrs/wk(97%)	15.5hrs/wk(95%)
TV in bedroom	23%	31%	49%	60%
Tablet	53%		73%	
Mobile			35%	77%
Social media profile				74%
Other device			43%	

better from native speaker than from screen.<sup>8</sup> Unstructured play time is critical to learn problem solving skills and fostering creativity.<sup>2</sup>

#### **Factors affecting media use includes the following<sup>1,2</sup>**

- i. Gender,
- ii. Race,
- iii. Home environment and media habits of parents,
- iv. Temperament,
- v. Realistic perception of the media,
- vi. Identification with characters and people on screen.
- vii. Age : One also needs to know that children older than 2 years and those younger than 2 years are at different levels of cognitive development and also process the information differently. TV is used by parents and caretakers as an educational and peacekeeping tool, for getting ready to work.

#### **Effect of media use**

Electronic media can have both positive and negative effects on child development.<sup>1</sup>

**Positive effects:** Prosocial media not only can help children and teen learn facts, but it can also help to teach social behaviour like sharing, co-operation, manners, empathy, racial and ethnic tolerance and whole range of interpersonal skills to increase child altruism.<sup>1,4</sup> Social media platforms are being used by many government agencies to reach out to citizens in seeking input for betterment of people.<sup>9</sup>

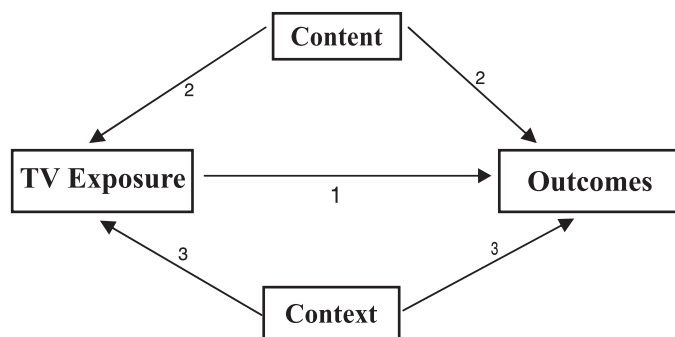
**Negative effects :** Media has both health and development consequences.<sup>2</sup> Screen based media has detrimental effects on academic performance, attitude towards school, reading, homework, long term educational outcome in adulthood.<sup>10</sup> It is negatively correlated with time spent interacting with family and friends.<sup>10</sup> Also it is risk factor for developing obesity as more time is spent without any physical activity.

Preschoolers are able to identify and differentiate basic emotions such as happiness, sadness, and fear experienced by television characters. Single exposure to media can alter the idea of child about emotion in real life. Children experience short term fright reaction to media. Viewing more than 6 hours/day has greater risk for trauma symptoms, insomnia, nightmares.<sup>1</sup> Electronic media influences children's perceptions of how dangerous the world is.<sup>1</sup>

Exposure to media violence is associated with a variety of physical and mental health problems for children and adolescents, including aggressive and violent behaviour, bullying, desensitization to violence, depression.<sup>11</sup> There is great concern about media violence, sex in media and substance use.<sup>4</sup> Expressive language delay is seen and short term effects on language skills are concerning.<sup>2</sup> Media influence on children depends on the content than the amount spent in front of screen. But not all children are influenced by media in the same way.<sup>1</sup>

#### **TV and its effects**

Consequences of television are focussed on exposure and series of outcomes as represented in Fig.1. Content (what children watch) and context (how they watch) is more important on outcome as represented by 2 and



**Fig.1. Conceptual model of television exposure and child outcomes.<sup>8</sup>**

3 respectively.<sup>8</sup> Children and adolescents are vulnerable to messages conveyed through TV influencing their behaviour and perception.<sup>12</sup>

**Obesity:** Television viewing in childhood and adolescence is associated with overweight, poor fitness, smoking and raised cholesterol in adulthood. Each hour increase in television viewing was associated with an additional 167 kcal/s.<sup>13</sup> With the increment of television viewing, the number of advertisements has also increased which has an influence on consumption of food leading to increased fast food intake, poor diet quality.<sup>13</sup>

**Language:** Early intense exposure to TV (defined as viewing 2 or more hours per day) before 12 months was associated with a six fold increase in the likelihood of language delay with no evidence that early exposure can enhance children's language development.<sup>8</sup>

**Cognitive development:** TV has negative impact during the first two years of life, but may have a positive impact for >2 years as very young children are very sensitive to sequential and linguistic comprehensibility of video.<sup>13</sup> Behavioural and sleep disorders - attention disorder, aggression, emotion and conduct problems, difficulty with peers, irregular sleep pattern, delayed onset of sleep, shortened sleep duration are seen.<sup>2,10,13</sup>

**Eye:** Viewing can cause eye strain. There is no evidence that it has a bad effect if viewed properly.<sup>14</sup> Ophthalmologists advice children to view television in a room where the television receiver is not the only source of light, sit at a distance of six feet from the screen, and at approximately eye level.<sup>14</sup>

## Second hand television

**Foreground versus background media:** Young children may not be paying close attention to a televised program that they cannot understand.<sup>2</sup> But it decreases infant vocabulary growth which is directly related to the amount

of time parents spend speaking to them.<sup>2</sup> Thus it directly distracts a child and indirectly takes away parent's attention from the child.<sup>2</sup> Background media might interfere with cognitive processing, memory, and reading comprehension.<sup>2</sup> As both foreground and background media have potentially negative effects with no known positive effects for children younger than 2 years, both media use is discouraged by the AAP.<sup>2</sup>

## Educational

Media industry executives claim that educational media programs are meant to be watched by both the parent and the child to facilitate social interactions and the learning process.<sup>2</sup> For young children, "e-books," have been linked to lower levels of story understanding and may hinder aspects of emergent literacy.<sup>10</sup> Audible television is associated with decreased parent-child interactions.<sup>2</sup> Though improved social skills, language skills, and even school readiness has been seen in children watching these programmes, the educational merit of media for children younger than 2 years remains unproven.<sup>2</sup> Media use does not promote language skills in <2 years group.<sup>2</sup> Although infant/toddler programming might be entertaining, it should not be marketed to be educational.<sup>2</sup> Optimal educational media opportunities begin after 2 years when media play a role in bridging learning achievement gap and certain high quality programs have educational benefits for children older than 2 years.<sup>2,3</sup>

Educational programmes taught more about emotions than science, history, culture.<sup>1</sup> Child-directed TV programming may only be beneficial when combined with a degree of parental involvement.<sup>15</sup> Parental joint media engagement is an important way to enhance impact of educational media. According to the American Academy of Pediatrics (AAP) there were significantly more potential negative effects of media than positive ones for infants and advised families to thoughtfully consider media use for infants.<sup>2</sup> It is the role of parents particularly (as television is watched mostly at home) to teach their young children about media literacy.<sup>13</sup>

## Recommendations

The AAP, The White House Task Force on childhood obesity, and others recommend discouraging any screen time for children under the age of two and less than two hours a day of educational programming for older children.<sup>10</sup>

The American Academy of Pediatrics recommends the pediatricians to enquire about recreational screen time the child or teenager consume daily and also if there is a TV set or an internet connected electronic device in the

child's or teenager's bedroom. Based on the responses age appropriate counselling for families at every well-child visit should be done.<sup>4</sup> Also they should become educated about critical media topics and examine their own media use habits.<sup>4</sup>

Pediatricians along with local chapters should work to challenge the following stake holders.

Entertainment industry : (i) To maximize prosocial content in media and minimize harmful effects and (ii) make movies smoke-free, without characters smoking or product placement.<sup>4</sup>

Government : (i) To issue strong regulations that would restrict the advertising of unhealthy food, alcohol in media<sup>4</sup> and (ii) establish ongoing funding for new media research.<sup>4</sup>

Manufacturers : To make socially responsible decision on youth marketing products.<sup>4</sup>

Parents : (i) Limit the amount of total entertainment screen time to <1 to 2 hours per day after 2 years of age<sup>4</sup>, (ii) Learning is best via two-way communication.<sup>3</sup> Discourage screen media exposure for children <2 years of age<sup>4</sup>, (iii) Keep the TV set and Internet connected electronic devices out of the child's bedroom<sup>4</sup>, (iv) Co-view with children and use this time for discussing important family values, be involved with them, kids need and expect limits which need to be set by parents<sup>3,4</sup>, (v) Parenting has not changed and role modelling is critical<sup>3</sup>, (vi) Have access and monitor content of media viewed by children<sup>2</sup>, (vii) Establish family use plan for all media and enforce mealtime and bedtime curfew for their use.<sup>4</sup>

Schools: (i) Educate school boards and school administrators about evidence based health risks associated with unsupervised, unlimited media access and use<sup>4</sup>, (ii) Educate ways to mitigate the risks such as violence prevention, sex education and drug use-prevention programs<sup>4</sup> and Encourage media education programme, implement curricula for school children.<sup>4</sup>

## Conclusion

There is growing evidence that from very early in infancy, babies are specifically and powerfully turned to information that comes to them from caregivers.<sup>7</sup> Parents can play an important and positive role in how electronic media affect young people's lives, they can not only enhance the benefits but also reduce the risks associated with children's media exposure.<sup>1</sup> To help mitigate negative health effect, pediatricians need to become familiar with consequences and begin providing anticipatory guidance to patients and families.<sup>12</sup>

## Points to Remember

- *Media is just another environment, can have both positive and negative effects.*
- *Media influence on children depends more on the type of content that children find attractive than on the sheer amount of time they spend in front of the screen.*
- *Time to be spent in creative play in < 2 years.*
- *Research shows benefits of reduced screen time.*
- *Media influences on children and teenagers should be recognized by pediatrician, schools, policymakers, product advertisers, and entertainment producers.*

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### CLIPPINGS

***Simplified antibiotic regimens for treatment of clinical severe infection in the outpatient setting when referral is not possible for young infants in Pakistan (Simplified Antibiotic Therapy Trial [SATT]): a randomised, open-label, equivalence trial.***

Parenteral antibiotic therapy for young infants (aged 0–59 days) with suspected sepsis is sometimes not available or feasible in countries with high neonatal mortality. Outpatient treatment could save lives in such settings. The study was aimed to assess the equivalence of two simplified antibiotic regimens, comprising fewer injections and oral rather than parenteral administration, compared with a reference treatment for young infants with clinical severe infection.

