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IAP-IJPP CME 2019

RECENT ADVANCES IN SEPTIC SHOCK

Deepika Gandhi

Abstract: *Septic shock is the most complex and controversial type of shock. Attempts to reduce the mortality associated with septic shock have prompted collaborative research and consensus worldwide for timely diagnosis, monitoring and appropriate management of the causative infection and associated organ dysfunction. In addition, better understanding of the underlying pathophysiological mechanisms and significant advances in the treatment of severe sepsis has helped to individualize the management of a patient with septic shock into phases of resuscitation, stabilization and de-resuscitation in order to avoid the complications of over-treatment.*

Keywords: *Septic shock, Bundle care, Resuscitation, Outcomes.*

Sepsis is life threatening organ dysfunction caused by dysregulated host response to an infection. In children, sepsis accounts for 60%-80% of annual mortality.[1] It is also a major contributor towards increased healthcare cost and utilization.

In 2001, the landmark trial by Rivers, et al., showed a significant decrease in mortality due to septic shock using a protocolized time-bound early goal directed therapy (EGDT), as compared to usual care.[2] The remarkable survival benefit showed by EGDT led to improvement of standard of care for septic shock worldwide. In 2004, the Surviving Sepsis Campaign (SSC) was launched to reduce mortality associated with sepsis.[3] SSC has released four sets of guidelines over the last fifteen years. The most recent update of American College of Critical Care Medicine/ Pediatric Advanced Life Support (ACCM/PALS) was published in 2017. Though SSC guidelines consist of many recommendations and best practices, sepsis bundles consisting of several measureable interventions have been the cornerstone of SSC's aim to reduce the sepsis associated mortality worldwide.[4] Last few years have provided several big steps towards understanding and management of sepsis and septic shock. This short review provides some of the recent advances in the management of septic shock.

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Advances in diagnosing septic shock

Early recognition of septic shock is as important for children as it is for adults. However, presentation of pediatric septic shock is different from that in adults. Diagnosing septic shock in children requires a low threshold because children present with subtle and distinct clinical signs of hemodynamic instability that may be easily over-looked.

New definition

Septic shock is a combination of distributive, hypovolemic and cardiogenic elements. The lack of specificity of systemic inflammatory response criteria (SIRS) and confusion around diagnosis of severe sepsis have led to the development of a new approach towards diagnosing sepsis ("Sepsis-3") which integrates the sepsis pathobiology better with clinical symptoms. The new Sepsis-3 definition, published in 2016, classifies sepsis into two groups viz., sepsis and septic shock.[5]

Sepsis is "a life-threatening organ dysfunction caused by dysregulated host response to an infection". In the absence of organ dysfunction, one may speak only of an infection, but not of sepsis. The term "severe sepsis" has been removed. Septic shock is a subset of sepsis in which the associated circulatory, cellular and metabolic abnormalities are profound enough to increase mortality substantially. In addition to the sepsis defining criteria, patients with septic shock have elevated arterial lactate levels and need vasopressor support despite correction of hypovolemia.[5]

Markers of shock

Early resuscitation is a key factor in preventing the progression of sepsis to septic shock, multiorgan failure and death. However, the optimal markers to identify septic shock early and determine response to therapy remain controversial because children have age-dependent variations of vital signs in response to hemodynamic compromise. These alterations in perfusion indices may

be subtle. This has led to the development of sepsis identification pathways and trigger tools, which may be extended to diagnose septic shock early.

Since hypotension is not a defining criterion of shock in children, septic shock in children can be diagnosed by the presence of varying combinations of abnormalities in clinical and hemodynamic variables like tachycardia, tachypnea (silent or associated with increased work of breathing), pulse volume (bounding or low volume), capillary refill time, blood pressure, along with signs and symptoms of end-organ hypoperfusion (oliguria, drowsiness, cold extremities, etc.).[4] Some children may even present in cryptic shock wherein they may not be hemodynamically compromised on physical examination but may show evidence of tissue hypoxia. Hence, monitoring oxygen utilization variables like arterial lactate, base deficit and mixed venous/superior vena cava oxygen saturation ($ScVO_2$) helps to diagnose tissue hypoperfusion and provide an objective assessment of response to therapy. Therefore, increased arterial lactate is an important defining criterion of septic shock in the latest SEPSIS-3 definition.[5]

Role of biomarkers

Biomarkers are biological molecules that characterize normal or pathogenic processes and can be objectively measured. They can help in diagnosis, predict disease severity, prognosis and to assess therapeutic response.

In a septic patient, the most studied biomarkers are acute phase reactants like C-reactive protein (CRP), procalcitonin (PCT), cytokines, lipopolysaccharide binding proteins (LBP), angiopoietin-1 (Ang-1), angiopoetin-2 (Ang-2), etc. The clinical relevance of these biomarkers is limited by the non-specificity and by non-availability, except for CRP and PCT.[6] Most of the biomarkers are more useful to rule out an infection and for the de-escalation of therapy. Serial monitoring is better than a single value. Though no single biomarker is specific for septic shock, more evidence is emerging with Ang-1 which is a marker of anti-inflammatory activity and Ang-2, a marker of pro-inflammatory activity and endothelial injury.[7]

Biomarkers to assess the global anaerobic metabolism secondary to shock include serial arterial lactate (defining criteria for septic shock) and venous-to-arterial CO_2 difference ($ÄPCO_2$).[8] Depending upon the severity of shock, various parameters of organ dysfunction may also need to be monitored serially.

Advances in monitoring septic shock

Septic shock is a dynamic disease in which significant changes in pathophysiology occur with progression of the underlying disease as well as with the type of treatment provided. Hemodynamic monitoring is a central component of shock management. It is context specific and monitoring increases in invasiveness as the risk for cardiovascular instability increases.

At the bedside, hemodynamic stability and tissue perfusion are monitored by a combination of clinical examination, monitoring devices and laboratory results. The focus of the treating physician should be the patient and not the technology because hemodynamic monitoring per se does not improve the outcome. Only the interventions based on the obtained hemodynamic data will impact the outcome. Hemodynamic monitoring can be approached in a series of steps aimed at assessing global and regional perfusion.[9]

Initial steps include a) clinical assessment, b) basic monitoring and assessment of global perfusion and c) preload monitoring and assessment of fluid responsiveness. Advanced monitoring measures focus on a) cardiac output measurement, b) assessment of cardiac contractility and c) assessment of tissue perfusion.

Another way of categorizing the multitude of hemodynamic monitoring technologies involves static measures and dynamic measures. Both these sets of parameters help to determine fluid responsiveness in an individual patient. As the name implies, static hemodynamic variables (CVP, BP, cardiac output, $ScVO_2$, etc.) give a value of a clinical parameter at a single point of time, while dynamic measures [stroke volume variation (SVV), systolic pressure variation (SPV), pulse pressure variation (PPV), respiratory variations in venae-cavae dimensions, etc.] provide a real-time assessment of the expected fluid need.[10,11] A new concept is that of functional hemodynamic monitoring which include monitoring techniques conducted to evaluate the effect of treatment. These include passive leg raise (PLR), venae-cavae respiratory variations in response to positive pressure ventilation, variations in left ventricular output (measured echocardiographically) in response to positive pressure ventilation, etc. Functional hemodynamic monitoring has more clinical relevance as it is used to guide treatment.[12]

Advances in management of septic shock

In the initial management of a patient with septic shock, “Time is life”. With this aim, SSC suggested a bundle-approach so as to guide physicians in taking certain mandatory steps of both treatment and monitoring. With constantly improving standards of general critical care, as EGDT (with its 6-hour bundle approach) fell out of favor,

ACCM/PALS classified its approach into "Recognition bundle", "Resuscitation and stabilization bundle" and "Performance bundle" for effective delivery and improvement in the process of care.[4] The tragic and well publicized death of a 12 years old boy in New York, Rory Stauton, following undiagnosed sepsis, led to the development of Rory's regulations or "3-hour bundle" which includes blood culture, measurement of blood lactate and administration of antibiotics within 3-hours of diagnosis of sepsis.

SSC updated its guidelines in 2016, in which the 3-hour and 6-hour bundles were combined into a single "1-hour bundle" with the idea to start treatment immediately.[13] Though more than one hour may be needed to complete the resuscitation, obtaining blood for cultures and lactate, starting isotonic fluids, giving appropriate antibiotics and in case of hypotension, initiation of vasopressors is done within the first hour of presentation with shock. After the initial hour sepsis bundle, the focus is now shifting away from a packaged protocolized approach towards a more individualized treatment based on the context and patient specific functional hemodynamic monitoring.

Fluids in septic shock

Since capillary leak and vasodilatation are hallmarks of septic shock, fluid therapy is the cornerstone of treatment. Decades of research has not yet been able to resolve the controversy whether crystalloids or colloids should be the preferred fluid for initial resuscitation. However, the basic physiological concept that colloids, owing to their greater molecular weight, stay in the intravascular compartment 3-4 times longer than crystalloids, is being questioned now. Endotoxemia induced animal research models, and subset analysis of few clinical studies have shown that endothelial and glycocalyx damage secondary to severe sepsis leads to extravasation of colloid molecules into the interstitium much faster that previously thought.[14] Hence, SSC and ACCM/PALS recommend isotonic crystalloids to be used as the initial fluid of choice.[15,4]

Fluid resuscitation in septic shock is divided into four phases - Resuscitation, optimization, stabilization and evacuation (ROSE). Each phase requires a different therapeutic attitude regarding fluid administration. Depending on which phase the patient is in, the type, dose and duration of fluids should be decided.[16]

The rate of fluid administration is dictated by presence or absence of hypotension, signs of myocardial involvement and signs/symptoms of fluid overload. A patient who is hypotensive should be given 20ml/kg of isotonic non-dextrose containing crystalloid fluid rapidly, preferably by pull-push technique. Subsequent fluid boluses should be given at a slower rate and guided by measures of fluid responsiveness. However, fluid responsiveness is not synonymous with fluid requirement. If a patient continues to be in shock despite 40 ml/kg isotonic fluids, colloids could be given and inotropes/vasopressors should be started early. Early intubation and mechanical ventilation also help in taking over the work of breathing and enable ongoing fluid resuscitation.

Though balanced salt solutions are being promoted as being more physiological compared to normal saline (decreased incidence of hyperchloremic acidosis), substantiating evidence is more robust for use of balanced salt solutions in diabetic ketoacidosis, burns resuscitation and post-operative fluids, as compared to the evidence in septic shock management.[16] Synthetic colloids, if given in large amounts, have the potential to cause coagulopathy and renal dysfunction; hence, should be avoided as the initial choice of fluid resuscitation.

Treating a patient with septic shock inevitably leads to salt and water retention. Capillary leak leads to extravasation of fluids, electrolytes and proteins into the interstitium causing anasarca and end-organ edema leading to organ dysfunction. Studies demonstrate a direct relationship between percentage of fluid overload with worse outcomes, especially mortality and occurrence of acute respiratory distress syndrome.[17,18] Hence, a strict monitoring of the cumulative fluid balance should be done to shorten the de-escalation phase of shock in which the primary focus is to achieve negative fluid balance, wean off vasoactive medications and ventilatory support.

Vasopressor regimens

Children in septic shock, unlike adults, may present with varying permutations of cardiac output and systemic vascular resistance (SVR). Children can also compensate for decreased cardiac output by increasing their heart rate. However, clinically it is difficult to predict accurately the underlying pathophysiology based on the warm or cold shock states. Multimodal hemodynamic monitoring helps at this stage to determine the state of cardiac output and SVR.[19]

In an emergency situation, if clinical and metabolic signs of shock persist despite giving more than 40 ml/kg fluids, vasoactive medications can be started through a peripheral venous access and changed to central venous access at the earliest. Though dopamine has been used for

many years as the first line inotrope in children with fluid refractory shock, evidence regarding use of epinephrine, which has greater inotropic and chronotropic action, as the initial agent in children with refractory hypotensive shock is coming through.[20] This view is also supported by ACCM/PALS.[4] With advanced multimodal hemodynamic monitoring, many children who had signs of cold shock, were found to have decreased SVR and relative hypovolemia. In such scenarios, ongoing optimization of preload and norepinephrine infusion was found to be a better treatment modality for management of shock. However, conclusive evidence to recommend norepinephrine as the first line agent in pediatric septic shock warrants good quality randomized controlled trials.

Antibiotic stewardship in septic shock

Studies indicate that 30%-60% of antibiotics prescribed in ICUs across the world are unnecessary, inappropriate or suboptimal.[21] Having said that, the time to appropriate antibiotics is a major outcome determinant of ICU patients with bacterial infections. Though no single strategy can help choose the ideal antibiotic in a specific patient, the points to consider include-

- Giving antibiotic early, within first hour; preferably after taking blood culture.
- Choosing a bactericidal antibiotic with broad antimicrobial coverage.
- Optimizing adequate dosing based on pharmacokinetics (time-dependent vs concentration-dependent).
- Giving maximum possible dose.
- If using combination, choosing antibiotics with different mechanism of action
- Source control.

Though it is a weak recommendation, SSC guidelines suggest the use of combination antibiotic therapy for patients with septic shock (survival benefit in patients with greater than 25% predicted mortality), but recommends against using combination antibiotic therapy in patients with sepsis without shock (possibility of increased mortality in patients with predicted mortality risk less than 15%).[15]

Based on the culture results, antibiotic cover should be de-escalated to a narrower spectrum antibiotic within 72 hours. The concern regarding de-escalation of antibiotics for culture negative septic shock has also been refuted by a recent retrospective cohort study of more than 8000 patients with septic shock by Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. The conclusion of this retrospective analysis was that patients with culture-negative septic shock behave similarly to those with culture-positive septic shock in all respects; early appropriate antimicrobial therapy appears to improve mortality in both groups.[22]

Therapeutic endpoints of resuscitation

Therapeutic goals and monitoring need to be adapted to the four different phases of shock management. In the first phase of resuscitation (or salvage), the goal of treatment is to achieve a minimal blood pressure and cardiac output compatible with immediate survival. In the second (optimization) phase, the goal is to increase cellular oxygen availability by targeting interventions to the hemodynamic status. In the third (stabilization) phase, the focus shifts more towards organ support. Finally, in the fourth (de-escalation) phase, the goal is to wean the patient from vasoactive agents, and promote spontaneous polyuria or provoke fluid elimination through use of diuretics or ultrafiltration to achieve negative fluid balance.[20]

As per the European Society of Intensive Care consensus published in 2004, end-points of shock resuscitation should include normalization of vital signs like normal heart rate and blood pressure, central and peripheral pulse volume, capillary refill <2 seconds. Once signs of shock resolution are achieved, decrease the rate of fluid resuscitation, initiate maintenance fluids, but continue to monitor hemodynamics for recurrence of shock.[23]

A recent multinational randomized control trial, the ANDROMEDA SHOCK Trial, studied more than 400 adult patients with early septic shock to determine the efficacy of peripheral perfusion targeted resuscitation over lactate-level targeted resuscitation.[24] They concluded that resuscitation strategy targeting normalization of capillary refill time did not decrease 28 day all cause mortality, when compared to strategy targeting lactate level.