The Simplified Antibiotic Therapy Trial (SATT), a three-arm, randomised, open-label, equivalence trial in five communities was undertaken in Karachi, Pakistan. Young infants (aged 0–59 days) who either presented at a primary health-care clinic or were identified by a community health worker with signs of clinical severe infection were enrolled. Infants who were not critically ill and whose family refused admission were included and randomly assigned to either intramuscular procaine benzylpenicillin and gentamicin once a day for 7 days (reference); oral amoxicillin twice daily and intramuscular gentamicin once a day for 7 days; or intramuscular procaine benzylpenicillin and gentamicin once a day for 2 days followed by oral amoxicillin twice daily for 5 days. The primary outcome was treatment failure within 7 days of enrolment and the primary analysis was per protocol. The experimental treatments was judged as efficacious as the reference if the upper bound of the 95% CI for the difference in treatment failure was less than 5·0.

Between Jan 1, 2010, and Dec 26, 2013, 2780 infants were deemed eligible for the trial, of whom 2453 (88%) were enrolled. Because of inadequate clinical follow-up or treatment adherence, 2251 infants were included in the per-protocol analysis. 820 infants (747 per protocol) were assigned the reference treatment of procaine benzylpenicillin and gentamicin, 816 (751 per protocol) were allocated amoxicillin and gentamicin, and 817 (753 per protocol) were assigned procaine benzylpenicillin, gentamicin, and amoxicillin. Treatment failure within 7 days of enrolment was reported in 90 (12%) infants who received procaine benzylpenicillin and gentamicin (reference), 76 (10%) of those given amoxicillin and gentamicin (risk difference with reference “1·9, 95% CI “5·1 to 1·3), and 99 (13%) of those treated with procaine benzylpenicillin, gentamicin, and amoxicillin (risk difference with reference 1·1, “2·3 to 4·5).

Two simplified antibiotic regimens requiring fewer injections are equivalent to a reference treatment for young infants with signs of clinical severe infection but without signs of critical illness. The use of these simplified regimens has the potential to increase access to treatment for sick young infants who cannot be referred to hospital.

***Mir F, Nisar I, Tikmani SS, Baloch B, Shakoore S, Jehan F, et al. Simplified antibiotic regimens for treatment of clinical severe infection in the outpatient setting when referral is not possible for young infants in Pakistan (Simplified Antibiotic Therapy Trial [SATT]): a randomised, open-label, equivalence trial. The Lancet Global Health 2016 Dec 15.***

<b>GENERAL ARTICLE</b>
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## **ROLE OF CELIAC SCREENING IN WHEAT EATING POPULATION**

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**Abstract:** *Celiac disease (CD) is recognized to be a common health problem in North India where wheat is a staple diet. However, despite increasing popularity of wheat in South as well as in Eastern India, CD is not often reported mainly because of disparity in the prevalence of disease-causing gene (HLA-DQ2/8). We have relatively simple and sensitive serological tests for screening but the disease burden and unknown natural history of asymptomatic CD detected by screening, do not favor mass population screening. Hence, at this point of time celiac disease screening should be restricted to high risk population only.*

**Keywords:** *Celiac disease, Screening, Serology.*

Celiac disease (CD) is an immune mediated small intestinal disorder which is induced by the protein gluten (found in wheat, rye, and barley) in genetically predisposed individuals. In many parts of the world, largely in Europe and in North America, it is a common disorder affecting approximately 1% of the general population. Till 1960s people used to believe that celiac disease is the disease of the European countries and is uncommon in India. The first report of celiac disease in children came from Delhi in the form of a case series by Walia, et al in 1966.<sup>1</sup> Subsequently there were sporadic reports of celiac disease mainly in children from north India. Nevertheless, in 1990s due to increasing awareness and availability of screening tools like celiac serology, there were plethora of reports, albeit mainly from north India.<sup>2-6</sup> All these studies are hospital based and in symptomatic cases.

Recently there are two population-based studies both in children as well as in adults from Punjab and Delhi.<sup>7,8</sup> Both these studies have found it to be common in India as in the western population. Though celiac disease is found to be common in wheat-eating north Indian population, it is uncommon in south India.<sup>9</sup> Genetic predisposition for celiac disease (HLA-DQ2/8) is shown to be at least three times more common in north India than in south India (32% vs. 10%).<sup>10</sup> Currently the diagnosis of CD is based on active case finding and screening of high risk population.

### **What is the need for screening?**

There has long been a debate regarding routine mass screening for celiac disease. Currently there is no recommendation regarding routine screening. In order to decide whether mass screening for CD should be implemented, principles of early disease detection by screening as led by Wilson and Jugner (Box 1) should be taken into account.<sup>11</sup>

<h4><b>Box 1. Wilson and Jugner criteria for screening</b></h4>
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| <ol style="list-style-type: none"> <li>1. The disease should be an important public health problem.</li> <li>2. There should be a recognizable latent or early symptomatic stage.</li> <li>3. There should be a suitable test for diagnosis which is acceptable to the general population.</li> <li>4. Diagnostic criteria well established.</li> <li>5. Natural history should be well understood and there should be clear advantage of earlier treatment.</li> <li>6. There should be an acceptable treatment available.</li> <li>7. There should be consensus as whom to treat as case and when.</li> <li>8. Cost benefit should be favorable for screening.</li> </ol> |
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Any disorder needs to fulfill these criteria before it may be considered for mass screening. In this review, we try to analyze whether CD merits routine screening by fulfilling these criteria or not.

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## Is Celiac disease an important public health problem in India?

Initially CD was perceived to be uncommon in India but with increasing awareness and availability of the serological tests, CD has turned out to be quite common, especially in North India. Earlier reports suggested that CD is diagnosed with classical or typical clinical features such as chronic diarrhea, failure to thrive, anemia and short stature (Table I).<sup>3-6</sup> However, over the years the spectrum of celiac disease has changed from diarrhea predominant manifestations to non-diarrheal or atypical form of celiac disease. At present almost half of the cases are diagnosed as non-classical celiac disease such as refractory anemia, short stature, constipation, recurrent aphthous ulcers and enamel hypoplasia. In a prospectively conducted study in 200 children we have shown that 18 of 42 (43%) cases of celiac disease had atypical or non-diarrheal presentations.<sup>12</sup> A celiac disease patient may present for the first time as an adult with unexplained infertility, recurrent abortions, osteoporosis, ataxia, seizures, etc. All these hospital-based studies have suggested that celiac disease is common in North India.

To find out the community prevalence of CD, two studies were conducted in North India and results are summarized in Table II.<sup>7,8</sup> Both these studies, one in school

children and the other in both adults and children, suggested that the prevalence of CD in North India is as common as that found in Europe or North America. On the contrary CD is extremely uncommon in south India<sup>9</sup> mainly because of less prevalence of disease causing gene in pure south Indian communities compared to north Indian communities.<sup>10</sup>

It has been shown that untreated CD is significantly associated with poor health related quality of life which improves after treatment with gluten-free diet (GFD).<sup>13</sup> CD is also associated with increased all causes of mortality than in general population (Hazard ratio: 3.9, P<0.001).<sup>14</sup> Celiac disease has also been associated with increased risk of developing lymphoma especially T-cell type compared to general population (odds ratio 3.1 for primary site lymphoma).<sup>15</sup> Hence, CD is an important health problem in north India.

### Early asymptomatic period

Celiac disease does have an early asymptomatic phase and enteropathic changes have been shown to evolve over time. Some patients may have silent disease such as presence of histological changes without symptoms. Children with positive serology but normal biopsy findings are considered to have potential CD. Many of these

**Table I. Clinical features of celiac disease in India**

	Poddar, et al <sup>6</sup> (n=300)	Mohindra, et al <sup>3</sup> (n=42)	Patwari, et al <sup>4</sup> (n=65)	Pooni, et al <sup>5</sup> (n=71)
Mean age of onset & diagnosis (years)	3.2/6.7	2.4/8.3	3.5/8.7	3.0/8.9
Diarrhea (%)	84	88	94	86
Failure to thrive (%)	91	90	100	92
Anemia (%)	84	90	100	68
Short stature (%)	60	100	100	63

**Table II. Results of population survey in India**

Study	No. of people surveyed	Survey positive	Blood test (tTG) positive	Celiac disease prevalence
Sood et al (Ludhiana, Punjab) <sup>7</sup>	4,347 (3-17 years) school children	198 (on the basis of questionnaire)	21 of 198 (duodenal biopsy in 17)	1 in 300 (0.33%)
Makharia et al (NCR-Delhi) <sup>8</sup>	12,573 (children:3,643)	5,622 (on the basis of questionnaire)	Done in 2,167 of 5,622 (positive: 45, biopsy done in 39)	Adults: 0.85% Children: 1.41%

potential CD go on to develop enteropathy later in life. Kurppa et al followed up 17 children who were endomysial antibody (IgA-EMA) positive with normal histopathology, 8 children who continued gluten consumption developed villous atrophy in next 2 years while those who were started on GFD had improvement in symptoms and disappearance of EMA antibodies.<sup>16</sup>

### Availability of screening tests

Various serological tests available to detect CD include anti-tissue transglutaminase (tTG), anti-endomysial antibody (EMA), anti-deamidated gliadin peptide (DGP) and anti-gliadin antibody (used no more). Anti-DGP and tTG are measured by ELISA and EMA is measured by indirect immunofluorescence assay. Normally IgA antibodies against these antigens are measured and IgG fraction is important in cases with selective IgA deficiency which is 10 times more common in CD patients than in general population. Sensitivity of tTG and EMA was found to be up to 95%,<sup>17</sup> but anti-DGP has lower sensitivity to the tune of 88% (Table III). It is important to note that in younger children (<2 years of age) the IgA antibody titers against tTG and EMA may not be adequate enough to be detected by these tests and in such situation anti-DGP (both IgG and IgA type) is found to be useful.

### Difficulty in using diagnostic criteria in asymptomatic population

As per the modified European society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) diagnostic criteria<sup>18</sup>, characteristic small bowel histology (showing villous atrophy) and unequivocal clinical response to gluten free diet in weeks are enough to make a diagnosis of celiac disease. However, in developing countries like in India, where malnutrition and enteric infections (both of which can give rise to villous atrophy) are rampant, villous atrophy is not synonymous with celiac disease. We need to have an added criterion over and above ESPGHAN criteria and positive serology has been proposed along with villous

**Table III. Performance of various serological tests in Indian setting (n=300 cases and 210 controls)<sup>17</sup>**

Tests	Sensitivity	Specificity
IgA-EMA (anti endomysial)	95%	91%
IgA-tTG (tissue transglutaminase)	95%	97%
IgA-AGA (antigliadin)	88%	89%

atrophy and disappearance of serology along with subsidence of symptoms on GFD to make the diagnosis of CD definite.<sup>19</sup> In a recent modification of ESPGHAN criteria,<sup>20</sup> intestinal biopsy is not required to diagnose CD in the subset of symptomatic patients who have tTG >10 times upper limit of normal along with HLA-DQ2/8 and EMA positivity. However, for asymptomatic and high risk population, the screening investigation should be HLA-DQ2/8, if positive then serology (tTG) and if tTG is >3 times upper limit of normal then duodenal biopsy. There are no recommendations for mass screening. With the availability of sensitive serological tests, it has become easy to screen the population for seropositivity but for the confirmation of diagnosis we still need duodenal biopsy.