Role of steroids

Although multiple guidelines suggest consideration of adjunctive stress dose corticosteroids in vasoactive-inotrope resistant refractory septic shock, no high quality evidence exists supporting the safety or efficacy of this approach. The Corticosteroid Therapy of Septic Shock (CORTICUS) Study published in 2008, hydrocortisone failed to show any mortality or shock reversal benefit in around 500 adult patients with septic shock.[25]

In a recent study of more than 3500 mechanically ventilated adult patients with septic shock, the ‘Adjunctive

Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial', a continuous infusion of hydrocortisone did not lower an all cause mortality at 90 days when compared to a placebo.[26]

The 'REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE (RESOLVE)' Study group also observed that in about 477 children with severe sepsis who required mechanical ventilation and vasoactive-inotropic support, adjunctive steroids did not show any outcome benefit.[27]

Extracorporeal circuits

Despite advances in critical care, mortality in patients who progress to catecholamine-resistant septic shock continues to be high secondary to organ dysfunction. Though for adults, use of extra-corporeal membrane oxygenation (ECMO) has not provided much of a mortality benefit, in neonates and children, ECMO is associated with improved survival and is considered a viable option. Myocardial dysfunction secondary to bacterial infection is reversible. Veno-arterial ECMO (VA-ECMO) provides a salvage therapy and rest to the failing heart, avoids adverse effects of high dose catecholamines and buys time for antimicrobials and other supportive care to provide maximum benefit.[28]

In severe sepsis and septic shock, exaggerated immune response secondary to infection, extends far beyond the site of infection, is multifactorial and has the potential to cause life-threatening organ dysfunction. Both pathogen-associated and host-associated factors can act as inflammatory mediators. Hence, different extracorporeal techniques have been studied in recent years in the hope to maximize the effects of renal replacement therapy in modulating the exaggerated host response. These techniques include high volume hemofiltration (HVHF), high cut-off (HCO) membranes, adsorption alone and coupled plasma filtration adsorption (CPFA).[29] However, in most setups, use of such extracorporeal techniques is highly dependent on the local expertise and resources.

Conclusion

The battle against septic shock is long standing. The fact that mortality in patients with septic shock is still high suggests that no single treatment modality is outcome modifying. It also means that as our understanding of sepsis - pathobiology and pathophysiology is evolving, so are the bugs causing sepsis. Hence, as we explore the new frontiers of modifying and controlling the human immune modulatory mechanisms, the basics of septic shock resuscitation i.e. 1-hour bundle, which includes measuring lactate, obtaining blood culture before giving appropriate antibiotics, starting rapid administration of 30 ml/kg crystalloid fluids for hypotension or lactate >2 mmol/L and an early use of vasopressors for fluid-refractory shock - all within the first hour of septic shock diagnosis - remain the cornerstone of improving outcomes of patients with septic shock.

Points to Remember

- ***Successful management of septic shock is challenging.***
- ***Early recognition of septic shock using a trigger-tool and a systematic approach to management increases the chance of a favorable outcome.***
- ***One hour bundle approach, which includes measuring lactate, obtaining blood culture before giving appropriate antibiotics, starting rapid administration of crystalloid fluids for hypotension or lactate >2 mmol/L and an early use of vasopressors for fluid-refractory shock remain the cornerstone of treatment.***
- ***After the initial fluid bolus, subsequent fluid resuscitation must be guided by measures of fluid responsiveness.***
- ***Positive fluid balance at 72 hours increases morbidity and mortality. All attempts must be made to de-escalate supports and achieve negative fluid balance.***

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CARDIAC FAILURE - RECENT ADVANCES

*Saileela R

Abstract: *Heart failure is a major cause of morbidity and mortality in children. The common causes of heart failure in children are congenital heart defects and cardiomyopathy. Heart failure management aims at symptomatic relief, reduction of readmissions, prevention of disease progression, improving longevity and quality of life. The initial step in the management of heart failure involves identification and management of the cause and precipitating factors. The medical management of heart failure includes a combination among the following drugs - ACE inhibitor, beta blocker, aldosterone antagonist, diuretic and digoxin. Advanced heart failure treatment includes cardiac resynchronization therapy, mechanical circulatory support and heart transplantation. This review gives an overview of important aspects of etiology, evaluation, management and recent advances in heart failure in children.*

Keywords: *Cardiac failure, Pharmacotherapy, Device therapy, Children.*

Cardiac failure is a pathophysiological syndrome resulting from ventricular dysfunction, volume or pressure overload, either alone or in combination.[1] The syndrome manifests with symptoms and signs secondary to circulatory, neurohumoral and molecular abnormalities. Heart failure commonly manifests with respiratory distress, feeding difficulty, diaphoresis and failure to thrive in infants, where as older children may have exercise intolerance, fatigue, abdominal pain, oliguria and edema. The severity of heart failure is assessed by Ross classification in infants and young children, while New York Heart Association (NYHA) classification is applied for older children (Table I).[2]

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Table I. Modified Ross classification for heart failure[2]

Class	Symptom
Class I	Asymptomatic
Class II	Mild tachypnea or diaphoresis with feeding in infants, dyspnea on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants, marked dyspnea on exertion, prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

Pathophysiology

The low cardiac output in heart failure triggers several compensatory mechanisms. These are helpful in the short-term; however, they are counterproductive in the long-term resulting in pathologic remodelling of myocardium and progression of disease.[3, 4]

a) There is activation of sympathetic nervous system in heart failure. This helps by improving the myocardial contractility and causes vasoconstriction to improve vital organ perfusion. However, it causes tachycardia, increases myocardial oxygen demand and leads to cardiomyocyte injury.

b) Activation of renin-angiotensin-aldosterone system (RAAS) also noted. Angiotensin II causes vasoconstriction, thus improving vital organ perfusion. Aldosterone increases preload by causing sodium and water retention, which results in improved cardiac output. But chronic activation of RAAS results in elevated systemic vascular resistance and myocardial oxygen demand. Aldosterone promotes myocardial apoptosis and fibrosis, leading to worsening of heart failure.

Insight into the pathophysiological mechanisms of heart failure have widened the list of drugs used in heart failure to target neurohumoral mechanisms and ventricular remodelling.

Table II. Common causes of heart failure based on age of onset[5]

Age	Etiology
Fetus	Tachyarrhythmia Severe bradycardia due to congenital heart block Severe tricuspid regurgitation (Ebstein anomaly) Anemia
First day of life	Myocardial dysfunction due to asphyxia, hypoglycemia, hypocalcemia, sepsis Anemia Systemic arteriovenous fistula Severe tricuspid regurgitation (Ebstein anomaly) Arrhythmias Myocarditis
First week of life	Duct dependent systemic circulation - hypoplastic left heart syndrome, coarctation of aorta, interrupted arch, critical aortic stenosis Obstructed total anomalous pulmonary venous connection Arrhythmias Hemodynamically significant patent ductus arteriosus in a preterm Hyperthyroidism Adrenal insufficiency
Beyond two weeks of life	Large left to right shunts - Ventricular septal defect, patent ductus arteriosus, aortopulmonary window. Cyanotic diseases with increased pulmonary flow- Total anomalous pulmonary venous connection, transposition of great arteries with ventricular septal defect, truncus arteriosus Myocarditis Arrhythmias Anomalous left coronary artery from the pulmonary artery
Older children	Rheumatic fever Rheumatic heart disease Infective endocarditis Myocarditis Cardiomyopathy Arrhythmias, pulmonary hypertension

Etiology

The causes and clinical presentation differ in different age group of children (Table II).[5] Arrhythmias and valve regurgitation are the common causes of fetal heart failure. Heart failure on first day of life is most often due to non-cardiac causes like asphyxia, hypoglycemia, hypocalcemia and sepsis. Congenital heart diseases with duct dependent circulation present with heart failure in the first week of life when the ductus arteriosus closes. Large left to right shunts become symptomatic after first month when the pulmonary vascular resistance decreases. Heart failure presenting in older children is most often due to acquired causes like myocarditis, infective endocarditis and rheumatic fever.

The causes of heart failure can be congenital (e.g. congenital heart defects like ventricular septal defect) or acquired (e.g. Rheumatic heart disease, myocarditis). While most often there is a cardiac etiology, non-cardiac causes (like systemic arteriovenous fistula) can also result in heart failure. Tachycardiomyopathy (ventricular dysfunction secondary to chronic tachyarrhythmia) should be considered and ruled out in all cases as it is potentially treatable and reversible.

Investigations

Blood investigations should include complete blood count (to rule out anemia), thyroid function test (hypo/hyperthyroidism can cause heart failure), liver function test (deranged in congestive hepatomegaly).

Table III. Dosage of common drugs used in heart failure

Drug	Dose
Furosemide	1 mg/kg/dose q12h, max 4 mg/kg/day
Spironolactone	0.5-2 mg/kg/dose q12h
Metolazone	0.1 mg/kg/dose q12h
Hydro chlorthiazide	1-1.5 mg/kg/dose q12-24h
Digoxin	5 mic/kg/dose q12h
Enalapril	0.1mg/kg/dose max upto 0.3 mg/kg/ dose q12h
Captopril	0.2 mg/kg/dose max upto 1 mg/kg/ dose q8h
Lisinopril	0.1-0.2 mg/kg once daily
Losartan	0.5 mg/kg once daily
Carvedilol	0.05 mg/kg/dose q12h, max upto 0.5 mg/kg/dose
Bisoprolol	0.2 mg/kg once daily
Metoprolol	0.1 mg/kg/dose q12h , increase to max of 1 mg/kg/dose
Dopamine	2.5 to 10 mic/kg/min
Dobutamine	2.5 to 10 mic/kg/min
Epinephrine	0.01 to 0.1 mic/kg/min
Milrinone	50 mic/kg loading dose followed by 0.5 to 1 mic/kg/min infusion
Levosimendan	6 to 12 mic/kg loading dose followed by 0.05 to 0.2 mic/kg/min infusion

Serum electrolytes: Serum calcium and phosphorus should be checked as their abnormality can result in ventricular dysfunction. Serum potassium and sodium should be monitored in children on chronic diuretic therapy.

Brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP): This can be used as a marker for evaluation and monitoring of heart failure patients for assessing severity, disease progression and response to therapy.

Chest X-ray: Cardiomegaly on chest X-ray usually correlates with the ventricular dilatation on echocardiogram. Left to right shunts show cardiomegaly, enlarged pulmonary artery and pulmonary plethora on X-ray. Severe left ventricular dysfunction can manifest with features of pulmonary venous congestion or pulmonary edema on X-ray.

Electrocardiogram: The most common ECG finding in a child with heart failure is sinus tachycardia. One should look for clues to etiology like tachyarrhythmia and atrioventricular block. Myocardial infarction pattern with deep 'q' waves in the inferolateral leads is suggestive of anomalous origin of left coronary artery from pulmonary artery.

Echocardiogram: Echocardiogram is the gold standard for diagnosis of structural heart defects. Fractional shortening, ejection fraction, LV wall thickness, LV mass, myocardial performance index and fractional area contraction are documented and monitored during follow up.

Cardiac MRI: In selected cases of myocarditis and cardiomyopathy, cardiac MRI is performed to evaluate myocardial edema, inflammation and scarring. It also gives estimation of ventricular volumes and cardiac output.

Cardiac catheterization: This is routinely performed in all patients awaiting heart transplantation. Pulmonary arterial pressure, vascular resistance, ventricular diastolic pressure and cardiac output can be estimated.

Genetic evaluation: Genetic testing is recommended in cardiomyopathies especially in the presence of family history of cardiomyopathy or premature sudden death.

Metabolic screening: Cardiomyopathy may be a manifestation of underlying metabolic diseases like glycogen storage disease, fatty acid oxidation defects and mitochondrial disorders.[6] Metabolic screening may be considered in infants with cardiomyopathy when there is a suspicion of these disorders.

Treatment

The management of heart failure includes treatment of the etiology, symptom relief and prevention of disease progression. Anemia, electrolyte imbalance, intercurrent infections, reactivation of rheumatic fever in rheumatic valvular disease, arrhythmia, improper drug dosage and noncompliance to drugs are some of the common reasons for worsening of symptoms in heart failure. These precipitating factors should be identified and corrected. Fluid and salt restriction should be considered in older children. Heart failure patients should receive all age appropriate immunizations including pneumococcal vaccine and annual influenza vaccine. Treatment approach is summarized in Fig.1.

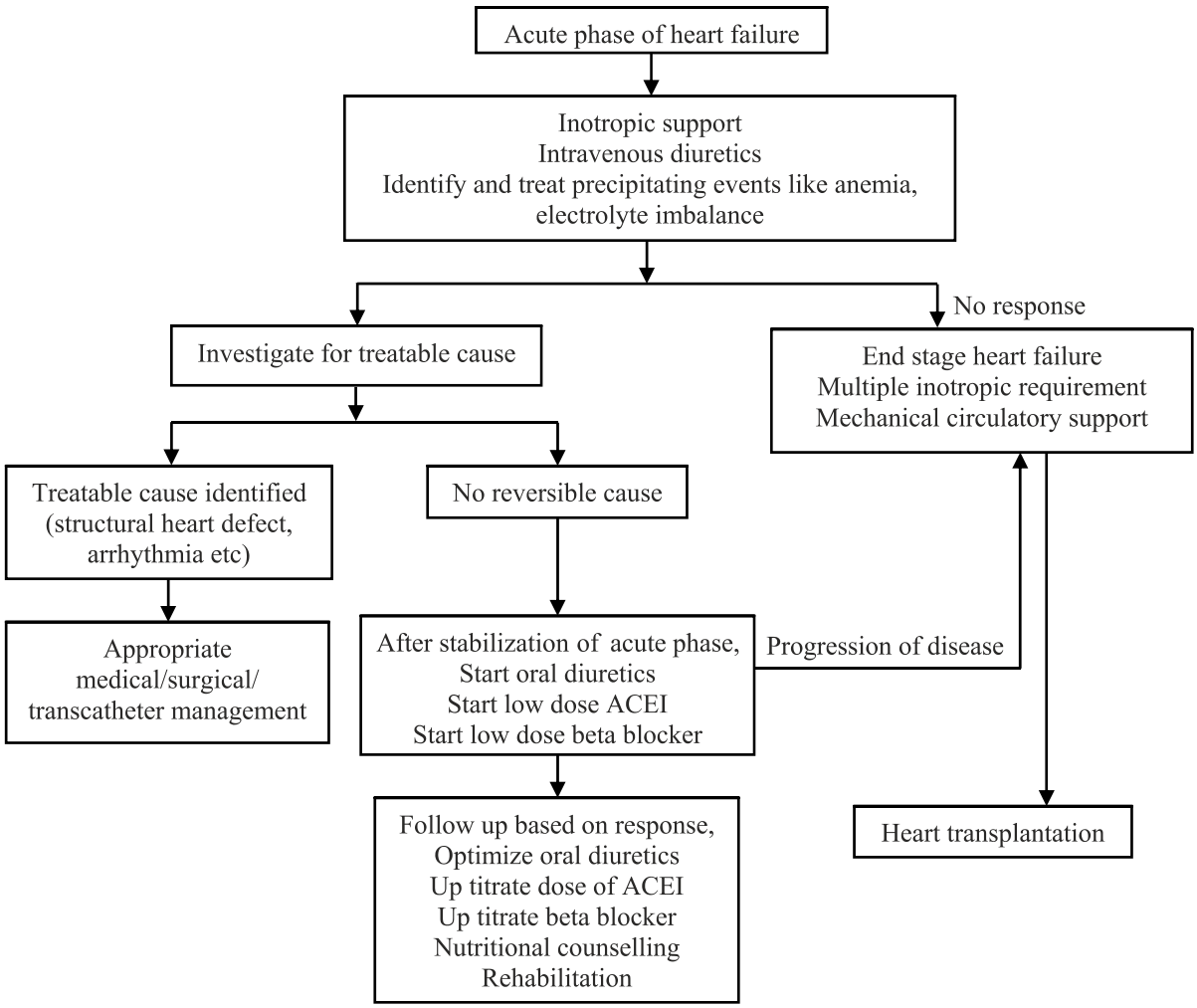

Fig.1. Approach to heart failure in children

Medical management

Management guidelines in children are most often adapted from adult guidelines as there is limited literature in pediatric heart failure.

Diuretics: Diuretics are indicated in symptomatic patients with evidence of fluid retention so as to achieve euvolemic state. Diuretics alleviate symptoms by reducing pulmonary and systemic venous congestion. A combination of loop diuretics and aldosterone antagonist (spironolactone) is preferred. Adding spironolactone not only reduces the hypokalemia induced by loop diuretics, but also decreases the aldosterone induced myocardial fibrosis in heart failure. Electrolytes should be monitored while on prolonged diuretic use, as dyselectrolytemia can trigger arrhythmias in a failing myocardium. Metolazone or hydrochlorthiazide may be added in refractory heart failure.

Angiotensin-converting enzyme inhibitor (ACEI): These are indicated in all patients with chronic LV dysfunction (in the absence of contraindications). ACEI decreases the afterload and prevents negative remodelling of the myocardium. They delay the progression of heart failure and prolong survival of patients. They should be started at a low dose and titrated up to maximum safe dose. Captopril, enalapril or lisinopril can be used in children. Blood pressure, renal function and serum potassium should be monitored during therapy. ACEI should be avoided in neonates. They are contraindicated in renal failure, bilateral renal artery stenosis, hypotension and obstructive lesions like aortic stenosis.

Beta blockers: Beta blockers are indicated in all patients with chronic LV dysfunction. Beta blockers counteract the deleterious effects of sympathetic system activation in heart failure and prevent myocardial remodeling.[3] They should be started at a low dose and slowly titrated to higher doses. Carvedilol is the most commonly used drug in children. Metoprolol and bisoprolol can also be used, which are more cardioselective.

Mineralocorticoid antagonist: Aldosterone antagonist is indicated in all patients with LV dysfunction. It causes diuresis and prevents aldosterone induced myocardial apoptosis.

Angiotensin receptor antagonist: These are considered in children who are intolerant to ACE inhibitors.

Digoxin: Though digoxin has been used routinely for children with heart failure, there is no robust data to support its use. No survival benefit was demonstrated in adults with heart failure. Hence, it is not routinely indicated in asymptomatic heart failure and left to right shunts but can be used in symptomatic children with low ejection fraction (EF). Lower serum levels of digoxin (0.5 to 0.9 ng/ml) should be targeted. Digoxin dose has to be reduced when used with carvedilol and amiodarone.

Anti-coagulants: Anticoagulants are indicated when there is an intracardiac thrombus or history of thrombus/ thromboembolic event. Presence of atrial fibrillation or flutter in the presence of low ejection fraction also warrants anti-coagulation.

Inotropes: Inotropic support is reserved as a short term therapy for those presenting with symptomatic low cardiac output. Intermittent or chronic inotropic therapy is only a bridge to transplant. There is no supportive data for the same in pediatric patients. The most commonly used inotropes are catecholaminergic drugs like dopamine and dobutamine.Phosphodiesterase III inhibitor like Milrinone, has vasodilatory effects and improves ventricular relaxation. Levosimendan, a calcium sensitizer, has been proven to be effective and safe in children. It has inotropic and vasodilatory effect but does not have proarrhythmic effects like milrinone.

Newer drugs: Ivabradine is a heart-rate-lowering agent that acts by selectively and specifically inhibiting the cardiac pacemaker current, a mixed sodium-potassium inward current (inward funny current - I_f) that controls the spontaneous depolarization in the sinoatrial (SA) node and hence regulates the heart rate. Neprilysin inhibitor (Sacubitril) and valsartan combination is a newer drug in heart failure management and is proven to be effective in adults. There are ongoing trials to evaluate this drug in heart failure in children.

Device therapy

Cardiac resynchronization therapy (CRT): Incoordinate electrical activation results in mechanical dyssynchrony and inefficient contraction.[6] Cardiac output can be improved by resynchronizing the electrical activity in selected patients. CRT may be considered in symptomatic patients with severe LV dysfunction (EF <35%), evidence of electrical dyssynchrony (left bundle branch block) and QRS duration more than upper limit for age.

Implantable cardioverter defibrillator (ICD): This is indicated in patients with ventricular dysfunction with history of aborted cardiac arrest, ventricular tachycardia and unexplained syncope.

Extra Corporeal Membrane Oxygenation: ECMO may be considered for temporary circulatory support in the event of cardiac arrest or cardiogenic shock due to a potentially reversible etiology.

Ventricular assist device (VAD): This can be considered as a bridge to transplant or as destination therapy when it is not possible to wean the patient off inotropic support or in the presence of other organ damage. It is preferred over ECMO in view of longer duration of support, decreased risk of thromboembolic complications and increased mobility of patients.

Surgical Treatment: Children with structural abnormalities like left to right shunts or ALCAPA should undergo surgical intervention at appropriate age. This can be curative in most cases. Some conditions like severe valvar aortic stenosis are amenable to transcatheter intervention.

Heart transplantation: This is indicated in refractory end-stage heart failure in children with cardiomyopathies or previously repaired/palliated congenital heart defects and in refractory ventricular arrhythmias with severe ventricular dysfunction, not responding to medications and ICD.[7]

Conclusion

The treatment guideline for heart failure in children is largely extrapolated from adult heart failure guidelines, due to lack of robust data in children. Unlike adults, several causes of heart failure in children are curable (like structural heart defects). Disease modifying drugs like ACE inhibitors and beta blockers should be part of chronic heart failure management. Cardiac resynchronization therapy and implantable cardioverter-defibrillator are helpful in selected cases of heart failure. Ventricular assist devices as a bridge to heart transplant is gaining importance.

Points to Remember

- ***Several causes of heart failure in children are curable and reversible. Early diagnosis and treatment of reversible causes like structural heart***

defects and tachyarrhythmia result in good long-term prognosis.

- ***Treatment of precipitating factors like anemia, electrolyte imbalance and intercurrent infections reduce the morbidity in heart failure.***
- ***Diuretics help in symptomatic improvement of heart failure. Drugs like ACE inhibitors and beta blockers counteract the neurohumoral mechanisms and alter the pathologic remodelling of heart in chronic heart failure.***
- ***Mechanical circulatory support (ECMO, ventricular assist devices) are being increasingly adopted in appropriate patients.***

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CLIPPINGS

Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus.

The authors have studied the choice of drugs for patients with status epilepticus that is refractory to treatment with benzodiazepine. In this randomised blinded adaptive trial they had compared the efficacy and safety of three intravenous anticonvulsants – levetiracetam, fosphenytoin and valproate in children and adults with status epilepticus. The outcome was absence of clinically evident seizures and improvement of level of consciousness by 60 minutes after the state of drug infusion without further medication for convulsions. Safety outcomes included life threatening hypotension, cardiac arrhythmia, endotracheal intubation, seizure recurrence and death. A total of 384 patients were enrolled and randomly assigned to receive levetiracetam (145 patients), fosphenytoin (118), or valproate (121).

In accordance with a prespecified stopping rule for futility of finding one drug to be superior or inferior, a planned interim analysis led to the trial being stopped Authors have reported the following in their study.The primary outcome of cessation of status epilepticus and improvement in the level of consciousness at 60 minutes occurred in 68 patients assigned to levetiracetam (47%; 95% credible interval, 39 to 55), 53 patients assigned to fosphenytoin (45%; 95% credible interval, 36 to 54), and 56 patients assigned to valproate (46%; 95% credible interval, 38 to 55). The posterior probability that each drug was the most effective was 0.41, 0.24, and 0.35, respectively.

The authors concluded the following in their study. In the context of benzodiazepine-refractory convulsive status epilepticus, the anticonvulsant drugs levetiracetam, fosphenytoin, and valproate each led to seizure cessation and improved alertness by 60 minutes in approximately half the patients, and the three drugs were associated with similar incidences of adverse events.

Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al., for the NETT and PECARN Investigators. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med 2019; 381:2103-2113.

IAP-IJPP CME 2019

KAWASAKI DISEASE – WHAT IS NEW?

Sathish Kumar

Abstract: *Kawasaki disease is an acute febrile illness of childhood that is characterized pathologically by vasculitis of medium-sized, extraparenchymal arteries, with a predilection for the coronary arteries. It is the leading cause of acquired heart disease in developed countries, whereas rheumatic heart disease continues to dominate the developing world. The natural history, treatment and sequelae of untreated Kawasaki disease are now well described. This article covers latest updates in Kawasaki disease.*

Keywords: *Kawasaki Disease, Children, Coronary artery involvement, Update.*

Kawasaki disease (KD) is an acute systemic vascular disease that affects mostly medium and small sized vessels. It is generally self-limited and the highest incidence occurs in children under five years of age. KD is the second most common systemic vasculitic illness of childhood after IgA vasculitis.[1] KD is the most common cause of acquired heart disease in children in developed countries, causing coronary artery aneurysms (CAA) in up to 25% of untreated patients due to coronary vasculitis. Clinical trials demonstrate that this declines to about 4% with intravenous immunoglobulin (IVIG) treatment. This article covers the recent developments in diagnosis, laboratory investigations and treatment of KD.

Diagnosis

Diagnosis of KD should be considered in any child with a febrile exanthematous illness and evidence of inflammation, particularly if it persists longer than 4 days having clinical signs as shown in Table I. KD has to be considered in the differential diagnosis with the features shown in Box 1.[1]

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Box 1. Features suggesting KD

- Infants <6 months old with prolonged fever and irritability
- Infants with prolonged fever and unexplained aseptic meningitis
- Infants / children with prolonged fever and unexplained or culture-negative shock
- Infants / children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy
- Infants / children with prolonged fever and retropharyngeal or parapharyngeal phlegmon (localized area of acute inflammation of the soft tissues) unresponsive to antibiotic therapy

The diagnosis and treatment of KD should not be delayed if a) 5/6 diagnostic criteria of KD are present before day 5 of fever, b) coronary artery aneurysm (CAA) or coronary dilatation are present and c) evidence of persistent ($\geq$5 days) elevation of inflammatory markers and/or persistent fever, especially in infants or younger children without other explanation.

In a patient in whom KD is suspected, but all criteria have not yet been fulfilled, irritability and new erythema and/or induration at the site of previous BCG immunization strengthen the suspicion of KD.

Evaluation of a child with suspected incomplete Kawasaki disease is given in Fig.1.[1]

Typical peeling begins under the nail beds of fingers and toes. Infants $\leq$ 6 months of age are the most likely to develop prolonged fever without other clinical criteria for Kawasaki disease; these infants are at particularly high risk of developing coronary artery abnormalities.