### Screening strategy

For mass screening we need to have a sensitive test for the disease and the serological tests especially tTG qualifies for that. However, this is still an invasive test (venipuncture is required) and may not be acceptable to the general population as a screening test. Ideal screening test should be sensitive, non-invasive so that it becomes easily acceptable to the community. We have to wait for such tests in CD.

### Natural history

Pathogenesis and natural history of manifested disease (both treated and untreated) is well known.<sup>13-15</sup> However, we do not have adequate information about the natural history of screening detected (asymptomatic or pre-symptomatic) celiac disease. Moreover, impact of GFD on this subset of cases is not well studied. Hence, at this point of time it is difficult to say whether screening is going to change the natural history of CD or not.

### Non-availability of agreed policy on whom to treat

Treatment of celiac disease is well defined but in asymptomatic patients, achieving compliance to GFD is a difficult proposition. The only and effective treatment is exclusion of gluten from the diet. But it is easier to prescribe than to follow. Compliance is bound to be poor in those who are asymptomatic and diagnosed by screening. Regarding potential CD, there is no consensus whether these patients should be treated or be kept on regular follow-up only.

### Cost effectiveness

Cost-effectiveness of mass screening has not well been evaluated so-far. As CD is a fairly common disorder with variable manifestations and long term health implications

and with relatively good serological tests available, routine screening may be considered especially in North India. However, we need studies to find out whether screening strategy is going to be cost-effective or not. Till that time, screening should be restricted to high risk population only (family members of a CD case, autoimmune disorders, Ig A deficiency, Down syndrome etc.)

## Conclusion

It is true that celiac disease is a common problem in North Indian wheat eating population (not in South or Eastern India where wheat has become more popular in recent time). However, the disease burden is not of that magnitude which merits population screening. Moreover, we do not have an acceptable tool to screen and the natural history of asymptomatic screening detected CD cases is not known. Hence, at this point of time celiac disease screening should be restricted to high risk population only.

## Points to Remember

- *Celiac disease is common in north India when compared to East and South Indian children.*
- *Celiac disease has an early asymptomatic phase.*
- *Screening tests available to diagnose CD are anti-tissue transglutaminase (tTG), anti-endomysial antibody (EMA) and anti-deamidated gliadin peptide (DGP).*
- *CD screening should be done in highrisk population.*

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<b>DRUG PROFILE</b>
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## PHARMACOTHERAPY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

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**Abstract:** *Attention deficit / hyperactivity disorder (ADHD) is the most common neurobehavioural disorder in childhood. It is the most common co-morbid condition associated with learning disorders in children. Early diagnosis and treatment help to improve the functioning of affected children in various domains. Though best results are reported with a combination of cognitive behavior therapy and pharmacotherapy, medication is the mainstay of therapy because non-pharmacological methods are labor intensive. Of the several agents that are effective in therapy, the two most studied and most used are methylphenidate and atomoxetine. The dosages, drug interactions, contraindications and monitoring of the various medications available for this condition are discussed.*

**Keywords:** *Attention deficit hyperactivity disorder, Methylphenidate, Atomoxetine*

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorder affecting school children with a prevalence of around 11% in India<sup>1</sup> similar to that reported from all over the world<sup>2</sup>. The affected children exhibit varying degrees of inappropriate functioning with inattention, hyperactivity and impulsivity. Delayed speech, language, social and adaptive development may be a pointer towards early diagnosis of ADHD. Early therapeutic intervention is associated with good prognosis. American Academy of pediatrics (AAP) committee on quality improvement, subcommittee on ADHD strongly supports the use of stimulant medications

for treating the core symptoms of children with ADHD and to a lesser degree, for improving functioning. Behavior therapy alone has only limited effect on symptoms or functioning of children with ADHD. Combining behavior therapy with medication seems to improve functioning and may decrease the amount of (stimulant) medication needed.<sup>3</sup> The various drugs available in India for the treatment of ADHD are discussed.

### Psychopharmacologic management of ADHD - General principles<sup>4</sup>

It is imperative that an accurate diagnosis of ADHD should be arrived before starting medications for this condition. A child below 6-7 years of age should not be started on medications unless the child is extremely accident prone. It needs to be started after careful evaluation by an expert in the field. Before starting medication the family (including parents, grandparents and kin involved in family decision making) and the child (especially if an adolescent) should be educated about the purpose and goals of the pharmacotherapy. They should understand that medications may not be curative always. The message that the medication, if found to be effective, may need to be administered for many years, must be emphasized. The clinician must await family and child approval for a trial medication period.

The medication should not be forced on any patient. Other management tools like psycho-education strategies and behavioral therapy should be instituted along with the pharmacologic treatment. Treatment should be started with a low dose and increased slowly till either symptoms improve, maximum dose is achieved or toxicity limits the increase in dose. Medication(s) that are helpful may change, as the child grows into adolescence and adulthood. Adolescents may require a medication dose higher than needed for adults because of increased renal clearance, lower body fat percentage, increased liver metabolism or idiosyncratic medication metabolism. It is important to share responsibility explicitly by clearly stating what issues the family, the school, the child and the physician must work on. Treatment of ADHD often needs to be continued into adolescence and may need to be continued into adulthood and the need for continuing the treatment should be reviewed at least annually.

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**Table I. ADHD medications**

CNS stimulants	Non-stimulants
Methylphenidate Pemoline Dextroamphetamine Modafinil	Norepinephrine reuptake inhibitor – atomoxetine  Antidepressants - Tricyclic antidepressants (imipramine, desipramine and nortriptyline and other antidepressants like bupropion)  Alpha-2 agonists - Clonidine and guanfacine

## Drugs

The medications useful in pharmacotherapy of ADHD are given in Table I. Of these agents, the two most studied and most used are methylphenidate and atomoxetine. Tricyclic antidepressants should not be prescribed concomitantly with a CNS stimulant. Newer drugs like lisdexamfetamine and dexamphetamine sulphate can be tried in children who do not respond to regular medications.<sup>5</sup>

## Comparison of the various drugs available

With the availability of new extended release products of most stimulants and new non-stimulant medications in other countries, many of which are not yet readily available in Indian market, the choice of drug to treat ADHD in children or adults with ADHD may not be clear. A recent review of evidence comparing efficacy of various drugs in children and adolescents indicated very few differences among the drugs in improving symptoms or in rate of adverse events. Atomoxetine was not found to be superior to some extended-release stimulant products and was found to have higher rates of vomiting and somnolence, similar rates of nausea and anorexia and lower rates of insomnia than stimulants. The review found no head to head comparisons to date with extended-release formulations of other nonstimulant drugs (clonidine, guanfacine). Also the effect of the immediate-release clonidine was similar to that of immediate-release methylphenidate.<sup>6</sup>

In children aged 6-12 years, there is no clear evidence of a difference in efficacy with sustained release (SR) formulations of methylphenidate, mixed amphetamine salts, dextroamphetamine or atomoxetine when compared to immediate release (IR) formulations of methylphenidate. A relative, but inconsistent, benefit was found on some outcome measures with the osmotic controlled release formulation of methylphenidate and mixed amphetamine salts compared with methylphenidate IR.<sup>7</sup>

Some studies suggest that though atomoxetine and methylphenidate are both useful in ADHD, the latter should be a first treatment option in most patients.<sup>8</sup>

## Methylphenidate

Methylphenidate is a 'schedule X' stimulant drug which is often considered as the drug of choice in the management of ADHD. It acts as a presynaptic dopaminergic agonist. Sixty to ninety percent of children with ADHD have been judged as positive drug responders. Stimulants like methylphenidate will affect normal children and adults in the same manner that they affect ADHD children. Behavioral or attention improvements with methylphenidate treatment therefore is not diagnostic of ADHD.<sup>9</sup>

**Pharmacokinetics:** Methylphenidate taken orally has a bioavailability of 11-52% with duration of peak action for 2-4 hours for instant release, 3-8 hours for sustained release and 8-12 hours for extended release (not available in India). The half-life of methylphenidate is 2-3 hours, depending on the individual. The peak plasma time is achieved at about 2 hours. Dextromethylphenidate is much more bioavailable than levomethylphenidate when administered orally and is primarily responsible for the psychoactivity of racemic methylphenidate. Contrary to the expectation, taking methylphenidate with a meal speeds up absorption. Methylphenidate is metabolized into ritalinic acid by carboxylesterase 1 (CES1A1). Dextromethylphenidate is selectively metabolized at a slower rate than levomethylphenidate.

**Dosage:** (i) 4-5 years: Start with 2.5mg twice daily, and increase by 2.5mg every week if necessary up to 1.4 mg/kg/day in 2-3 divided doses, (ii) 6-17 years: Start with 5mg 1-2 times a day and increase in steps of 5-10 mg daily if required, at weekly intervals. If necessary, it can be increased up to 60 mg/day in 2-3 divided doses.<sup>10</sup>

The drug should be taken preferably 30 to 45 minutes before breakfast and lunch, and a third dose may be added later between 2 and 4 PM, if necessary but not later than 6 pm as it may interfere with sleep. Immediate release tablets are available with duration of action around 4 hours and sustained release tablets with duration of action of around 8 hours are available.

**Contraindications:** Contraindications for the use of methylphenidate include psychosis and other agitated states, structural abnormalities of heart, cardiomyopathy, arrhythmias, pre-existing hypertension, tic disorder, seizure disorders, concomitant use of MAO inhibitors etc. Tic disorder is a relative contraindication where an anti-tic drug (risperidone, haloperidol, pimozide) may be combined.<sup>9</sup>

**Adverse effects:** Dose related increase in blood pressure, heart rate, respiration and body temperature, appetite suppression, increased alertness / sleep disturbances can occur. Weight loss and growth retardation on chronic methylphenidate pharmacotherapy also has been documented. Serious side effects include facial tics and muscle twitching. With higher than therapeutic doses, children may have excessive CNS stimulation, euphoria, nervousness, irritability and agitation, paranoid psychosis and occasional rebound hyperactivity after each dose.

**Overdose:** Acute overdose may result in agitation, tremor, hyperreflexia, twitching, hyperpyrexia, tachycardia, seizures, hallucinations, delirium, sweating, flushing, headache, cardiac arrhythmias and hypertension. There is no specific antidote available. In the presence of severe intoxication, a carefully titrated dose of a short-acting barbiturate can be given cautiously. Intensive care should be provided to maintain adequate circulation and gas exchange; external cooling procedures may be required for hyperpyrexia.

**Monitoring for side effects:** Most transient side effects may be reduced by starting with a low dose and gradually increasing to achieve maximum effect with reduced side effects. Nausea and vomiting often improves if medication is given with meals. In case of dizziness, try changing from short acting to long acting (SR) tablet. Headaches may be related to peak plasma levels or to drug withdrawal. Decreased appetite can be managed by offering feed when stimulant effect wears off (evening); by giving high calorie diet; drug holidays; or by changing the drug.<sup>9</sup>

**Side effects to look out for on follow-up:** Insomnia can occur, which usually diminishes with time or by adjusting the dosing or by changing to sustained release tablets. Occasionally rebound hyperactivity may occur. Anxiety, unmasking tics / Tourette syndrome can occur, where another drug can be tried except bupropion. Every patient should be carefully evaluated for cardiovascular side effects like increased blood pressure, tachycardia, palpitations etc. Other side effects include dysphoria, auditory hallucinations, paranoid psychosis, priapism and abdominal pain.<sup>9,10</sup>

**Monitoring children on long term methylphenidate:** BP and pulse may be recorded at each medication visit. Periodic growth monitoring including height and weight measurement to look for any signs of growth retardation is recommended. The need for periodic CBC with platelet count is not routinely advised.<sup>11</sup>

### **Dextroamphetamine sulphate**

It is also a CNS stimulant which can be tried in refractory ADHD, under supervision. It also has similar side effect profile as in any stimulants and cardiovascular complications need to be monitored. It is not available in India.

**Dosage:** 6-17 year: Start with 2.5 mg/dose 2-3 times daily, increase in steps of 5mg/day if required, dose to be increased at weekly intervals, increased up to 1mg/kg daily, maintenance dose to be given in 2-4 divided doses, up to 20mg daily or even up to 40mg daily in some children.<sup>10</sup>

### **Atomoxetine**

Atomoxetine is a non-stimulant drug licensed by FDA in November 2002 for the treatment of ADHD in children and adolescents.<sup>12,13</sup> It is a selective inhibitor of the presynaptic norepinephrine transporter in the central nervous system, thus increases both nor-epinephrine and dopamine levels, especially in the prefrontal cortex.

**Pharmacokinetics:** It is well absorbed after oral administration. It is metabolized through the cytochrome P450 2D6 (CYP 2D6) pathway and has a plasma half-life of approximately 4 hours in CYP 2D6 extensive metabolisers and 19 hours in CYP 2D6 poor metabolisers. The slow metabolisers have 10-fold higher area under curves (AUCs) and 5-fold higher plasma concentrations. The active metabolite, 4-hydroxyatomoxetine, is glucuronidated and excreted in the urine.<sup>14</sup>

**Advantages:** It is not a controlled substance hence, it does not require observance of the stringent prescribing rules necessary for 'schedule X' drugs such as methylphenidate and dextroamphetamine. It does not appear to be habit forming and is the drug of choice in adolescent ADHD associated with substance abuse disorder. It is also preferred to stimulant drugs in patients with psychiatric co-morbidities, contraindications to stimulants, or relatively heavy use of behavioral health care.<sup>13</sup>

**Dosage** 6-17 years : Start at 0.5mg/kg/day for 7 days and then dose is increased according to response to a target maintenance dose of 1.2mg/kg/day. It can be given once daily or rarely in 2 divided doses in the morning and late



**Table II. Comparison of methylphenidate and atomoxetine in ADHD**

<b>Methylphenidate</b>	<b>Atomoxetine</b>
Schedule X drug	Non-scheduled drug
Stimulant drug	Non-stimulant drug
Sleep disturbances	Does not cause or worsen insomnia but in the early phase can cause drowsiness
Onset of action - within 20 to 60 minutes of dose	Slower onset to action - thus, effects may not be seen until the end of the first week of treatment
Duration of action - 3 to 6 hours with immediate release tabs and 5-10 hrs with the long and very long acting tabs which are not available in India	Longer duration of action after a once-a-day dose with suggestions of symptom relief during the evening and early-morning hours
Substance abuse disorder - contraindicated	Drug of choice
Patients with psychiatric comorbidities and those requiring frequent use of behavioral care services - less preferred drug.	Preferred drug

afternoon. No additional benefits are seen in doses >1.2-mg/kg/day. Do not exceed 1.8mg/kg/day or 120mg/day. The drug has not been evaluated in children less than 6 years of age.<sup>15</sup>

**Contraindications:** Atomoxetine should be avoided in children with narrow angle glaucoma due to increased risk of mydriasis. Caution is needed in patients with hypertension, tachycardia, cardio-vascular or cerebrovascular disease. The drug needs to be used carefully in any condition that may predispose to hypotension. Dose should be reduced by 25% and 50%, respectively, for moderate and severe hepatic dysfunction. Dose changes are not necessary in patients with endstage renal disease.<sup>14</sup>

**Side effects:** Adverse effects of atomoxetine are similar to that of methylphenidate (appetite suppression, initial weight loss), with the exception that atomoxetine does not cause or worsen insomnia though, in the early phase of treatment it can cause drowsiness.<sup>16</sup> Atomoxetine treatment was associated with small but statistically significant increase in mean systolic pressure in adults and diastolic pressure in children and adolescents.<sup>17</sup> Blood pressure and pulse tended to increase early in therapy, then stabilized in change in QT interval and returned toward baseline after drug discontinuation. There was no significant difference as revealed by electrocardiogram between atomoxetine and placebo groups for all study populations. Discontinuation because of cardiovascular-related events did not occur in the child/adolescent group.

Other documented side effects mentioned are dizziness,

light-headedness, and fainting when you get up too quickly from a lying position.<sup>14</sup> To avoid this problem, children are advised to get out of bed slowly, resting their feet on the floor for a few minutes before standing up. Atomoxetine has caused severe liver damage in some patients.<sup>18</sup> Heartburn, vomiting, loss of appetite, constipation, dry mouth, excessive tiredness, difficulty falling asleep or staying asleep, headache, mood swings, irritability, weight loss, decreased sex drive or ability, difficulty urinating, painful menstrual periods, crying, fever, chills, muscle pain, sweating and hot flushes have also been reported. Rarely Reynaud's phenomenon and angle closure glaucoma can also occur.<sup>15</sup>

**Monitoring for side effects:** At follow up look for sedation, mydriasis (avoid therefore, in patients with narrow angle glaucoma), hepatotoxicity (baseline LFT and periodic monitoring), and suicidality (US FDA black box warning as for antidepressants).<sup>15</sup>

**Overdose:** The most common symptom of acute and chronic overdose is somnolence. Agitation, hyperactivity, abnormal behavior and gastro-intestinal symptoms may also occur. Sympathetic nervous system stimulation may occasionally manifest as mydriasis causing blurring of vision, tachycardia and dryness of mouth. No specific information is available on the treatment of overdose. These children and adolescents should be monitored carefully and given supportive care. Gastric emptying and repeated doses of activated charcoal may prevent systemic absorption. Since atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

## Clinical trials

Improvement may be seen in children as early as 1 week after the initiation of treatment though generally takes longer to have a full effect. The median time to response using 25% improvement in ADHD symptoms in pooled trials was 3.7 weeks. Data from these trials indicate that the probability of symptom improvement may continue to increase up to 52 weeks after treatment is initiated. It has been shown to be safe and effective in combination with stimulants<sup>19</sup> - this drug combination may benefit some, but not all, patients who have tried several ADHD medications without success.<sup>20</sup> It has also been studied systematically in subjects with ADHD and comorbid oppositional defiant disorder, anxiety, depression, and substance use disorders

Atomoxetine has demonstrated a statistically significant reduction in core ADHD symptoms and improvement in social and family functioning compared with the placebo group in randomized, placebo-controlled trials in children and adolescents 8 to 18 years of age.<sup>21,22</sup> Another study has demonstrated the positive impact of atomoxetine on health related quality of life (HRQL) in children with ADHD.<sup>23</sup> Atomoxetine was compared with methylphenidate in a randomized, open-label trial in children with ADHD during a 10-week study period.<sup>24</sup> Significant improvements were noticed in inattentive and hyperactive/impulsive symptom domains with both medications to a comparable extent.

Atomoxetine has a slower onset to action than do stimulants; thus, effects may not be seen until the end of the first week of treatment. However, it seems to have a longer duration of action after once-a-day dose with suggestions of symptom relief during the evening and early-morning hours. The treatment effect for core ADHD symptoms is similar when once-daily dosing is compared with twice-daily dosing; parent ratings document a sustained effect late in the day.<sup>25</sup>

Treatment with atomoxetine is preferred over stimulants in patients with psychiatric co-morbidities, contraindications to stimulants, or relatively heavy use of behavioral health care.<sup>26</sup> Further, it is the drug of choice in adolescent ADHD associated with substance abuse disorder because it has a lower risk of abuse potential.<sup>27</sup> In children and adolescents with ADHD and co-morbid tic disorders, atomoxetine does not exacerbate the tic symptoms. Rather, there was some evidence of reduction in tic severity.<sup>28</sup> It is also effective for the treatment of ADHD in patients with comorbid oppositional defiant behavior (ODD) though it did not significantly reduce the

severity of ODD symptoms.<sup>29</sup> The drug has not been evaluated in children less than 6 years of age. Comparison of methylphenidate vs atomoxetine in ADHD is given in Table II.<sup>30,31</sup>

## Antidepressants

Antidepressants that have been used in the treatment of ADHD include tricyclic antidepressants (Imipramine, desipramine, nortriptyline) and dopamine reuptake inhibitors (bupropion). These medications usually are reserved for children and adolescents who respond poorly to a trial of stimulants or atomoxetine, have unacceptable side effects, or have significant comorbid conditions.

Tricyclic antidepressants inhibit the reuptake of norepinephrine and serotonin. Tricyclic antidepressants have been associated with adverse cardiovascular events. Additional side effects that may limit the usefulness of tricyclic antidepressants include anticholinergic effects (e.g. dry mouth, constipation, urinary retention), fatigue and lowering of the seizure threshold.

Bupropion, an antidepressant that blocks the reuptake of norepinephrine and dopamine, has more stimulant properties than the tricyclic antidepressants. It is of modest efficacy in decreasing hyperactivity and aggressive behavior.<sup>32</sup> According to observational research, bupropion may increase cognitive functioning and reduce depression, aggression, and hyperactivity in adults with ADHD, but the drug is not indicated for these uses. Adverse effects include irritability, anorexia, insomnia, motor tics, and a decreased seizure threshold at higher doses.<sup>33</sup> Bupropion should not be used in patients with a history of tic disorders or seizures, and it should be used with caution in patients with anxiety.