Echocardiography is considered positive for purposes of this algorithm if any of the three conditions are met: Z score of left anterior descending coronary artery or right coronary artery $\geq$ 2.5; coronary artery aneurysm is observed; or $\geq$ 3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending

Table I. Diagnosis of Kawasaki disease

Criterion	Description
Fever	Duration of 5 days* or more, plus four of five of the following
1. Conjunctivitis	Bilateral, bulbar, conjunctival injection without exudate
2. Lymphadenopathy	Cervical, often >1.5 cm usually unilateral
3. Rash	Maculopapular, diffuse erythroderma or erythema multiforme
4. Changes of lips or oral mucosa	Red cracked lips, strawberry tongue or diffuse erythema of oropharynx
5. Changes in extremities	Erythema and edema of palms and soles in acute phase and periungual desquamation in subacute phase

**KD may be diagnosed with fewer than four of these features if coronary artery abnormalities are detected*

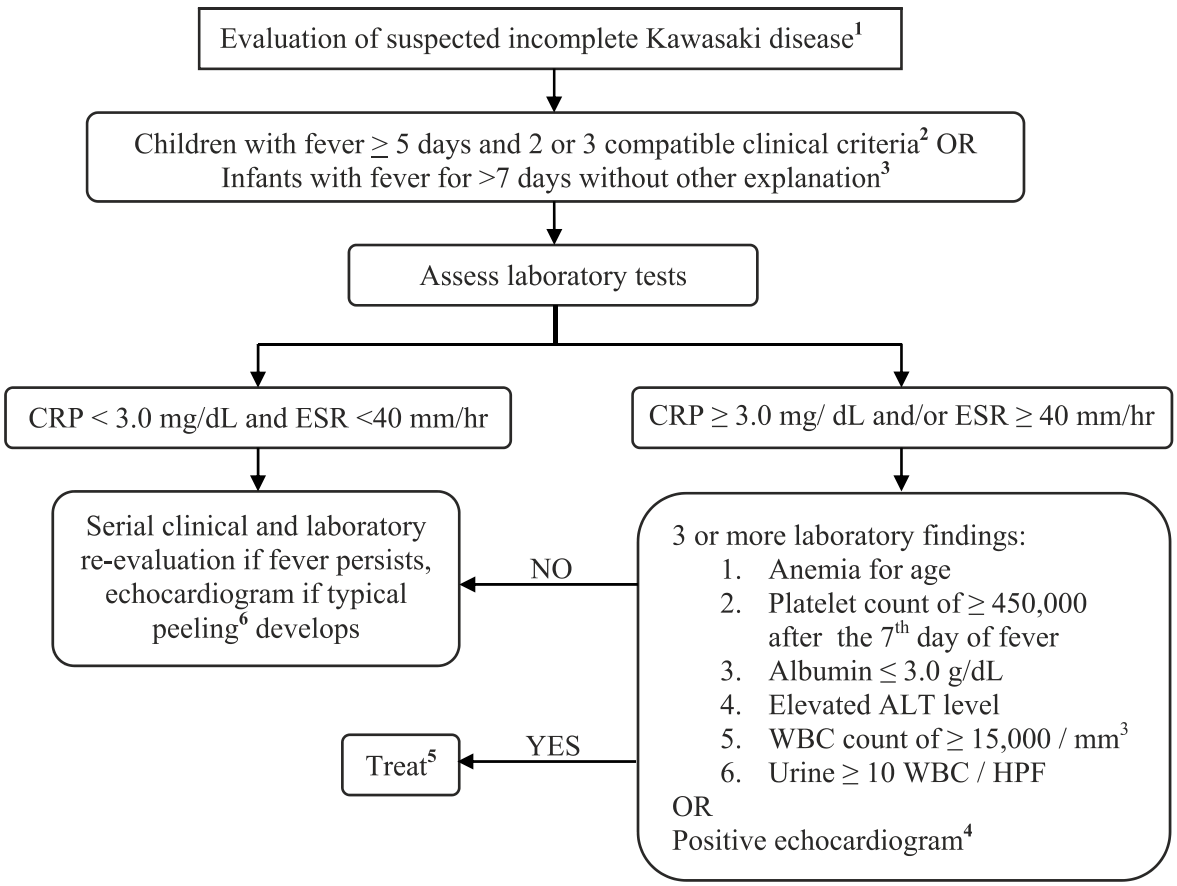

Fig.1. Evaluation of suspected incomplete Kawasaki disease*

**In the absence of a "gold standard" for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee.*

coronary artery or right coronary artery of 2 to 2.5. If the echocardiogram is positive, treatment should be given within 10 days of onset of fever even if the diagnostic criteria not fulfilled or after the tenth day of fever in the presence of clinical and laboratory signs of ongoing inflammation.

Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy or splenomegaly.

Scoring system to predict high-risk cases

Several scoring systems have been developed to identify children at highest risk of IVIG resistance and hence highest risk of developing CAA. Kobayashi, et al.[2] developed a model to predict unresponsiveness to IVIG in Japanese children with KD based on a cut-off point ≥4 calculated as per below: sodium ≤133 mEq/L (2 points); days of illness at initial treatment ≤4 (2 points); aspartate aminotransferase≥100 IU/L (2 points); percentage of neutrophils ≥80% (2 points); CRP ≥100 mg/L (1 point); age ≤12 months (1 point); platelet count ≤300x 10^9/L (1point). In non-Japanese children, a positive Kobayashi score might identify a patient at high risk of IVIG resistance, but a negative score may not reliably exclude a high-risk case.

Investigations[3]

- In a child with KD, the following laboratory values should be determined: ESR, CRP, complete blood count and liver function tests (bilirubin, AST/ALT), albumin, electrolytes, renal function and urinalysis.
- Cerebrospinal fluid analysis may be important to rule out infectious meningitis.
- All patients with suspected KD should undergo echocardiography and ECG at baseline, as soon as the diagnosis is suspected.
- An intermediate echocardiogram, 2 weeks after the first IVIG, should be performed in all patients with KD whose initial echo was normal and in whom disease activity has been arrested.
- All patients with KD should undergo echocardiography at 6-8 weeks after disease onset.
- In those with ongoing active inflammation (increasing or persistently elevated CRP and/or persisting signs and symptoms), ECG and echocardiography should be performed at least weekly to monitor the possible development of cardiac sequelae.
- In those with coronary abnormalities detected on initial echo, echocardiography should then be performed at least weekly to monitor progression until there is clinical stabilization.
- In children with CAA, ECG and echocardiography should be performed 3- to 6-monthly, depending on the severity of the CA.
- The following laboratory values are important in monitoring inflammation: ESR, CRP and complete blood count.
- Ferritin and fibrinogen should be considered if there is a concern for macrophage activation syndrome.
- The following laboratory values can be important in assessing risk stratification for IVIG resistance: low sodium, raised bilirubin, raised ALT, low platelet count, high CRP, low albumin.

Classification of coronary artery abnormalities[3]

Z-Score classification

1. No involvement: Always <2

2. Dilation only: 2 to <2.5; or if initially <2, a decrease in *Z* score during follow-up ≥1

3. Small aneurysm: ≥2.5 to <5

4. Medium aneurysm: ≥5 to <10 and absolute dimension <8 mm

5. Large or giant aneurysm: ≥10, or absolute dimension ≥8 mm

Treatment[3]

1. Patients with complete KD criteria and those who meet the algorithm criteria for incomplete KD should be treated with high-dose IVIG (2 g/kg given as a single intravenous infusion) within 10 days of onset but as soon as possible after diagnosis.

2. It is reasonable to administer IVIG to children presenting after the 10th day of illness (i.e. in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation or coronary artery abnormalities together with ongoing systemic inflammation, as manifested by elevation of ESR or CRP (CRP >3.0 mg/dL). IVIG generally should not be administered to patients beyond the tenth day of illness in the absence of fever, significant elevation of inflammatory markers, or coronary artery abnormalities.

3. The ESR is increased by IVIG therapy and therefore should not be used to assess response to IVIG therapy. A persistently high ESR alone should not be interpreted as a sign of IVIG resistance.

4. Administration of moderate- (30-50 mg/kg/day) to high-dose (80-100 mg/kg/day) acetyl salicylic acid (ASA) is reasonable until the patient is afebrile, although there is no evidence that it reduces coronary artery aneurysms.

IVIG resistance[3]

Approximately 10% to 20% of patients with KD develop recrudescence or persistent fever at least 36 hours after the end of their IVIG infusion and are termed IVIG resistant.

Options for IVIG-Resistant KD (Table II)

1. It is reasonable to administer a second dose of IVIG (2 g/kg) to patients with persistent or recrudescent fever at least 36 hours after the end of the first IVIG infusion.

2. Administration of high-dose pulse steroids (usually methyl prednisolone 20-30mg/kg intravenously for 3 days, with or without a subsequent course of oral prednisolone (2mg/kg/day and tapered over 15 days) may be considered as an alternative to a second infusion of IVIG or for retreatment of patients with KD who have had recurrent or recrudescent fever after additional IVIG.

3. Administration of infliximab (5 mg/kg) may be considered as an alternative to a second infusion of IVIG or corticosteroids for IVIG-resistant patients.

4. Administration of cyclosporine may be considered in patients with refractory KD in whom a second IVIG infusion, infliximab or a course of steroids has failed.

5. Administration of immunomodulatory monoclonal antibody therapy (except TNF-á blockers), cytotoxic agents, or (rarely) plasma exchange may be considered in highly refractory patients who have failed to respond to a second infusion of IVIG, an extended course of steroids or infliximab.

In children with presence of giant aneurysms (internal diameter $\geq$ 8 mm, or Z-score $\geq$10, and/or coronary artery stenosis) warfarin should be administered (in addition to aspirin), after initial heparinization; heparin can be stopped when a stable INR between 2 and 3 is reached. Low molecular weight heparin is a suitable alternative, particularly in young infants where safe warfarinization can be challenging. If symptoms of ischemia or obstruction occur in a patient with KD, a pediatric cardiologist/cardiac

Table II. Treatment options for IVIG-Resistant KD

Agent	Description	Dose
Most frequently administered		
IVIG: Second infusion	Pooled polyclonal IG	2 g/kg IV
IVIG + prednisolone	IVIG + steroid	IVIG: 2 g/kg IV + Inj. Methyl prednisolone 30 mg/kg/day (max 1g) x 3 days or prednisolone 2 mg/kg/d IV dividedevery 8 hour until afebrile, then prednisone orally until CRP normalized, then taper over 2-3 weeks
Infliximab	Monoclonal antibody against TNF-α	Single infusion: 5 mg/kg IV given over 2 hours
Alternative treatments		
Cyclosporine	Inhibitor of calcineurin- nuclear factor of activated T cell cytoplasmic (NFATc) pathway	IV: 3 mg/kg/d divided every 12 hours PO: 4-8 mg/kg/d-1 divided every 12 hours Adjust dose to achieve trough 50-150 ng/mL; 2 hourspeak level 300–600 ng/mL
Anakinra	Recombinant IL-1β receptor antagonist	2-6 mg/kg/d given by subcutaneous injection
Cyclophosphamide	Alkylating agent blocks DNA replication	2 mg/kg/d IV
Plasma exchange	Replaces plasma with albumin	Not applicable

surgeon/interventional radiologist (depending on local expertise available) should be consulted immediately.

Live vaccines such as MMR or varicella should be deferred for at least 11 months after administration of IVIG 2g/kg for KD.

Summary

The ultimate goal in the treatment of Kawasaki disease is the prevention of significant coronary artery abnormalities. However, young adult patients continue to present with CAD or sudden death presumed to be secondary to complications of a remote episode of KD during childhood. The Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations provide international, evidence-based consensus recommendations among pediatric rheumatologists for the diagnosis and treatment of KD in children, facilitating improvement and uniformity of care.

Points to Remember

- ***Children with acute Kawasaki disease should be treated promptly with intravenous immunoglobulin to prevent coronary artery abnormalities.***
- ***Children with persistent or recrudescent fever after primary therapy with IVIG should receive additional immunomodulatory therapy. The most common practice is administration of a second dose of IVIG at 2 g/kg.***
- ***Other secondary therapies to be considered include corticosteroids and infliximab.***
- ***Echocardiography is an excellent modality for assessing proximal coronary artery changes in infants and young children with early KD.***
- ***In patients with KD and coronary aneurysms, cardiac evaluation is tailored to the degree of coronary artery involvement and involves serial assessment of coronary function and structure.***

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CLIPPINGS

DNA Viremia Is Associated with Hyperferritinemia in Pediatric Sepsis.

Study was undertaken to evaluate the detection of DNA viruses, ferritin and outcomes in children with severe sepsis.

75 children were enrolled with severe sepsis at a pediatric tertiary care hospital for this study. Plasma ferritin was measured within 48 hours of admission and subsequently biweekly. Herpes simplex type 1, human herpes virus 6, Epstein-Barr virus, cytomegalovirus and adenovirus DNA viremia were assessed by PCR.

Authors have stated that the incidence of DNAemia was increased significantly in patients with ferritin $\geq$1000 ng/mL (78% vs 28%; $P < .05$). Patients with ferritin $\geq$1000 ng/mL were more likely to have multiple DNA viruses detected in plasma (39% vs 4%; $P < .001$). The number of viruses detected in plasma directly correlated with the degree of hyperferritinemia and development of combined hepatobiliary and hematologic dysfunction after controlling for bacterial and fungal co infections ($P < .05$) .(OR 2.6, 95% CI 1.1-6.3, $P < .05$).

Authors concluded that viral DNAemia was associated with hyperferritinemia and adverse outcomes in pediatric sepsis. Occult DNAemia may be identified by serum ferritin levels in children with sepsis.

Simon DW, Halsted ES, Davila S, Keran KF, Clark RS, Storch G, et al. DNA Viremia Is Associated with Hyperferritinemia in Pediatric Sepsis. J Pediatr 2019: 213:82-87.e2.

IAP-IJPP CME 2019

N-ACETYL CYSTEINE IN LIVER DISEASE

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Abstract: *N-acetyl cysteine, a glutathione precursor has been accepted universally for nearly five decades for paracetamol or acetaminophen induced hepatitis and acute liver failure. However early administration with appropriate dosing needs to be stressed since it may not be that effective if there is a delay in administration. Paracetamol toxicity may occur either due to acute poisoning or multiple supra-therapeutic dosing and the management differs. Liver transplantation can be deferred if the pediatrician recognizes the etiology and initiates therapy at the right time. Interest has now turned to use of N-acetyl cysteine in non-paracetamol drug induced liver injury, acute liver failure and in other liver diseases associated with oxidative stress. This article highlights the use of N-acetyl cysteine in various liver diseases and opens vistas where further studies are required.*

Keywords: *N-acetyl cysteine, Paracetamol, Supratherapeutic dose.*

N-acetyl cysteine (NAC) is a precursor of glutathione (GSH). It is a slightly modified form of a sulphur containing amino acid cysteine, which is produced in the body from methionine and serine and is a semi essential amino-acid. Foods containing cysteine are chicken, meat, onion, garlic, yogurt, eggs and turkey.

Metabolism of NAC: When NAC is administered orally it is rapidly absorbed in the intestine, achieves plasma concentration in 1-2 hours and only 3% is excreted in the feces.[1] NAC goes through an extensive first pass metabolism in the liver, then undergoes deacetylation to form cysteine which combines with glutamate in the presence of glutamate cystein ligase and forms glutamylcysteine. The latter in combination with glycine in the presence of GSH synthase forms glutathione (Fig.1).