## Alpha 2 adrenergic agonists

Clonidine and guanfacine, have been shown to improve symptoms of ADHD when used as monotherapy or in conjunction with stimulants or nonstimulant medications such as atomoxetine. They may be particularly useful as part of combination therapy in children with comorbidities such as Tourette syndrome or tic disorders.<sup>34</sup> The mechanism of action for these agents in ADHD may include both direct activity on presynaptic receptors in the prefrontal cortex and indirect modulation of input from the locus coeruleus to the prefrontal cortex via postsynaptic  $\alpha_2$  adrenergic receptors.

The US Food and Drug Administration (FDA) has approved clonidine hydrochloride, 0.1-mg and 0.2-mg, extended-release tablets alone or with stimulants for the treatment of attention-deficit/hyperactivity disorder

(ADHD) in pediatric patients aged 6 to 17 years.<sup>35</sup> Guanfacine is an FDA approved drug, less successful for hyperactivity but found to be effective in controlling impulsivity. Due to its role in treating motor and vocal tics, it is used especially in children with comorbid tic disorder. Guanfacine has a longer half-life and fewer side effects than clonidine.

### Clonidine

**Pharmacokinetics:** It is well absorbed after oral administration. Elimination half-life is 20-25 hours but this is increased to approximately 40 hours in severe renal impairment.

**Dosage:** Oral initially 0.05 mg/24 hr once daily increased by 0.05 mg once in 5-7 days up to max of 0.4 mg/kg/day in 3-4 divided doses. Clonidine extended release 3-10 mcg/kg/day twice daily to 4 times a day. Discontinuation of clonidine requires tapering to prevent a rebound increase in blood pressure.<sup>35</sup>

**Contraindications:** Porphyria; lowers blood pressure; can intensify depression; abrupt withdrawal can result in rebound hypertension; withdraw gradually.

**Side-Effects:** Drowsiness, restlessness at night, dry mouth. Bradycardia, QT lengthening and Hypotension, subjectively cold extremities, dizziness, depression, nausea.

### New drug - Lisdexamfetamine dimesylate

Lisdexamfetamine dimesylate provides a cost-effective treatment option for children and adolescents who are inadequate responders to methylphenidate.<sup>36</sup> It is a pro-drug of Dexamphetamine with almost similar side effect profile.

**Dosage:** 6-17 years : Start with 30mg orally once daily. Dose can be increased in steps of 20mg every week if required. Medicine is to be taken in the morning and discontinued if there is insufficient response after 1 month. Maximum dose is 70mg/day.<sup>37</sup>

### Points to Remember

- *ADHD is managed better by combining behavior therapy with drug therapy.*
- *Most of the children require long term maintenance therapy often extending to adulthood.*
- *Methylphenidate and Atomoxetine are the two first line agents preferred.*
- *It is advised to start at a lower dose and to slowly increase the dose to attain the optimal dose for each child.*

- *Longer acting forms are also available to improve the compliance.*
- *Periodic monitoring required when children are on these agents due to their side effect profile.*
- *Atomoxetine is the preferred drug in children with history of substance abuse and psychiatric disorders.*

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## DERMATOLOGY

### SUNSCREENS IN CHILDREN

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**\*\*Kopika Vasan**

**Abstract:** *Sunscreens have been in use over the past 70 years for photoprotection. This photoprotection is of particular importance in children and teenagers because there is increasing evidence to show that overexposure to ultraviolet (UV) rays in childhood is associated with increased risk of developing skin cancer later in life. Adequate sunscreen application and photoprotection are of increasing importance in recent years.*

**Keywords:** *Sunscreens, Organic and inorganic filters, Skin carcinoma, Application thickness, Photoprotection*

Sunscreens are mostly topical formulations that contain agents that filter and/or scatter ultraviolet radiation and provide photoprotection. Besides protection against sunburn, these agents prevent harmful effects of ultraviolet (UV) radiation.<sup>1</sup> Excessive sun exposure in the first 15 years of life has been shown to be a risk factor for melanoma.<sup>2</sup> Many children are at subsequent risk of skin cancer because of suboptimal sunscreen use and high rates of sunburning. Of late, various systemic agents in the form of antioxidants, vitamins and minerals, designated as systemic sunscreens have emerged.<sup>3</sup> A broad spectrum sunscreen is one which provides protection against both UV-A and UV-B.

#### Classification

According to US-Food and Drug Administration (US-FDA) sunscreen monograph, sunscreens are broadly classified as (a) organic filters (b) inorganic filters and (c) broad spectrum filters (Table I).<sup>3</sup>

#### Indications

The primary goals of sunscreen are to protect against UVB radiation and long-wavelength UVA radiation,

scavenge reactive oxygen species (ROS), activate cellular repair systems and also DNA repair. The common indications for sunscreen usage is given in Box 1.

Sunscreens decrease the incidence of non melanoma skin cancers and melanoma and solar elastosis in children.<sup>4,5</sup> The optimum sun protective factor (SPF) of a sunscreen in children should not be below 15 while above 30 is not necessary.

In Indian children the most common dermatological condition requiring sunprotection is photodermatoses like polymorphic light eruption (PLE). Apart from this conditions like actinic prurigo and phytophotodermatitis are also common among school going children in India and require adequate photoprotection.<sup>6</sup> It is not a compulsion that a sunscreen is must for all children but regular usage has proved to postpone photo ageing and solar elastosis.

#### Method of application

Correct method for sunscreen application is essential for effective photoprotection. It must be applied sufficiently with the right thickness. Application thickness has a significant effect on the amount of protection provided by a sunscreen. Adequate thickness is 2mg/cm<sup>2</sup> of the body surface area in children and adults. But the application thickness has often found to be inadequate in children due to self usage where the thickness was found to be around only 0.48mg/cm<sup>2</sup>.<sup>7</sup> A simple method used to determine application thickness has been to divide the amount (grams) of sunscreen used by the sunscreen treated skin area (cm<sup>2</sup>).

WHO recommends that sunscreen should be applied 20 minutes before sun exposure to allow the sunscreen time to form a protective film on the skin. Sunscreen should be re-applied every two hours at minimum, even on cloudy days and after swimming and heavy sweating. Children exhibit a greater ratio of skin surface area to body weight and their skin has been shown to be more permeable than that of an adult. So caution and direction by prescribing practitioner is necessary before its use in children. When moisturizers are to be used along with sunscreen it is better to use sunscreen before the application of moisturizers to prevent them from interfering with the efficacy of sunscreens in photoprotection.

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**Table I. Sunscreens - Classification and mechanism of action**

Category	Filters	Mechanism of action
Organic filters (chemical sunscreens)	(a) UVA filters Benzophenones, avobenzene, meradimate  (b) UVB filters Para amino benzoic acid (PABA), Cinnamates, Salicylates, Octocrylene, ensulisole	Absorb UV radiations
Inorganic filters (physical sunscreens)	Zinc oxide, titanium oxide, red petroleum	Reflect or scatter UV photons
Newer generation (Broad spectrum filters)	Ecamsule, silatriazole	

**Box 1. Sunscreens - Indications**

1. Sunburn
2. Freckling, discoloration
3. Photo-aging
4. Skin cancer
5. Phototoxic/ photo-allergic reactions
6. Photosensitivity diseases
  - Polymorphous light eruption (290-365 nm)
  - Solar urticaria (290-515 nm)
  - Chronic actinic dermatitis (290 nm-visible)
  - Persistent light reaction (290-400 nm)
  - Lupus erythematosus (290-330 nm)
  - Xerodermapigmentosum (290-340 nm)
  - Albinism
7. Photo-aggravated dermatoses
8. Post-inflammatory hyper-pigmentation (post-procedure)

It has been generally recommended that sunscreens with SPF of 15 and above are best for effective protection in children<sup>8</sup> against most of the commonly occurring photodermatoses since it blocks 93% of UV radiation.<sup>3</sup>

**Adverse effects**

Though not hazardous, use of sunscreen is not recommended in infants less than 6 months of age due to increased percutaneous absorption.<sup>9</sup> Contact dermatitis may occur due to constituents like aminobenzoic acid, oxybenzone also contact urticaria and worsening of acne. UVB is essential for 90% of vitamin D production, leading

to a concern that widespread use of sunscreens may lead to its deficiency. There are no evidences as such to prove it. It has been found that normal usage of sunscreens doesnot usually cause vitamin D insufficiency.<sup>10</sup>

**Conclusion**

Sunscreens are only one of the many forms of photoprotection. Sole dependence on sunscreen alone may have the drawback of overexposure to sun.<sup>4</sup> Therefore sun avoidance must be practiced in concordance with usage of sunscreens for best photoprotection especially in children where the usage of sunscreens is often inadequate. At present though sunscreens are not routinely prescribed for children in India it must be emphasized, as regular use of sunscreen in children have found to reduce the lifetime incidence of skin cancers.<sup>11</sup>

**Points to Remember**

- *Excessive sun exposure in the first 15 years of life has been shown to be a determinant risk factor for melanoma.*
- *Many children are at subsequent risk of skin cancer because of suboptimal sunscreen use and high rates of sunburns.*
- *Use of sunscreens in children must be emphasized.*

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### CLIPPINGS

#### ***Juice Is Best for Treating Mild Gastroenteritis with Minimal Dehydration.***

Oral rehydration with electrolyte maintenance solutions has become a mainstay in treating moderate to severe dehydration, but could less-expensive, better-tasting fluids such as diluted juice be just as effective in milder cases?

In a single-blind noninferiority trial, researchers randomized 647 children (aged 6"60 months) presenting to a Canadian pediatric emergency department with gastroenteritis and minimal dehydration to receive either 1) half-strength apple juice for initial hydration followed by fluids of the child's choice or 2) apple-flavored electrolyte maintenance solution. The primary outcome was treatment failure, defined as occurrence of any of the following within 7 days: intravenous rehydration, hospitalization, unscheduled visit to a physician, treating physician's request to cross over to other study arm, weight loss  $\geq 3\%$  or Clinical Dehydration Scale score  $\geq 5$  at follow-up.

Treatment failure was significantly lower in the juice/preferred fluids group (16.7% vs. 25.0%); the difference met the study's criteria for noninferiority and superiority. Significantly fewer children in the juice/preferred fluids group received intravenous rehydration at the index visit (0.9% vs. 6.8%) and within 7 days (2.5% vs. 9.0%). Juice/preferred fluids was most beneficial in children  $\geq 24$  months of age (treatment failure rate, 9.8% vs. 25.9%).