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Box 1. Pharmacological actions of N-acetyl cysteine

- Replenishes cytosolic and mitochondrial stores of glutathione
- Promotes detoxification
- Scavenger of free oxygen radicals
- "Powerful" antioxidant
- Anti inflammatory properties
- Positive inotropic effects
- Increases local nitric oxide concentration
- Improves insulin sensitivity
- Alters immune mechanisms
- Promotes microcirculatory blood flow
- Enhances oxygen delivery to peripheral tissues
- Nutritional supplement excellent source of sulphdryl groups
- Prevents apoptosis and oxygen related genotoxicity
- Reduces reactive oxygen species (ROS)

NAC has a wide spectrum of pharmacological actions (Box 1). The main functions are to replenish cytosolic and mitochondrial stores of glutathione, promote detoxification, act as a powerful antioxidant and help in scavenging free oxygen radicals.[2]

It has been more than 50 years since NAC is an established drug and has been listed in WHO list of essential medicines. Its wide spread indications are listed in Table I. In liver disease, NAC acts as a glutathione precursor and protects against metabolic hepatocellular injury especially from acetaminophen overdosage.

Indications of NAC in liver disease

The main indications for NAC in liver disease can be divided into two groups (Fig.2).

I. Paracetamol related liver disease

Paracetamol or acetaminophen is a safe, effective, well

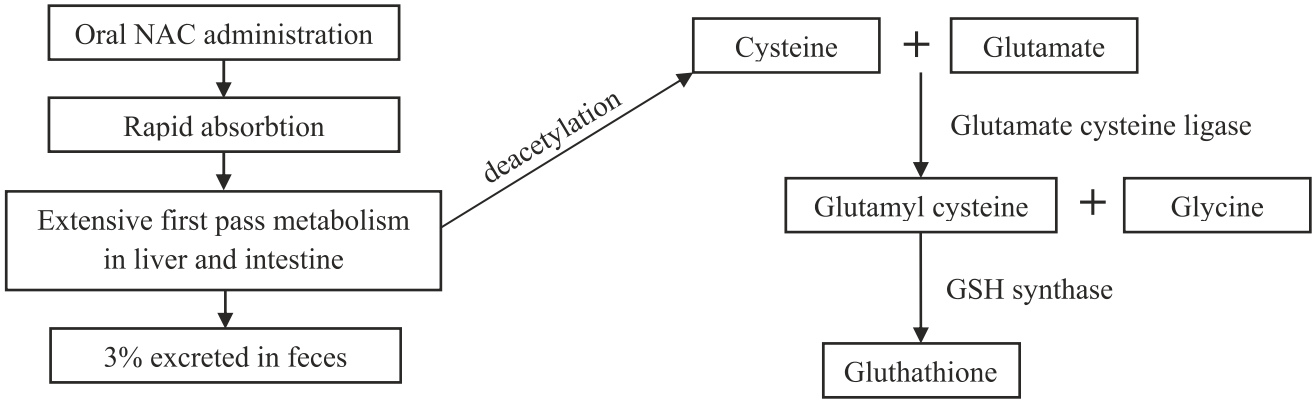

Fig.1. Metabolism of NAC

Table I. Uses of NAC

Speciality	Use
Pulmonology	Chronic bronchitis, chronic emphysema, chronic obstructive pulmonary disease, asthma, influenza, idiopathic pulmonary fibrosis, smoke induced cancer prevention and cystic fibrosis because of its mucolytic, anti inflammatory and antioxidant properties
Dermatology	Skin lightener because of the antioxidant property
Nephrology	Kidney protective specially in contrast induced nephropathy
Neurology	Alzheimer disease, obsessive compulsive disorder and schizophrenia, by decreasing the level of oxidative markers it protects mitochondria.
Gynaecology	Polycystic ovarian disease, recurrent pregnancy loss and in prevention of prematurity by decreasing placental oxidative stress and regulating some gene expression responsible for it.
Infertility	Improves male infertility
Cardio vascular disease	Decreases risk of heart disease
	Regulates scores of genes and alters immune mechanism
Gastroenterology	Gastric ulcer, anti H pylori (by breaking the mucous layer under which H pylori resides, reduces inflammatory cytokines), ulcerative colitis and prevention of colon cancer
Sport's medicine	Helps in maintaining good exercise performance
Endocrinology	Reduces oxidative stress and decreases insulin resistance and maintains blood sugar
Oncology	Prevents cancer because of its anti-oxidative stress and anti-inflammatory property. In addition, causes programmed cell death, induce apoptosis and stops DNA synthesis in cancer cells.
Ophthalmology	Diabetic retinopathy, age related macular degeneration, dry eye syndrome

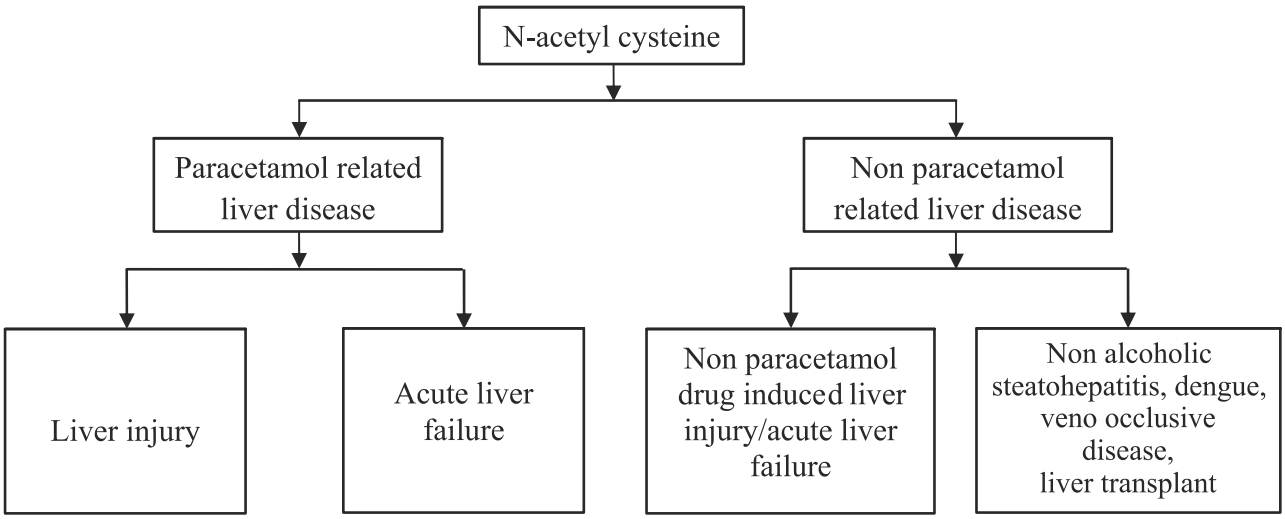

Fig.2.Indications for NAC in liver disease

tolerated antipyretic and analgesic when age appropriate therapeutic doses are administered for a limited period. The toxic potential of ingestion of a single large dose is well recognized. However, the hepatotoxic potential of multiple supratherapeutic doses of paracetamol in sick children is less well recognized. In USA and Europe, paracetamol (acetaminophen - N-acetyl-p-aminophenol, APAP) is the most common cause of acute liver failure (ALF) and was seen in 14% of 348 cases of ALF.[3] An unpublished data from Chennai reveals APAP contributing around 22% of pediatric acute liver failure. The incidence of hepatotoxicity increases with age; 5.5% in children <5 years and 29% in adolescents at comparable toxic blood levels.[4] Paracetamol causes dose dependent direct hepatotoxicity.

When paracetamol is taken in therapeutic doses, most of the drug is metabolized by a) glucuronidation (50-60%) into a non toxic glucuronide moiety and b) sulfation (30-40%) into non toxic sulfate moiety. A very small amount is metabolized to a toxic product N acetyl p benzo quinone imine (NAPQI) by the hepatic enzyme P450 2E1 (CYP2E1). This is normally conjugated by glutathione provided by the liver into non toxic metabolite mercapturic acid and cysteine. When there is overdosage of paracetamol, the sulfation and conjugation pathways are saturated and NAPQI is in excess. The liver is unable to provide sufficient glutathione and therefore the toxic metabolites NAPQI accumulate. NAPQI is highly reactive and binds to cell macromolecules, impairs mitochondrial and nuclear function leading to cell death. NAPQI is formed within minutes of paracetamol presentation to cytochromes P450 and continues to be formed as long as substrate is available (Fig.3).

NAC reduces the amount of NAPQI formed through a prearylation mechanism. It can prevent NAPQI induced cytotoxicity and may restore cellular function sufficient to reduce tissue injury. NAC has demonstrated therapeutic superiority both in efficacy and safety to other treatments and has been globally adopted as the antidote of choice for paracetamol toxicity. NAC provides the glutathione which is required to tide over the problem (Fig.3).

Paracetamol toxicity can occur in two situations: (a) Acute overdose or poisoning (>150-200mg/kg/day): This may occur as suicidal attempt in older children/adolescents, accidental ingestion by toddlers and rarely homicidal and (b) Repeated supra therapeutic dose (>75 mg/kg/day over 48 hours or 100 mg/kg/day).[5,6] This untoward event can occur as a therapeutic misadventure or as suicidal attempts. Toxicity is seen when the calculated paracetamol dosage is >200 mg/kg or (10g) ingested over 24 hours, $\geq$150 mg/kg/day (or 6g) ingested over a 48 hour period or $\geq$100 mg /kg/day ingested over a 72 hour period.[6]

Lower dose becomes hepatotoxic in the presence of malnutrition, poor diet, prolonged febrile illness, underlying inborn error of metabolism, fatty acid oxidation defects and when there is concomitant administration of drugs (phenobarbital, rifampin, phenytoin and carbamazepine) which induce cytochrome P450 activity. Though the risk of toxicity is less in infants and younger children compared to adolescents, the delay in presentation and treatment increases the risk of hepatocellular injury.[7,8]

Clinical presentation of paracetamol toxicity: The following four phases are usually seen.

Phase 1: First 24 hours: Initial 4-6 hours the child may be

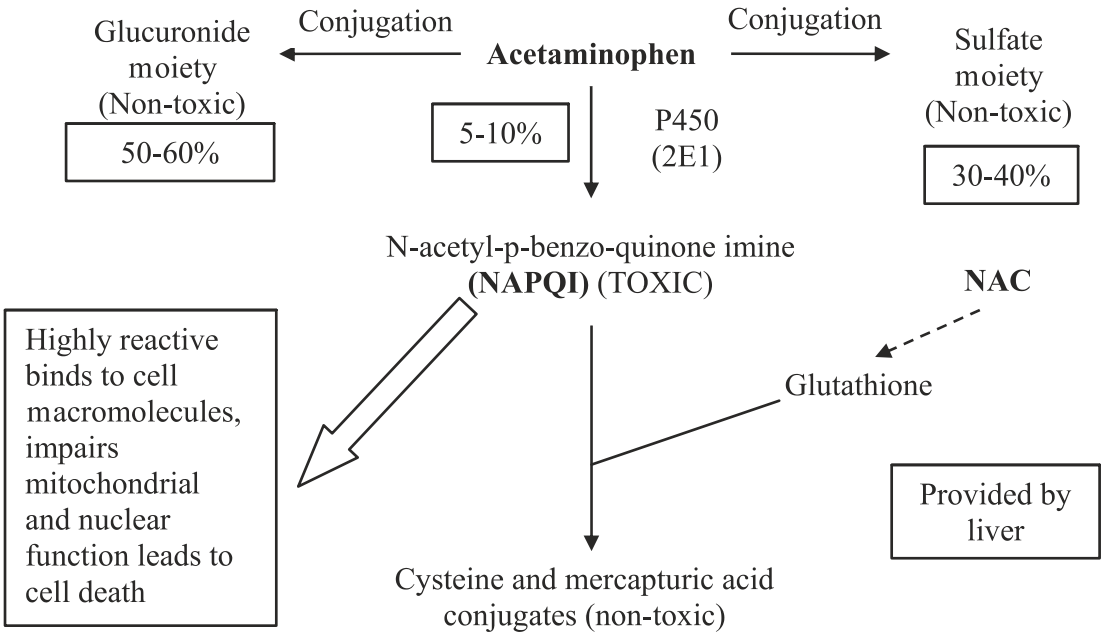

Fig.3.Paracetamol metabolism and toxicity

asymptomatic. Malaise, nausea, pallor, vomiting may be present. The majority will show elevation of liver enzymes within 24 hours.

Phase 2: 24-72 hours. The child presents with right hypochondrial pain, tenderness, tachycardia, oliguria and hypotension. The laboratory parameters show elevation of bilirubin, transaminases and prothrombin time.

Phase 3: 72-96 hours. Maximal hepatotoxicity is seen in this phase. Child continues to be sick with jaundice and peak level of transaminases. The hepatitis progresses to acute liver failure (ALF), encephalopathy, GI bleed, renal failure, multi organ dysfunction syndrome and death.

Phase 4: 4 days - 3 weeks. This phase may lasts for 3 weeks. Those who survive phase 3 recover without sequelae. There is no report of progressing to chronicity.

Predictors for low risk of hepatotoxicity

The predictors for low risk are[9]

1. Normal value of transaminases and prothrombin time 48 hours after ingestion.

2. The combination of paracetamol level below the probable toxicity line on the nomogram combined with the absence of elevated transaminases and prothrombin time 24 hours after ingestion.

In children, toxic levels of serum paracetamol with an elevated prothrombin time 24 hours post ingestion has higher sensitivity and better negative predictive value for hepatotoxicity than elevated transaminases.

Acetaminophen-cysteine adducts: Accurate history of paracetamol exposure in children is at times difficult and therefore Acetaminophen-cysteine adducts (APAP-CYS) are often used as a specific biomarker of acetaminophen exposure and a concentration >1.1 nmol/ml indicates hepatic injury with an ALT >1000 IU/L.[10] However this investigation is not readily available and is used more for research purposes.

Management of paracetamol toxicity

In acute poisoning: Baseline investigations like complete blood count, biochemical tests of the liver, prothrombin time, creatinine, arterial blood gas (ABG) analysis should be checked. Paracetamol levels should be checked 4 hours post ingestion since the peak plasma level occurs at this time. There is no benefit in checking levels earlier than 4 hours. The level obtained is marked on the Rumack–Mathew nomogram which is widely available. A level more than 200 mcg/ml is considered as probable toxicity and if level is 150-200 mcg/ml it is taken as possible toxicity and treatment is initiated. This nomogram is useful only in acute poisoning.

The treatment for paracetamol poisoning with NAC should be started as soon as possible since NAC works best when started within 8 hours post ingestion and hepatotoxicity during this period is as low as 10%.When

treated appropriately 94% recovery has been noted. Incidence of hepato toxicity is 8-50% when NAC is given more than 8 hours post ingestion.[8] Though NAC works best when given early it may be given even up to 24 hours post ingestion.

ii) In therapeutic misadventure: The baseline investigations and paracetamol level are done. NAC is administered even if paracetamol levels are normal and if the symptoms of vomiting, right hypochondriac pain, jaundice or alanine transaminase (SGPT) >50 IU/L or INR is elevated. NAC is also administered if level of paracetamol is more than 10 mcg/ml.[11]

NAC preparation and dosage: The oral and intravenous preparations of NAC are both effective. The oral dose is 140 mg /kg loading dose followed by 17 doses of 70 mg / kg every 4 hours given for over 72 hours. The intravenous route is preferred since it is well tolerated and the correct dosage can be administered. The loading dose of 150 mg / kg is infused over 60 minutes then 50 mg /kg over 4 hours followed by 100 mg /kg over 16 hrs .Blood samples for serum bilirubin, transaminases, prothrombin time and paracetamol should be drawn 2 hours before completion of the dosing. NAC should be administered till paracetamol levels are <10 mcg/ml and child is well with normal liver parameters.

In case of ALF, NAC should be continued till i) transaminases fall to less than 1000 IU/L, bilirubin and prothrombin time are normal and child is well or ii) child receives liver transplant or iii) child dies.

Adverse reactions

Adverse reactions to N-acetyl cysteine are seen in 5-10% of children. The adverse reactions depend on the route of administration. The side effects with oral NAC are nausea, vomiting, abdominal pain, diarrhea, rash and a peculiar smell may interfere with intake. For intravenous route the side effects are nausea, vomiting, abdominal pain, diarrhea, rash (less than seen with oral). Higher incidence of anaphylactoid reactions (0-48%) like urticaria, pruritus, angioneurotic edema, severe bronchospasm and hypotension may occur at the start of treatment when concentrations are highest.[11,12] Life threatening reaction is seen in <5% .

A simple, relatively safe, cheap molecule (Rs.47/ 200mg ampoule, Rs.18 /600 mg tab) when given at the right time can avoid a complicated, costly (Rs.17-30L) therapeutic intervention like liver transplantation.

II. Non paracetamol induced liver disease and NAC

i) Non paracetamol drug induced liver injury (DILI): NAC in the management of non paracetamol DILI has always been a topic of interest. In 2016, a systematic review of transplant free survival in NAC group versus placebo showed similar survival rate. Hence, NAC is not recommended in non paracetamol DILI till further studies.[13]

ii) Non paracetamol induced ALF: NAC for paracetamol induced ALF has been accepted and recommended as the treatment of choice. The efficacy, safety and the several useful pharmacological mechanisms of action of NAC were strong reasons for researchers to study the usefulness of NAC in non paracetamol induced ALF. In 2005, a retrospective analysis of 171 children with ALF was published with very encouraging results. 111 children mean age 3.5 years with ALF were given IV NAC.150 mg/kg/ 24hr continuously till INR normalised. Mean duration of treatment was 5 days. Survival with native liver was better in the NAC group. Liver transplant (LT) and death following transplant were also less in the NAC group which was statistically significant. They concluded that NAC administration in non-acetaminophen ALF is safe and is associated with higher native liver recovery without LT, and also better post- LT survival.[14] Similar results were published in 2009 in adults in a prospective, double-blind trial, in patients with ALF without clinical or historical evidence of acetaminophen overdose.[15] The possible mechanism for the action in non paracetamol ALF could be the effect of NAC on cytokines.[16] Contrary to these results, in 2013 a double masked placebo controlled study in 184 children with ALF (92 placebo, 92 NAC) was published. Secondary outcome 1 year liver transplant free survival was lower in NAC group 35% vs 53% in placebo group and this was more significant in children <2 years of age. There was no benefit of NAC in those with milder grade (I-II) of hepatic encephalopathy.[17] Thus NAC could not be accepted as the treatment of choice in non paracetamol ALF.

iii) Liver transplantation: NAC has shown to have protective effects on hypothermic and warm ischemia reperfusion liver injury in animal studies. However, NAC has not shown proven efficacy to improve hemodynamics and graft function in liver transplantation. In a prospective double blind randomised control trial administering perioperative NAC had no benefit on i) early graft function, ii) post operative renal function iii) post operative recovery following living donor liver transplantation (LDLT).[18]

iv) Hepatic veno occlusive disease (VOD) following allogenic stem cell transplant (ASCT): Hepatic VOD is a serious complication following allogenic stem cell transplantation and following chemotherapy. The incidence is 10-70% with a mortality of 30-50%. NAC has been proposed to reduce cell death mediated by oxidative stress. A case series of 9 children with VOD treated with N-acetyl cysteine intravenously responded well to NAC therapy.[19]

v) Non alcoholic steatohepatitis (NASH): In a few studies NAC has shown a significant decrease of serum alanine aminotransferase after three months, compared to vitamin C. This effect was independent of the grade of steatosis in the initial diagnosis.[20] NAC was also able to significantly decrease the span of the spleen.[21]

vi) Dengue associated ALF: Case reports of improvement in liver indices following NAC in dengue has been reported suggesting possible usefulness of paracetamol in dengue associated ALF.[22,23] The actual dosing and duration of therapy is still not known.

Points to Remember

- ***N-acetyl cysteine is the drug of choice in paracetamol overdose in children.***
- ***In non paracetamol pediatric acute liver failure response to NAC is not uniform and more studies are required.***
- ***NAC has been reported to be beneficial in veno occlusive disease, NASH, dengue induced ALF and wherever glutathione depletion and oxidative stress is evident.***
- ***NAC should not be used as a panacea for all liver diseases.***
- ***Paracetamol toxicity is preventable and utmost care should be taken to give the correct dose.***

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VESICOURETERAL REFLUX IN CHILDREN - A PRACTICAL GUIDE

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Abstract: *Vesicoureteral reflux is commonly present in children with urinary tract infections or antenatal hydronephrosis. The gold standard for vesicoureteral reflux diagnosis remains micturating cystourethrogram. Vesicoureteral reflux may be associated with renal scarring, hypodysplasia and bowel bladder dysfunction. The goal of vesicoureteral reflux management is to prevent recurrent urinary tract infections and long term consequences in the form of hypertension and chronic kidney disease. Continuous antibiotic prophylaxis remains the recommended management strategy for all vesicoureteral reflux children while awaiting spontaneous resolution. Surgery is indicated only for a few selected children with vesicoureteral reflux. Long term follow up of vesicoureteral reflux patients by pediatric nephro-urologist as well as the pediatrician is crucial.*

Keywords: *Vesicoureteral reflux, Renal scarring, Continuous antibiotic prophylaxis, Bowel bladder dysfunction.*

Vesicoureteral reflux (VUR) is defined as the retrograde passage of urine from the urinary bladder to the ureters and kidneys.[1] VUR is the commonest congenital anomaly of the urinary tract in children. The reported prevalence in the general population is about 0.5 to 3% but is much higher (30-40%) in children undergoing evaluation for urinary tract infections (UTI). VUR is present in 30% of infants with antenatal hydronephrosis.[2] Siblings of children with VUR and children of a parent with VUR have an increased prevalence of having reflux, approximately 30%.[3]

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Primary vs secondary VUR

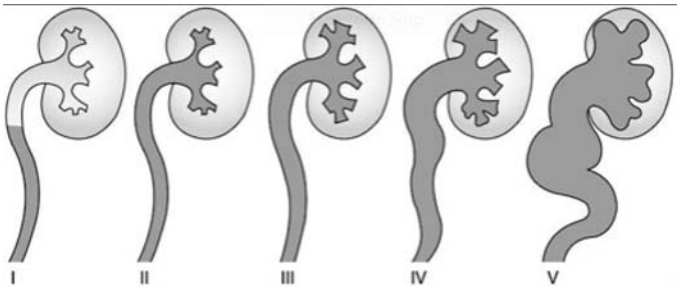
Primary VUR is a common but isolated condition where urine "flows backwards" from the bladder into the ureters and/or kidneys. A shortened intramucosal length of the ureter within the bladder wall leads to an incompetent ureterovesical junction. Secondary VUR is rare. It occurs due to high pressures in the bladder during voiding. Children with posterior urethral valves (anatomic bladder obstruction) or neurogenic bladders (functional obstruction) may have secondary VUR. This article focuses on primary VUR only.

Natural course of VUR

VUR often undergoes spontaneous resolution, but the likelihood of resolution depends on age, sex, the severity of reflux and the presence of bowel bladder dysfunction (BBD). Higher grades of VUR are much less likely to resolve spontaneously. During a mean follow up of two years, VUR grade I to V had rates of spontaneous resolution of 72%, 61%, 49%, 25%and 10% respectively.[4] Bilateral reflux and BBD are associated with delayed resolution. Quicker resolution is observed in children who are less than 1 year at presentation, with a lower grade of reflux (I-III) and those who are asymptomatic (e.g. detected during sibling screening).[4] Recognizing and managing VUR is also associated with a decrease in the development of chronic kidney disease (CKD) which occurs more commonly in children with severe VUR.

VUR - When to suspect?

Screening for VUR should be done in children with an episode of UTI, in those with antenatal hydronephrosis or if there is a sibling/parent with known VUR. A micturating cystourethrogaram (MCU) also known as voiding cystourethrogram (VCUG) is the gold standard test to confirm the diagnosis of VUR. MCU can provide information about the presence and severity of VUR. In addition to making the diagnosis, it is important to note if the VUR is unilateral or bilateral. The bladder and urethral anatomy are also important to note on an MCU, especially during voiding. Abnormalities in the latter may indicate a secondary cause for VUR. MCU is performed in a radiology suite after catheterising the child with a small



Grade I	Reflux does not reach renal pelvis Varying degrees of ureteric dilatation present
Grade II	Reflux reaches renal pelvisNo dilatation of collecting system
Grade III	Mild to moderate dilatation of ureters with or without kinking Moderate dilatation of collecting system
Grade IV	Grade 3 with blunted fornices Papillary impressions visible
Grade V	Gross dilatation and kinking of ureter Marked dilatation of collecting system Papillary impressions not visible Intraparenchymal reflux present

Fig.1. Grading of vesicoureteric reflux[5]

feeding tube. Antibiotic prophylaxis is administered and the entire procedure is done under strict aseptic conditions. Fig.1 describes the grades of VUR.[5] Table I summarises the three important radiological tests required to evaluate a patient with suspected VUR.

Associations of VUR

Renal scarring: VUR is associated with an increased risk of UTI and renal scarring.[6] UTI is associated with morbidity and increased risk of hospitalisation. Infections trigger inflammatory pathways culminating in renal scarring and fibrosis.[7] Renal scarring is associated with proteinuria, hypertension and permanent reduction in renal function.[8] The latter cause for chronic kidney disease (CKD) is termed reflux nephropathy.[6] The main risk factors for renal scarring are febrile UTIs, high-grade VUR (IV and V), history of recurrent UTI before diagnosis of VUR and age more than 1 year at diagnosis.[9] Among children with CKD, reflux nephropathy was the etiology in 19% in a large prospective study of American children.[10] Prevalence of reflux nephropathy was found to be 6% of CKD patients.[11]

Renal hypodysplasia: Primary VUR can be associated with congenital renal hypodysplasia. Renal hypoplasia refers to a reduced number of nephrons, whereas dysplasia refers to the presence of qualitatively abnormal nephrons. Both hypoplasia and dysplasia are often present together.[12]

Table I. Radiological investigations in a child with suspected VUR

Test & Procedure	Findings to note	Advantages	Challenges	Role
Ultrasound of Kidneys and Urinary Bladder	-Ensure normal kidney number and location -Hydronephrosis (if present, indicates likely VUR) -Bladder anatomy	-Easily available -CheapNoninvasive -Can be performed at UTI diagnosis	-Low sensitivity in diagnosing VUR as well as scarring.	-Screening test for VUR
MCU -Contrast Xray of urinary bladder-Spot, filling and voiding films obtained	-Presence of VUR -Accurate grading of reflux -Bladder anatomy* -Urethral anatomy*	-Outpatient procedure- -No sedation -Determines primary vs Secondary VUR	-Invasive (bladder catheterization) -Risk of UTI despite antibiotics -Radiation exposure	-Essential to make VUR diagnosis
DMSA Nuclear imaging of renal parenchyma	-Scarring of renal parenchyma -Also split renal function	-Low radiation exposure -Useful for longitudinal monitoring of scarring	-Must wait 8-12 weeks after UTI has resolved	-Essential to detect renal scarring

*To diagnose posterior urethral valves or neurogenic bladder

MCU-Micturating cystourethrogram, DMSA-Dimercapto succinic acid, VUR-Vesico ureteral refux, UTI-Urinary tract infection

VUR, in association with hypodysplasia, indicates an increased risk of progression to CKD when compared to VUR alone. DMSA can help to differentiate renal scarring from dysplasia clearly. Congenital renal hypodysplasia shows a diffusely reduced tracer uptake by the affected kidney, whereas scars appear as focal defects of uptake. If hypodysplasia is present in a child with VUR, careful long term monitoring for deterioration of kidney function by a pediatric nephrology team is important.

Bowel bladder dysfunction (BBD): Bowel bladder dysfunction is a combined term for bowel and lower urinary tract disturbances (which simulate the bowel and bladder problems in children with neurological illness), without any recognisable neurologic illness.[13] A significant association is noted between BBD and VUR. Children with BBD have a lower spontaneous resolution of VUR, higher risk of UTI and higher rate of failure after endoscopic VUR surgery.[14] Symptoms and signs of BBD include urinary frequency and urgency, prolonged voiding intervals, daytime wetting, perineal pain, holding maneuvers, constipation and encopresis.[15] A tool like the dysfunctional voiding scoring system(DVSS) is useful to screen for BBD.[16] Simple measures like treating constipation and frequent, complete bladder emptying can improve BBD symptoms. Persistent or severe symptoms indicate a need for referral to a pediatric nephro-urology centre.