***John D. Cowden, Freedman SB, et al. Juice Is Best for Treating Mild Gastroenteritis with Minimal Dehydration. JAMA 2016 Apr 30.***

### NEWS AND NOTES

#### **Certificate Course in Pediatric Pulmonology and Flexible Bronchoscopy, Chennai**

**Date: 24<sup>th</sup> – 30<sup>th</sup> April, 2017**

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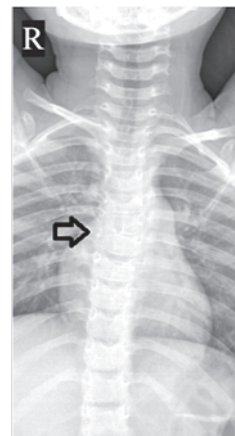
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**RADIOLOGY**

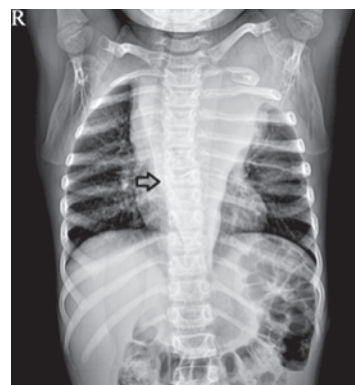
**OSTEOMYELITIS - 3**
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**\*\*Karthik C**
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We saw about pyogenic osteomyelitis in the previous issues. The disease is heralded by acute symptoms like fever, pain, swelling and inability to move the limb. On the contrary tuberculous infection is indolent and clinical symptoms and signs are mild though bone destruction is well established by the time of presentation. Spinal involvement is the commonest form of skeletal tuberculosis. The commonest site is the dorsal spine. The lumbar and cervical spine are more often affected in children. Infection is hematogenous. The bacilli lodge in the marrow and inflammation sets in with caseous necrosis, lysis of trabeculae and destruction of the cortex. The pus escapes from the bone through the destroyed periosteum, collects under the spinal ligaments and then penetrates the ligaments to track along fascial planes often presenting far from the original site of infection.

The initial site of infection in the vertebra most often is para-discal near the vertebral endplate. The inflammation extends to the disc which is destroyed and the disc space is narrowed (Fig.1). There is a mild reduction in height of the sixth dorsal vertebra due to destruction and collapse of the vertebral body. The space on either side of D6 is narrow. This is a hallmark of tuberculous infection. Fig.2 is the spine xray of a child with neuroblastoma which shows a large soft tissue shadow in the cervicothoracic region on the left. The sixth dorsal vertebra shows a reduction in height. However, the intervertebral spaces on either side are normal. In neoplasia the spaces are preserved. Though this is a working rule, there are reported instances of discovertebral disease in metastases and involvement of the vertebral body alone in tuberculous spondylitis.



**Fig.1. Spinal tuberculosis-narrow disc space (arrow)**



**Fig.2. Vertebral secondaries-normal disc space (arrow)**

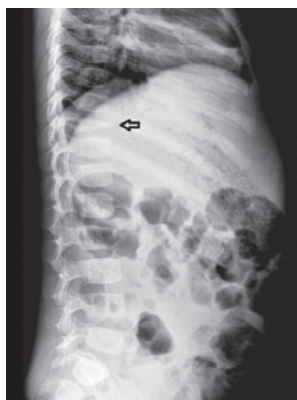
The involvement of the body alone is considered atypical presentation giving rise to problems of differentiation from neoplastic involvement. Another point to recall is that the absence of a pedicle used to be taken as a first sign of metastases. But it has been shown that the vertebral body was the commonest site of metastatic disease and involvement of the pedicle without affecting the vertebral body is very rare.

Fig.3 is that of a 3 year old girl with back pain. The X-ray shows flattened D10 vertebra. The disc space and the posterior arch are normal. There was no other lesion. All other investigations were normal and a diagnosis of Langerhans cell histiocytosis was made. Neural arch involvement is uncommon. Fig.4 and 5 show two vertebrae close to each other with narrow disc space giving a false impression of tuberculous discitis. This is a block vertebra.

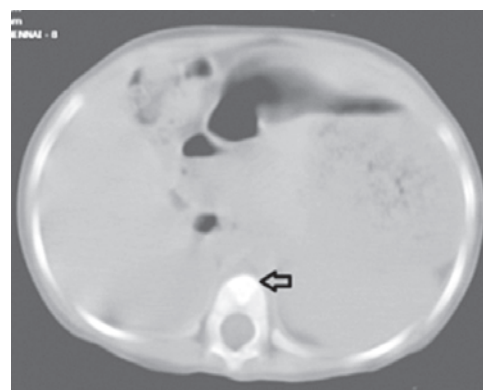
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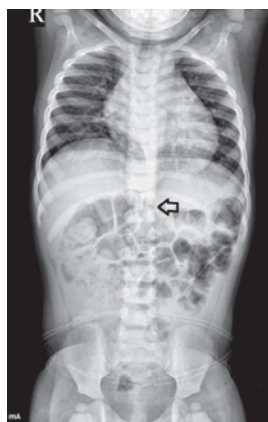




**Fig.3. Vertebra plana-Langerhans cell histiocytosis (arrow)**



**Fig.6. Block vertebra-CT (arrow)**



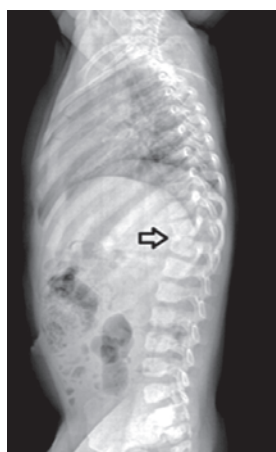
**Fig.4. Block vertebra AP view (arrow)**



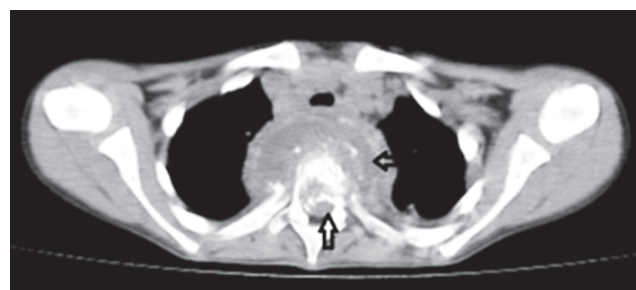
**Fig.7. Paraspinal cold abscess. Multiple sites of involvement (arrows)**

On careful scrutiny of Fig 5 one can see that the height of the block vertebra is more than the expected sum of two vertebrae. CT (Fig.6) confirms that both the vertebrae are fused.

is necessary for delineating the extension of pathology into the spinal canal. CT is the first and preferred modality for the spine as bone destruction is visualised very well early and clearly.



**Fig.5. Block vertebra lateral view (arrow)**

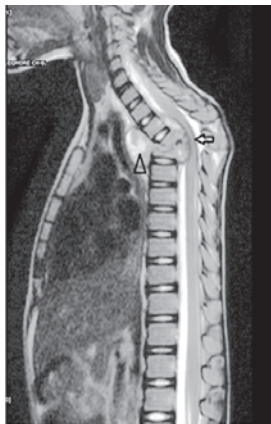


**Fig.8. Extension of tuberculous abscess into vertebral canal causing cord compression (Upward arrow points to cord)**

Fig.7 shows a large paravertebral abscess seen as fusiform soft tissue shadows on either side of the spine. The presence of abscesses and bony fragments are definitely in favour of tuberculosis. Cross sectional imaging

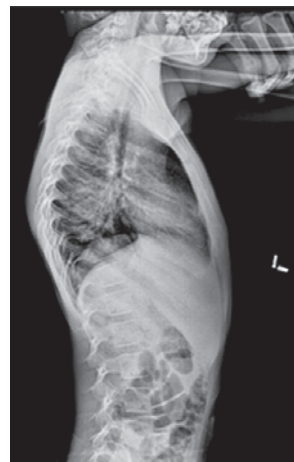
Fig.8 shows a destroyed vertebra, a large anterior and paravertebral cold abscess with bony fragments, both within the abscess and in the spinal extradural space. The cord is displaced posteriorly. On contrast injection granulation tissue

will enhance while the cold abscess will show an enhancing peripheral rim. MRI is better for disclosing the state of the cord. If the cord is mildly swollen with diffuse increased signal then it is edema which will resolve. Inhomogenous signal changes in the cord denotes poor prognosis.



**Fig.9. Subligamentous collections (arrow-head) with displacement of cord (arrow)**

Fig.9 shows complete destruction of a vertebra. There is an oval high signal abscess beneath the anterior spinal ligament. The abscess extends posteriorly bulging the posterior spinal ligament, displacing and compressing the cord posteriorly. The cord is stretched tight over the epidural abscess but does not show any altered intensity.



**Fig.10. Gibbus in dorsal spine**

Fig.7 also shows narrowing of D7-8, D9-10 and L2-3 disc (arrows). Multiple sites of involvement are common in tuberculosis and should be searched for. The pedicles and the posterior arch elements are rarely involved and are associated with more severe destruction of the vertebrae and therefore more severe kyphosis and deformity. Fig.10 shows a focal gibbus as a result of vertebral collapse due to spinal tuberculosis. With healing, the bones regain their density and sharpness of outline. Paravertebral cold abscesses reduce in size, but do not disappear completely.

### NEWS AND NOTES

#### 2<sup>nd</sup> PEDIATRIC GASTRO INTERVENTIONS – WORKSHOP

Department of Pediatrics, Mahatma Gandhi Medical College, Jaipur

Date : 2<sup>nd</sup> April, 2017

**Enquiries to:**

Dr. Natwar Parwal

Mob : 9610951425; Email : dr.nats@yahoo.com; www.mgumst.org

#### Department of Neonatology

Institute for Child Health Announces yearly conference on Advances in Neonatology

Date : April 8<sup>th</sup> to 11<sup>th</sup> 2017

**Enquiries to:**

Ms Renu Bisht

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<b>CASE STUDY</b>
-------------------

## **FETAL VALPROATE SYNDROME – BE AWARE!!**

\***Vindhiya K**  
\*\***Ratnakumari TL**  
\*\*\***Gautham G**  
\***Sana AMH**

**Abstract:** *Fetal valproate syndrome is a relatively uncommon congenital syndrome caused by teratogenic effects of fetal exposure to valproic acid. VPA crosses the placenta and presents at a higher concentration in the fetus than the mother. Exposure during first trimester is associated with increased risk of neural tube defects. We describe a male baby with fetal valproate syndrome who had intrauterine growth restriction, characteristic facial features, umbilical hernia, divarication of recti and generalized mild hypotonia.*

**Keywords:** *Fetal valproate syndrome, Facial features*

Dysmorphism in neonates can be due to various etiologies like genetic, metabolic, drugs or birth defects. It can be an isolated finding in an otherwise normal neonate. Antenatal exposure of drugs on growing fetus plays an important role on the baby evincing dysmorphic features. Anticonvulsant medication in pregnancy is a challenge for the physician to balance seizure control with its harmful effects on the growing fetus.

### **Case report**

A full term male baby first born to non-consanguineous parents by natural delivery was admitted to NICU for respiratory distress. On examination, baby had intrauterine growth restriction (IUGR) with a weight of 2.3kg and length of 45cm, both falling between 5<sup>th</sup> to 10<sup>th</sup> centile for

gestational age. Head circumference was 33cm (between 10<sup>th</sup> and 15<sup>th</sup> centile). Baby had characteristic facial features of fetal valproate syndrome (FVS) as evidenced by broad forehead with epicanthic fold, mongoloid slant, lower eyelid puffiness and forked brow medially (Fig.1). He also showed broad and depressed nasal bridge, upturned nose, long philtrum, thin upper lip, small mouth and low set ears.<sup>1</sup> There was generalized hypotonia with umbilical hernia and divarication of recti (Fig.2). Spine and cranium were normal. Cardiac examination was normal. Radiological evaluation of vertebral column was normal. Ultrasound abdomen showed bilateral pelviectasis and mild hydronephrosis. Ultrasound cranium was normal.

Mother had been taking sodium valproate 800mg/day for the epilepsy for the past 8 years which was later tapered to 200mg/day since the 5<sup>th</sup> month of pregnancy. With the typical facial features and maternal history of intake of sodium valproate during pregnancy, a diagnosis of FVS was made.

### **Discussion**

Fetal valproate syndrome (FVS) results from prenatal exposure to valproate. Valproic acid (VPA) is one of the most commonly used drug during pregnancy as an anti-epileptic but is teratogenic. Various factors contribute to the teratogenicity of VPA. The risk is highest with doses exceeding 1000mg/day and polytherapy regimen containing



**Fig.1. Typical facial features**

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**Fig.2.Umbilical hernia with divarication of recti**

VPA.<sup>2,3</sup> It affects the intracellular distribution of zinc thereby resulting in zinc deficiency which can be the possible cause of neural tube defects (NTD) but there is no definitive evidence as of now.<sup>4</sup>

Prenatal diagnosis includes estimation of maternal serum alpha-fetoprotein which is the screening test to assess for NTD. Periodic ultrasound is required to monitor the growth and to detect anatomical abnormality of the brain. Folic acid should be supplemented prior to conception and continued during pregnancy.<sup>5</sup> Pregnancy usually is uneventful. Baby should ideally be delivered in a tertiary care center. Birth asphyxia and withdrawal symptoms are the immediate post natal complications. Withdrawal symptoms are irritability, jitteriness, seizures and hypotonia which typically occur between 12 to 48 hours of life.

FVS is characterized by a distinctive facial appearance and cluster of major and minor anomalies. Major congenital malformation is neural tube defect which is the most common; others are congenital heart defects, oral clefts,

genital abnormalities and limb defects. Minor abnormalities like inguinal and umbilical hernia, supernumerary nipple, postaxial polydactyly, hypospadias and bifid ribs are also seen.<sup>6</sup> Fetal hydantoin syndrome is differentiated by flat, broad nasal bridge with short nose, hypertelorism strabismus, ptosis, wide mouth; malformed ears, pterygium colli and microcephaly. Affected infants often have cleft lip and palate. In contrast children with fetal alcohol syndrome have thin upper lip, smooth philtrum and small palpebral fissures.

Dysmorphism in neonates has to be thoroughly investigated by history and detailed clinical examination. Obstetricians and parents should be aware of the effects of certain drugs taken during antenatal period. Lasting neurological effect has to be assessed as the child grows.

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## NEWS AND NOTES

### International Developmental Pediatrics Association Congress

Mumbai, December 7-10, 2017

#### Enquiries to:

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<b>CASE STUDY</b>
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## UNILATERAL DUANE SYNDROME - A CASE REPORT

\***Ramakrishnan TCR**  
\*\***Saleem Akhtar**

**Abstract:** Duane syndrome is a strabismus syndrome characterized by congenital non progressive horizontal ophthalmoplegia involving abducent nerve. A case of unilateral Duane syndrome is described.

**Keywords:** Duane retraction syndrome, Strabismus, Abduction abnormality.

Duane syndrome (DS) or the Duane retraction syndrome (DRS) is a congenital form of strabismus characterized by limitation of horizontal eye movement and globe retraction with palpebral fissure narrowing during attempted adduction. It constitutes 1% to 5% of all cases of strabismus. It usually presents as an isolated unilateral condition and is rarely associated with systemic anomalies. We are presenting a 11 month child with isolated 6<sup>th</sup> nerve palsy (with globe retraction on adduction).

### Case report

A 11 month old boy presented to us with history of abnormal position of left eye at times since 6 months of age without history of fever or vomiting. The antenatal and perinatal history were normal. On examination, he had normal pupillary size and reaction but abduction deficit in the left eye along with globe retraction on attempted adduction without ptosis. Other cranial nerves and rest of the neurological examination did not reveal any deficit. His ophthalmological evaluation showed normal visual acuity and fundus without any abnormal head position. Position of eyes in primary gaze and adduction are shown in Fig.1 and 2. MRI of the brain was done which revealed absence of 6<sup>th</sup> nerve on the left side (Fig.3a & b).

### Discussion

Congenital lateral rectus palsy is rare and may be related to birth trauma or Duane syndrome (DS) unless

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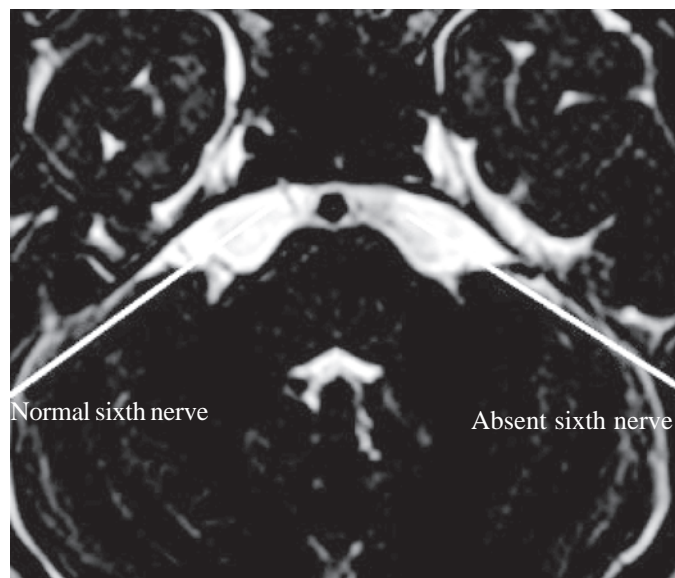
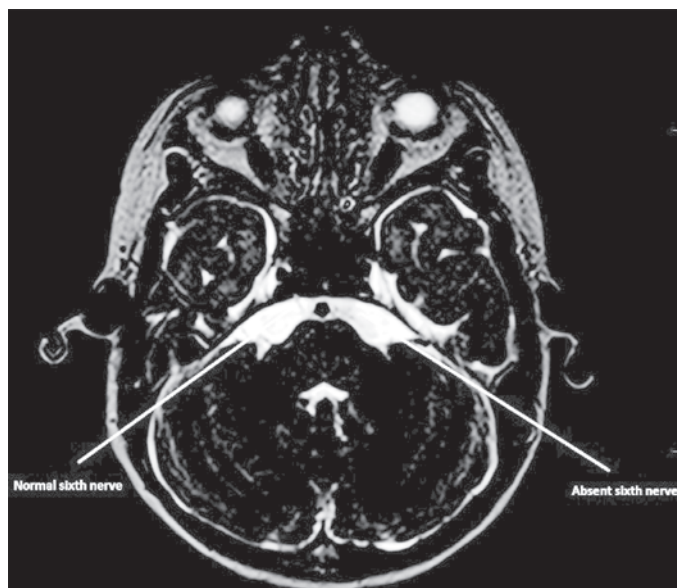
**Fig.1. Eyes in primary gaze**



**Fig.2. Eyes in adduction**

proved otherwise.<sup>1,2,3</sup> Duane syndrome is a congenital strabismus with a prevalence of 1/1000 in general population accounting for 1 to 5% of all strabismus cases. 70% cases are isolated and 30% are associated with other congenital anomalies. DS occurs due to faulty development of the abducent nerve by about the sixth week of pregnancy. Clinically the patient will present with limited abduction, less marked limitation of adduction of affected eye and poor convergence. Alexandrakiss and Saunder's found that in most cases the abducent nucleus and nerve are either absent or hypoplastic and the lateral rectus muscle is innervated by a branch of oculomotor nerve.<sup>4</sup> This view is supported by earlier work of Hotchkiss et al. who reported on autopsy finding of 2 patients, where in 6<sup>th</sup> cranial nerve nucleus and nerve were absent and lateral rectus muscle was innervated by inferior division of oculomotor nerve.<sup>5</sup> This misdirection of nerve fibers results in opposing muscles being innervated by the same nerve. Thus on attempted abduction, stimulation of lateral rectus via the oculomotor nerve will be accompanied by stimulation of opposing medial rectus via the same nerve.<sup>5</sup> The gene sal-like 4(SALL4) has been implicated as a cause.<sup>6</sup> It is more common in girls (60%) as compared to boys (40%). A French study reports this syndrome in 1.9% of strabismus patients with 53.5% of patients being female, 78% unilateral with left eye (71.9%) being affected more frequently.<sup>7</sup>

In 1974 based on electromyography studies, Huber classified DRS into 3 types; (a) Type 1 with a marked limitation of abduction, (b) Type 2 with a limitation of adduction and (c) Type 3 with limitation of both adduction



**Fig.3a & b. MRI - Constructive interference in steady state sequence**

and abduction.<sup>8</sup> Duane syndrome can occur with other syndromes like the Okhiro (Duane syndrome with hearing loss and arm malformation), the Wildervanck (Duane syndrome, Klippel-Feil anomaly, and deafness), Mobius (Congenital paresis of facial and abducens cranial nerves) and the Towns-Brocks (ear, limb, anal, renal and heart anomalies) syndromes. Differentials considered in this infant were Mobius syndrome and acquired Duane syndrome following trauma or infection both of which are unlikely.