Key issues in the management of VUR

1. Missing the diagnosis

Any child with UTI, antenatal hydronephrosis or with siblings/parents with a history of VUR must be screened for VUR. Although a renal ultrasound is a useful, noninvasive tool to screen for hydronephrosis (a finding specific for high-grade VUR), it is not a sensitive test. A normal ultrasound does not rule out either VUR or renal scarring. Box 1 lists the key indications for obtaining an MCU in children.[17,18] Recent western guidelines advocate withholding an MCU for children with febrile UTI in many instances.[19] However, these recommendations assume that children will not have undiagnosed or inadequately treated UTI or lost to follow up. In our setting, where follow up is not as reliable, making the diagnosis of VUR is the key. The Indian society of pediatric nephrology (ISPN) recommend that an ultrasound, MCU, as well as DMSA, be obtained in all infants with UTI. From 1 year to 5 years, an MCU is advised if the ultrasound shows hydronephrosis, renal parenchymal scars on DMSA or if there are more than 1 UTI (recurrent UTI) in any child.[17] A normal DMSA scan without MCU may fail to detect about 5-27% of cases of VUR, but most of them would be expected to be of milder grades and likely to be of lower significance.[20] After 5 years of age, if the ultrasound is normal, further radiological workup is not necessary. A second (recurrent) UTI at any time point is an indication for an MCU.

Box 1. Indications for MCU in children[17,18]

- All infants with 1st episode of UTI
- Recurrent UTI in any age group
- Follow up of antenatal hydronephrosis if
  a) unilateral or bilateral hydronephrosis with APD >10 mm
  b) if they develop UTI
- Renal parenchymal scars detected on DMSA
- (First episode of UTI in post infancy boys and sibling screening of children with VUR are relative indications.)

MCU-Micturating cystourethrogram, UTI-Urinary tract infection, APD-Anteroposterior diameter, DMSA-Dimercapto succinic acid

2. Continuous antibiotic prophylaxis (CAP)

CAP is the long term administration of a small dose of oral antibiotics at night time. It is intended to attain good urinary levels in the bladder to maintain the sterility of the refluxing urine. CAP is based on the premise that prevention of recurrent UTI will reduce the risk of scarring while waiting for VUR to resolve spontaneously. In addition to the theoretical reduction in scarring risk, CAP may also prevent the morbidity associated with febrile UTIs in children. There is a concern that CAP may lead to antibiotic resistance in the long term. There have been several key studies evaluating the role of CAP in the prevention of recurrent UTIs.[2,21,22] These are summarised in Table II. Essentially, there was a reduction in the incidence of recurrent UTI with CAP when compared with placebo. However, CAP was not associated with a lower risk of scarring. These studies have limitations – very few patients with high-grade VUR were studied, and this group is the most at risk for development of CKD. Also, the studies were not powered adequately to detect a difference in scarring. A recent Cochrane review on long term antibiotics for preventing recurrent UTI in children concluded that there is a modest reduction in repeat symptomatic UTI in children on CAP.[23] While western guidelines may advocate the role of surveillance (monitoring for clinical symptoms of UTI without CAP), in our setting this approach may be associated with the risk of undetected recurrent UTI in children with poor

Table II. Key randomised clinical trials of antibiotic prophylaxis in the prevention of recurrent UTI[2,21,22]

Study Title	Study intervention	Patients	Duration of Follow up	Primary outcome	Secondary outcome
RIVUR	Cotrimoxazole vs placebo	603 children with VUR grade I-IV2 to 71 months	2 years	Recurrence of UTI reduced by 50% in CAP group	Scarring and antibiotic resistance was more in CAP group, but difference was not statistically significant
PRIVENT	Cotrimoxazole vs Placebo	780 children<18 yrs with UTI+/- VUR	1 year	Reduction of UTI episodes irrespective of VUR status in CAP group	No difference in renal scarring
Swedish Reflux trial	Surveillance vs CAP vs endoscopic correction	203 children 1 to 2 years Grade III-IV VUR	2 years	Reduction of UTI in girls on CAP	Scarring was high in the surveillance group

CAP-Continuous antibiotic prophylaxis, VUR-Vesico ureteral reflux, RIVUR-Randomised intervention for children with VUR, RCT-Randomised controlled trial, PRIVENT-Prevention of recurrent UTI in children with VUR and normal renal tracts, UTI-Urinary tract infection

Table III. VUR - ISPN Guidelines regarding continuous antibiotic prophylaxis (CAP)

Grade of VUR	Administration of CAP
I and II	Antibiotic prophylaxis till 1 year of age Restart antibiotic prophylaxis if breakthrough UTI afterwards
III to V	Antibiotic prophylaxis till 5 year of age Consider surgery if breakthrough febrile UTI
	Prophylaxis to be continued beyond 5 year if BBD present

CAP-Continuous antibiotic prophylaxis, ISPN-Indian society of pediatric nephrology, VUR-Vesico ureteral reflux, UTI-Urinary tract infection, BBD-Bowel bladder dysfunction (Adapted from reference.[17])

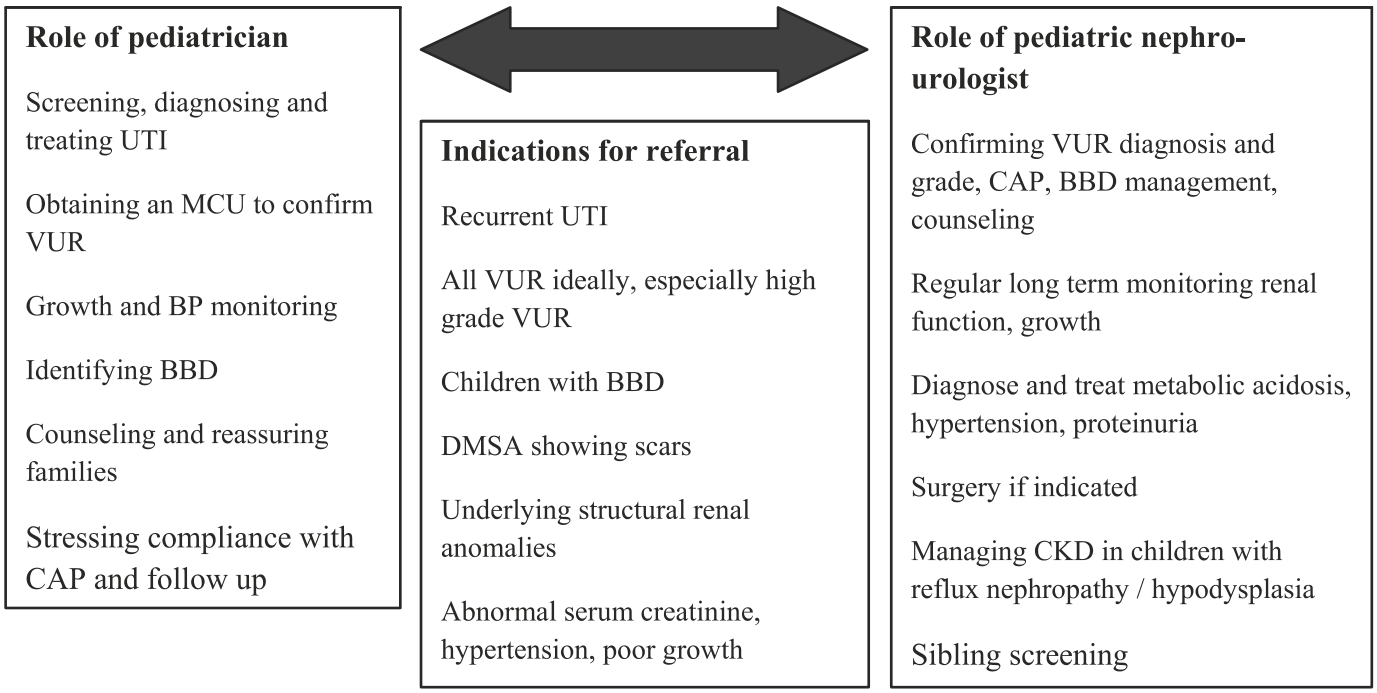
follow up. Therefore, the ISPN recommends CAP in all children with VUR for varying lengths of time as summarised in Table III.

3. Role of surgical treatment for VUR

Since the majority of VUR spontaneously resolve over time, surgical correction is usually not considered as a first line option. Surgical correction of VUR has not been proven to be superior to medical management.[24] Low grades of VUR almost never require surgical correction. Children with the persistence of grade IV/V reflux beyond 4-5 years (who are unlikely to resolve spontaneously), those with recurrent breakthrough UTI, the progression of renal scarring, progressive reduction in renal function or other congenital anomalies of the kidneys and urinary tract (CAKUT) should be referred to a pediatric surgery/urology centre. Open surgical reimplantation is associated with high success rates, but longer hospitalisation. Endoscopic techniques are also available, but their success rates depend on the centre and complications are possible. Circumcision is advised for male infants with a history of febrile UTI and higher grades of VUR and has been shown to prevent recurrent UTI.[14,25]

4. Ensuring long term follow up

The children with VUR require long term follow up to monitor for breakthrough UTI, the progression of



UTI-Urinary Tract Infection, BP-Blood pressure, BBD-Bowel bladder dysfunction, MCU-Micturating cystourethrogram, VUR-Vesico ureteral reflux, CAP-Continuous antibiotic prophylaxis

Fig.2. Managing VUR successfully: A partnership among pediatricians

scarring and documentation of resolution of VUR. Although most children with VUR should establish care with a pediatric nephro-urology centre, the role of the primary pediatrician is critical in ensuring follow up. Pediatricians should monitor growth, monitor for hypertension and educate families regarding symptoms of UTI. Every suspected UTI must be confirmed with a urine culture collected appropriately before starting empiric antibiotics. This is required to document breakthrough UTIs. Encouraging families to visit the pediatric nephro-urology centre will make a greater impact on the outcomes of the child with VUR than counselling by a specialist centre alone. Fig.2 outlines the ideal roles of both pediatrician and specialist centre as a partnership.

Conclusion

VUR is one of the most frequently encountered urological abnormalities in children and is likely to be encountered in a pediatrician's practice. Confirming the diagnosis of VUR with an MCU is vital in children with risk factors. Being familiar with the role of various radiological tests in VUR is useful in diagnosing and planning further management. VUR, especially high grades or if associated with hypodysplasia, may be associated with the risk of CKD and therefore warrants CAP, screening for BBD, monitoring and treatment of breakthrough UTIs and long term regular follow up. Although referral of all children with VUR to a pediatric nephron-urology centre is important, the role of the pediatrician is critical in improving outcomes.

Points to Remember

- ***The most common congenital anomaly of the urinary tract is VUR with serious consequences such as CKD.***
- ***Any child with UTI, antenatal hydronephrosis or with siblings/parents with a history of VUR must be screened.***
- ***MCU is the gold standard for the diagnosis of VUR.***
- ***Renal scarring, hypodysplasia and bowel bladder dysfunction may be associated with VUR.***
- ***Management includes proper early diagnosis, continuous antibiotic prophylaxis, surgical management in a few and long term follow up.***
- ***Role of the pediatrician is critical for early diagnosis and improving outcomes.***

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IAP-IJPP CME 2019

NEUROREHABILITATION IN NEURO DEVELOPMENTAL DISABILITIES

Vijayalakshmy J

Abstract: *Neurodevelopmental disorders occur when the central nervous system development is disturbed. Neurorehabilitation aims at intervention to develop skills in different areas like sensory, motor, cognition, language, social and emotional. Sleep disorders also need to be treated. The neurorehabilitation activities are planned taking advantage of the plasticity of the brain and to minimize the effect of brain damage. Multidisciplinary team is required initially to assess and then to rehabilitate. Transdisciplinary approach could be used after sharpening the skills of the team members and discussion with the parents about their needs. Various adaptations are needed to develop a skill.*

Keywords: *Neurorehabilitation, Neurodevelopmental disorders*

Any disorder, in which the central nervous system development is disturbed, is collectively called neurodevelopmental disorder. The insult to development may occur during antenatal, natal or postnatal period. Early identification and intervention will minimize the effect of brain damage.

The commonly occurring conditions are autism spectrum disorder, attention deficit hyperactivity disorder, cerebral palsy, specific learning disorder, language and communication disorder, intellectual disability, psychiatric disorders, visual impairment, hearing impairment and chronic neurological conditions like ataxias, white matter degeneration, hydrocephalus, neuropathies and motor neuron disorders. Neurorehabilitation activities are planned after assessment by a multidisciplinary team. This includes clinicians, psychologist, physiotherapist, occupational therapist, speech therapist, special educator, prosthetic and orthotic professionals, social worker, parents, caregivers, audiologist and optometrist.

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The various therapeutic interventions are given to the child with specific disorder, in a way to develop various areas of development like sensory, motor, cognition, language, emotional and social development. When exercises and activities are given repeatedly, the child develops skills. The plasticity of the brain really does wonders when intervention is given at the earliest as the function of the damaged area of the brain can be taken over by another area of the brain. This will lead to improvement in the developmental milestones in the child. The priority is stimulation of sensory and motor areas as they are the initial stages in the development of cognition.

Sensory stimulation

The child is received with a smile and a song by the interventionist. Frequent light and deep touch is given with close contact and also by using different textures with a sensory mat (Fig.1). The day of the week is introduced by making the child touch a vegetable. Each day a different vegetable is given. The child will be able feel the texture and smell of the vegetable as well. The interventionist will be talking to the child when activities are given. The body is massaged with a powder and a song is sung about the body parts. The child is then put inside a 'Be Active Box' (Fig.2).[1] This box has textures inside. There are shining objects hanging from the top, windows on the side for the mother to see and call name. This box was used for the first time by Lilly Neilson. This box is very useful as there is stimulation of body parts when the child accidentally touches the sides of the box. When children see the shining object hanging, they will try to reach for the object.

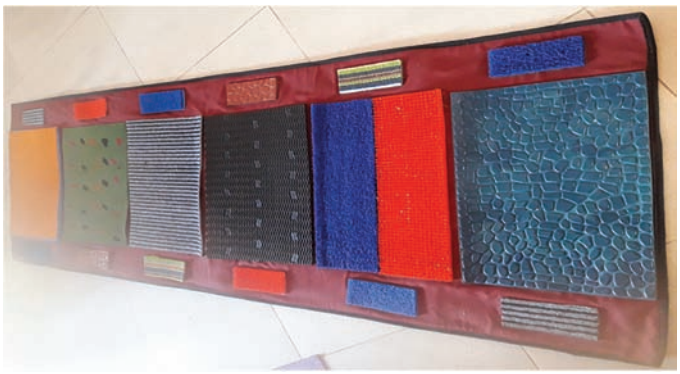

Fig.1. Sensory mat

Fig.2. Be Active Box

Another activity is putting the child on a resonance board which is made of plywood supported on four sides with bush and it is kept on the floor so that the baby can be placed on the board. Any vibration on the board will stimulate the child's body.