Neuroimaging can serve as a useful diagnostic tool in children with isolated cranial nerve palsy. CISS sequence (constructive interference in steady state) is a gradient echo MRI used where routine MRI sequence is unable to provide desired anatomical information. CISS is used in the assessment of fine structures like cranial nerves, membranous labyrinth of internal ear or cerebellopontine angle lesion. In Sankara Nethralaya Abducens Palsy Study (SNAPS) study analyzing the diagnostic yield of imaging in 6<sup>th</sup> nerve palsy, 6 of the 104 cases of isolated 6<sup>th</sup> nerve palsy were attributed to congenital sixth nerve palsy (6%).<sup>9</sup>

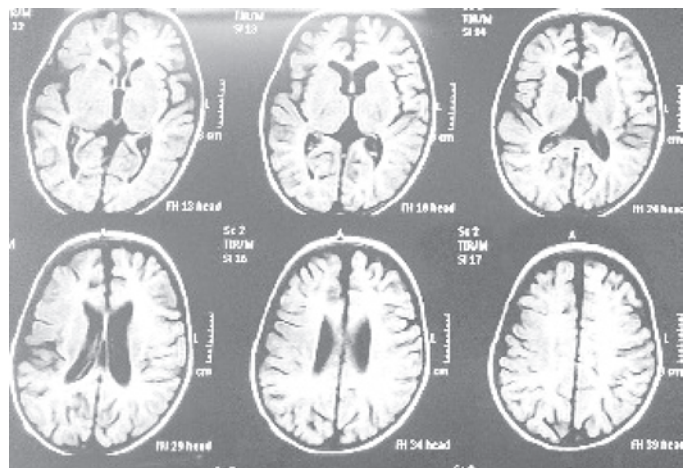
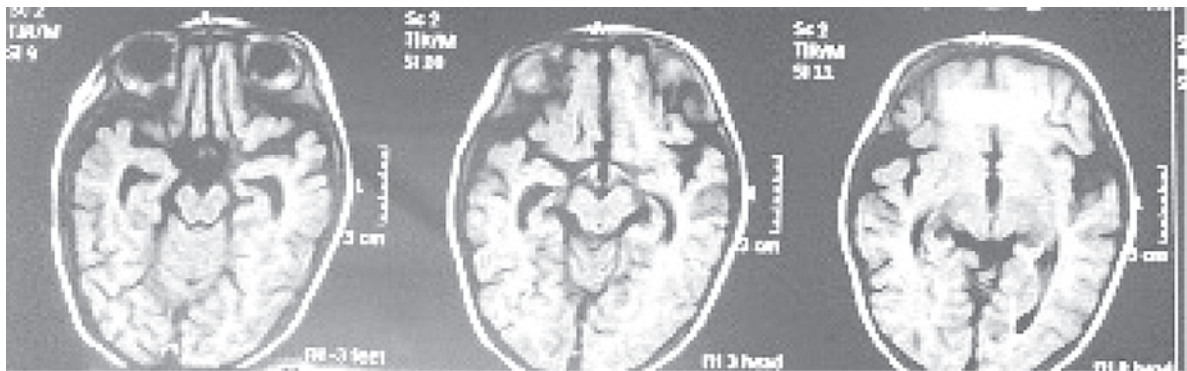
Treatment for DS may involve correction of the refractory error, squint and surgical interventions like muscle recession procedures, vertical transposition of the rectus muscle, or a combination of the two, for improving or eliminating the head turns and misalignment of the eyes.

In conclusion any child who has narrowing of palpebral fissure on adduction with globe retraction with limitation of abduction the possibility of congenital 6<sup>th</sup> nerve palsy should be thought of. We have presented this child with Duane syndrome for its rarity and to impress upon the utility of CISS sequence MRI in children with isolated cranial nerve palsy.

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**PICTURE QUIZ**



- A. What is the diagnosis?
- B. What are the MRI findings?

Compiled by: **\*Rupali Jain, \*Kavita Tiwari, \*Amzad Khan, \*\*Anuradha Harish, \*\*\*Suresh Goyal**  
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 RNT Medical College, Udaipur. email: kgneuro@gmail.com.

**Answer on page: 80**

### CLIPPINGS

#### ***Etiology of Acute Respiratory Infections in Infants: A Prospective Birth Cohort Study***

A birth cohort was followed for the first year of life; for each episode of ARI, nasopharyngeal aspirates were collected to identify the causative respiratory virus(es) using multiplex real-time polymerase chain reaction assay. For lower respiratory tract infections blood culture, serum procalcitonin, serum antibodies to *Mycoplasma* and *Chlamydia* and urinary *Streptococcus pneumoniae* antigen were also assayed.

A total of 503 ARI episodes were documented in 310 infants for an incidence rate of 1.8 episodes per infant per year. Of these, samples were processed in 395 episodes (upper respiratory tract infection: 377; lower respiratory tract infection: 18). One or more viruses were detected in 250 (63.3%) episodes and viral coinfections in 72 (18.2%) episodes. Rhinovirus was the most common virus [105 (42%)] followed by respiratory syncytial virus [50 (20%)], parainfluenza virus [42 (16.8%)] and coronavirus [44 (17.6%)]. In lower respiratory tract infections, viral infections were detected in 12 (66.7%) episodes, bacterial infections in 17 (94.4%) episodes and mixed bacterial–viral infections in 8 (44.4%) episodes. Peak incidence of viruses was observed during February–March and September–November. There was no significant difference in symptom duration with virus types.

In this cohort of infants, ARI incidence was 1.8 episodes per year per infant; 95% were upper respiratory tract infections. Viruses were identified in 63.3% episodes, and the most common viruses detected were rhinovirus, respiratory syncytial virus and parainfluenza virus.

***Kumar P, Medigeshi GR, Mishra VS, Islam M, Randev S, Mukherjee A, Chaudhry Ret al., Etiology of acute respiratory infections in infants: A prospective birth cohort study. The Pediatric Infectious Disease Journal. 2017 Jan 1;36(1):25-30.***

### NEWS AND NOTES

#### **National Conference of Developmental Pediatrics, Delhi-2017**

**Pre-Conference workshops: 8<sup>th</sup> September – 2017    Main Conference: 9<sup>th</sup> & 10<sup>th</sup> September, 2017**

**Venue: Hotel Eros, Nehru Place**

#### **For enquiries contact**

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Organizing Secretary

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### ERRATUM

Article titled “A rare case of virginal breast hypertrophy in a 12 year child treated with reduction mammoplasty” Indian J Pract Pediatr 2016; 18(4): 387 – 389.

The names of co-authors ‘Anitha S Prabhu, Nithu N, Satish Bhat’ were missed in the above article due to typographical error. The authorship of the article should read as “Supriya Kushwah, Anitha S Prabhu, Nithu N, Satish Bhat”. The error is deeply regretted.

Editorial Board

Indian Journal of Practical Pediatrics

### PICTURE QUIZ ANSWER

A. Sturge–Weber syndrome

B. MRI - Diffuse cerebral atrophy with gyriform abnormal signals in right fronto-temporoparietal region





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# 10<sup>th</sup> NATIONAL IAP-IJPP CME 2017

11<sup>th</sup> June, 2017 (Sunday), Hotel Savera, Chennai - 4



## SCIENTIFIC PROGRAMME

TIME	SESSIONS	SPEAKERS
08.00-08.30 am	<b>REGISTRATION</b>	
08.30-09.30 am	<b>SESSION I</b>	
08.30-08.50 am	• Growth charts and monitoring	Dr.Hemchand K Prasad
08.50-09.05 am	• H1N1 revisited	Dr.Vidya Krishna
09.05-09.20 am	• Sedation and analgesia in office practice	Dr.A.R.Mullai Baalaaji
09.20-09.30 am	<b>Discussion</b>	
09.30-10.30 am	<b>SESSION II</b>	
09.30-09.50 am	• Money matters - Financial advice for doctors	Dr.S.Thirumalai Kolundu
09.50-10.05 am	• Thrombocytopenia	Dr.Janani Sankar
10.05-10.20 am	• Late talking toddler-When to worry?	Dr.A.Somasundaram
10.20-10.30 am	<b>Discussion</b>	
10.30-11.00 am	<b>INAUGURATION</b>	
11.00-12.00 noon	<b>SESSION III</b>	
	Panel discussion I: Neonatal sepsis	<b>Moderator:</b> Dr.T.L.Ratnakumari <b>Panelists:</b> Dr.J.Shyamala Dr.C.N.Kamalarathinam Dr.N.Chandrakumar
12.00-01.00 pm	<b>SESSION IV</b>	
12.00-12.20pm	• Clinical examination does make a difference	Dr.S.Thangavelu
12.20-12.35pm	• Child with elevated transaminases - Approach	Dr.Malathi Sathiyasekaran
12.35-12.50pm	• Intravenous immunoglobulin	Dr.S.Balasubramanian
12.50-01.00 pm	<b>Discussion</b>	
01.00-02.00 pm	<b>LUNCH</b>	
02.00-03.00 pm	<b>SESSION V</b>	
	Panel discussion II: Antimicrobials in office practice	<b>Moderator:</b> Dr.P.Ramachandran <b>Panelists:</b> Dr.C.V.Ravisekar Dr.Sunil Srinivasan Dr.P.Senthur Nambi
03.00-04.00 pm	<b>SESSION VI</b>	
03.00-03.20 pm	• Hypopigmented skin lesions - What a pediatrician should know?	Dr.R.Madhu
03.20-03.35 pm	• Early childhood caries - Causes and management	Dr.M.S.Muthu
03.35-03.50 pm	• Head trauma-Imaging and triaging	Dr.Leema Pauline
03.50-04.00 pm	<b>Discussion</b>	
04.00-05.00 pm	<b>SESSION VII</b>	
04.00-04.20 pm	• Pneumonia – Dilemmas in management	Dr.N.C.Gowrishankar
04.20-04.35 pm	• UTI - Pitfalls in management	Dr.E.Sudha
04.35-04.50 pm	• Cardiac emergencies - Management in ER	Dr.Indumathy Santhanam
04.50-05.00 pm	<b>Discussion</b>	



# 10<sup>th</sup> NATIONAL IAP-IJPP CME 2017

11<sup>th</sup> June, 2017 (Sunday), Hotel Savera, Chennai - 4



Dear Colleagues,

Greetings from the Organising Committee of "10<sup>th</sup> National IAP - IJPP CME 2017".

We cordially invite you to participate in the "10<sup>th</sup> National IAP - IJPP CME 2017" jointly organised by "Indian Academy of Pediatrics (IAP)" and "Indian Journal of Practical Pediatrics (IJPP)" on 11<sup>th</sup> June, 2017 Sunday at Hotel Savera, Chennai, between 8AM and 5PM. The Scientific Programme has incorporated common pediatric and neonatal problems.

We would also like to bring to your kind attention that "2 credit hours" by Tamil Nadu Medical Council and "10 CME credit points" by The Tamil Nadu Dr.MGR Medical University for the CME are expected.

We have great pleasure in inviting you to register and participate in the CME to enrich your knowledge and make the CME a fruitful and successful one.

Expecting your active participation.

Yours in Academy Service,

**Dr.N.C.Gowrishankar**  
Organising Chairperson

**Dr.S.Thangavelu**  
Organising Secretary

**Dr.G.Duraiarasan**  
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