Presenting the child with two sensory stimuli at a time is important. The interventionist will not only be talking but also showing a bright object to the child which stimulate both ears and eyes. Also one can combine massage and singing. A mild vibration can be given with a vibrating toy and a torch light can be shown in front. The interventionist should be attentive to avoid flickering light. Joint compressions are given using rudraksha beads (Fig.3). Mild rocking helps in vestibular stimulation (Fig.4).

Fig.3. Rudraksha beads

Fig.4. Vestibular stimulation

Fig.5. Visual stimulation

Graded visual stimulation could be given by putting the child on prone wedge (Fig.5). Speech stimulation is a continuous process as we have to talk to the child during activities. Oromotor stimulation is also a part of therapy.

Motor stimulation

Neurodevelopmental therapy and specific physiotherapy are given to the child to achieve age appropriate motor milestones. Positioning, weight bearing and exercises to facilitate attainment of motor milestones are given. The stages of motor development are followed. The swiss ball, prone wedge, crawling board, walker, parallel bar and obstacle walking (Fig.6) activities have to be practiced. Fine motor skills could be imparted simultaneously (Fig.7, 8 and 9).

Fig.6. Obstacle walking

Fig.7. Twin device for standing and sitting balance

Fig.8. Fine motor skill

Fig.9. Writing skill

Cognitive development

All sensory motor activities will lead to cognitive development. Specific activities to develop cognition include thumb printing, cutting outline of the child's figure on a paper, introducing body parts, putting inside 'be active box', giving lot of real life activities and doing lot of matching and sorting activities. Activities to increase attention span have to be included. The concept development follows a pattern. The child is allowed to explore the world. They should know that objects are there in the world, even if they are taken away from the child, they are present in the surroundings. Thus the child should learn object permanence. Two things that are same and the difference - 'big and small' should be taught. Always the name of the object, attributes of the object and function of the object should be explained.

Speech and language development

Group activity and speech stimulation work well. Individual stimulation is to be done by therapist. Alternate mode of communication may be needed. Objects can be used to indicate activity. Tadoma (method of communication used by deafblind people by keeping the fingers over lips, cheek and chin of the person who is talking and understanding speech by the vibration felt on the fingers), picture communication, sign language, Braille and devices that talk could be used.[2]

Emotional development

Child needs to develop eye to eye contact. Emotional attachment should be given attention by parents. Screen time with children should be restricted. More interaction at home should be encouraged. Self regulation has to be developed. Sensory comfort and sensory overload should be avoided.

Socialisation

Socialisation occurs through group activities. Different kinds of group play activities need to be planned. Children should be part of all celebrations.

Activities of daily living (ADL)

Eating skill is the most difficult part. Special oromotor exercises have to be practiced along with other ADL skills.

Sleep

Sleep disorders have to be identified and investigated**.** Lack of sleep can cause irritability and behavioural issues.

Behavioural modification

Definite interventions like reward and punishment have to be carefully planned but no corporal punishment should be given.[3]

Try to make the child smile at least five times every day during stimulation as learning takes place when it is pleasurable.

Points to Remember

- ***Neurodevelopmental disorders occur due to insult during antenatal, natal or postnatal period.***
- ***Early diagnosis and intervention will minimize the adverse effects.***
- ***Following assessment by a multidisciplinary team neurorehabilitation is planned with sensory and motor stimulation as the first set of activities.***
- ***Activities of daily living and group activities for socialization should be encouraged.***
- ***Make the child smile at least five times a day.***

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IAP-IJPP CME 2019

FOLLOW-UP OF PRETERM INFANTS – GROWTH CHARTS, FEEDING ADVICE, IMMUNIZATION

Anitha M

Abstract: *The post discharge follow-up program for preterm Neonatal Intensive Care Unit graduates should possess growth monitoring with appropriate tools, plans for post discharge nutrition, schedules for immunization and regular neurodevelopemental assessments. Fenton charts 2013 are descriptive reference charts for plotting growth of preterm infants from 22 weeks onwards and smoothly transiting after 50 weeks postmenstrual age to WHO Multicentric Growth Reference Study 2006 growth standards charts. Standard charts obtained from INTERGROWTH - 21st Preterm Postnatal Follow-up Study can be used to assess preterm babies ≥ 33 weeks up to 64 weeks postmenstrual age after which they overlap with the WHO Multicentre Growth Reference Study 2006 charts making them the recommended charts for growth monitoring in preterm neonates post discharge. Feeding plans after discharge lack guidelines and needs to be individualised based on the infant's postnatal growth pattern. Nutrient enrichment seems to have a role only in babies who have difficulties to grow postnatally. Preterm infants can be immunized according to their chronological age with all routine and special vaccines in the usual dose except hepatitis B vaccine.*

Keywords: *Preterm infants, Follow-up, Growth charts, Nutrition, Immunization*

Advances in perinatal and neonatal care have led to increased survival of preterm infants. However, many of these preterm neonates tend to have higher incidences of growth failures, infections and ongoing medical illnesses.[1] Therefore their post discharge follow-up program should include growth monitoring with appropriate tools, plans for post discharge nutrition, schedules for immunization apart from their regular neurodevelopmental assessments.

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Growth monitoring and growth charts

Preterm infants are at risk for poor growth while in NICU and after discharge from the NICU. Growth monitoring is vital in preterm infants follow-up. Growth parameters include infants' weight, length and head circumference and should be monitored on a weekly to biweekly basis for the first four to six weeks after hospital discharge. After this initial period, infants who are growing normally can be monitored every month and then every two months. Biweekly or monthly follow-up visits should continue for infants with slow weight gain who remain below the third percentile on a standard growth curve when they have reached 40 weeks post-menstrual, or who have chronic health problems e.g. bronchopulmonary dysplasia (BPD). Close monitoring should continue until a steady adequate growth pattern is established.[2]

An important tool for growth monitoring in neonates is growth chart. Two common types of growth charts are growth references and growth standards. A 'growth reference' is a statistical summary of anthropometry in a reference group of infants, whose health status is not taken into consideration. These charts are descriptive and show how infants grow rather than how they should grow. A 'growth standard' is essentially the same as a growth reference except that the underlying reference sample is selected representing a healthy pattern of growth and shows how the infants should grow. It is a prescriptive model which can diagnose both under nutrition as well as overnourishment.[3]

Reference growth charts used in preterm

Intrauterine growth charts: These are derived from data of anthropometric measurements of preterm infants of different gestational age at birth. These charts are cross-sectional and lack the ability to describe longitudinal fetal growth.[4] The draw-backs of these intrauterine charts are that they are based on small sample size and are not gender specific. Most of these charts used last menstrual period (LMP) to estimate gestation age instead of first trimester ultrasound (USG). There are serious concerns about using them as standards, as preterm infants are different from fetus.[5]

Postnatal growth charts: These growth charts are based on longitudinal measurements of parameters of infants as they grow and as such provide actual postnatal pattern of infant's growth; weight loss pattern after birth, regain of birth weight and subsequent growth in infants, who received more advance treatments such as surfactant replacement therapy, antenatal steroids and early aggressive nutritional regimens.[6] Defining a healthy preterm among them was not possible and growth charts thus constructed were not prescriptive and standards.[5]

Fetal-infant growth charts: These charts are constructed by merging two sets of reference data: cross-sectional data of anthropometric measurement of preterm infants at birth and postnatal longitudinal anthropometric data of term infants. Therefore, these charts permit growth comparison with fetus first and then to term infant standards. The advantage of using fetal-infant growth chart is that it allows assessing if a preterm neonate is achieving catch up growth or not. e.g. Revised Fenton charts published based on large preterm birth sample size from developed countries.[7] Though Fenton charts 2013 are descriptive reference charts for preterm infants and lack standard prescriptive benefits, they are popular for preterm infants because they include data from 4 million preterm infants, allows precise sex specific plotting from 22 weeks onwards and smooth transition to WHO MGRS (Multicentre Growth Reference Study) 2006 growth standards charts after 50 weeks postmenstrual age (PMA).[5]

Standard growth charts in preterm

Due to continuous efforts to develop a standard growth chart for preterm infants that can be used with confidence across all gestations and population, INTERGROWTH-21st postnatal growth standard for preterm infants (PPFS - Preterm Postnatal Follow-up Study) was created. This tracks the preterm postnatal growth standards with a prospective cohort from different geographical areas. The standards obtained are population-based, multiethnic, multi-country and sex-specific and they arise from a prospective study with uniform research methodology and same protocol using accurate gestational age estimation by 1st trimester USG, identical equipments, training, a centralized electronic data management system and close monitoring of staff. Therefore, the standards are prescriptive and show the optimum growth in fetus and neonates. Limitations were that despite a large sample size, there were relatively few early preterm births below 33 weeks for PPFS study. So, they may not be useful in infants of lower gestation (<33 weeks).[8] But above e"33 weeks, standard charts obtained from INTERGROWTH - 21st PPFS study can be used to assess preterm babies up to 64 weeks PMA after which they overlap with the WHO MGRS 2006 charts making them the recommended charts for growth monitoring in preterm neonates post discharge.[9]

Post discharge feeding plan

Growth patterns and outcomes

Postnatal growth of preterm infants in NICU fall into 4 different patterns

1. Infants with birth weight and discharge weight (DW) appropriate for postconceptional age (appropriate growth)
2. Infants born AGA but DW below reference growth curve (post natal growth restriction)
3. Infants born SGA and have DW still below the reference curve (Intra uterine growth retardation)
4. Infants born SGA but DW is appropriate for postconceptional age (early postnatal catch up growth carrying a risk for metabolic syndrome).[10]

In studies on VLBW infants, postnatal growth pattern rather than SGA status was significantly associated with neurodevelopmental outcome at 2 years. A better neurodevelopmental outcome was observed in AGA preterm infants maintaining favourable growth velocity or in SGA demonstrating early catch-up growth after the term equivalent.[11] In many LBW infants, growth is inadequate and their weights are below the 10th percentile at the time of discharge. It is a problem that occurs in 60-100% of preterm births globally. VLBW infants discharged with a subnormal weight for postconceptional age are at increased risk for long-term growth failure and poor neurodevelopmental outcome.[12] So before discharge, it is very important to make a nutritional evaluation, establish a feeding plan and follow-up individually based on their growth patterns.

Feeding choices

Human milk is the preferred feed for preterm infants and breast-feeding should be advocated by pediatricians and lactation resources should be made available.[13] Human milk fed PT infants who are not meeting their growth targets may benefit from multinutrient fortification of a portion of their daily feeds. But this implies the use of breast pump and bottle and may potentially interfere with breast feeding. Cochrane analyzed the effect of human milk (HM) fortification after hospital discharge in preterm infants (<37 weeks of gestational age). The limited data did not provide convincing evidence that feeding all preterm infants at home with multi-nutrient fortified HM compared with

unfortified affects important short term outcomes including growth rates during infancy and there were no data on long term growth.[14] As studies that evaluated post discharge HM fortification showed no deleterious effect on breastfeeding rates, it is proposed that HM fortification post discharge can be considered in breastfed and low birth weight babies (<2.5 kg), particularly if they have not grown well while in the neonatal unit.[15]

In case of infants on formula feeding during NICU for some reason, post discharge they have the options of being started on either

1. Standard term formula (<72 kcal/100 ml, protein 1.7g/ 100ml),
2. Post discharge formula (>72 kcal/100 ml, protein >1.7g/100ml), PDF or
3. Nutrient enriched preterm formula (>75 kcal/100 ml, protein >2.0g/100ml) preterm formula (PTF) fed during their NICU stay

Cochrane, analyzing 16 trials with a total of 1251 preterm infants, did not find differences in growth and development between PDF fed infants and standard formula fed infants. Hence, it does not support the recommendations to prescribe PDF after hospital discharge for all preterm infants. Limited evidence suggests that feeding with PTF after hospital discharge may increase growth rates up to 18 months post term.[16] A systematic review, mapping evidence about the role of macronutrient enrichment revealed that when energy requirements are adequate, increased protein results in increased growth and lean mass accretion. In particular, higher protein to energy ratios (>2.5-2.7) led to increased lean mass accretion and head circumference at one year. Particularly boys, SGAs and those with bronchopulmonary dysplasia (BPD) showed benefit from protein and nutrient enrichment (PTF) with regard to growth and its quality.[17]

Individualized approach

Thus an individualized feeding plan is essential for the post-discharge nutrition of the preterm infant. In conclusion, breast feeding infants who are appropriate for postconceptional age at discharge may be continued on exclusive human milk feeding or if on formula feeds may even be put on standard term formulas. Complementary feeding may be initiated at the corrected age of 4 months. Preterm infants discharged with a subnormal weight for postconceptional age (PCA) are at increased risk for long-term growth failure. Hence, they may benefit from human milk fortifiers in breast milk fed infants and nutrient enriched PTFs among formula-fed infants at least until 40 weeks PCA, preferably until 52 weeks PCA. Complementary feeding should be started not later than 6 months corrected age.[10,13,15,16,17]

Micronutrient supplementation

It is known that babies exclusively breastfed post discharge can have reduced bone mineral density and lower lean body mass than formula fed babies.[18] Preterm infants fed human milk require supplementation for calcium (150mg/kg/day) and phosphorus (75mg/kg/day) until term with vitamin D (800-1000 IU) and iron (2-3mg/kg/day) until 1 year corrected age. (Table I & II).[19] Preterm formulas have higher protein (>75 kcal/100 ml, protein >2.0g / 100 ml) and the required calcium (150mg/kg/day) and phosphorus (75mg/kg/day) than term formulas which improves bone mineralization. Daily oral vitamin A and routine zinc supplementation are not recommended at present, because there is not enough evidence of benefits to support such a recommendation.[19] The target intakes for vitamin E remain consistent for preterm infants after discharge and need multivitamin (0.5-1.0 ml per day) supplementation.[19,20] Infants on human milk fortification need iron and vitamin D supplements. Multivitamins, calcium and phosphorus are not required. Long chain polyunsaturated fatty acids supplementation or monofortification with medium chain triglycerides have not shown to be beneficial.[18]

Preterm immunization

Young infants are especially vulnerable to a number of vaccine preventable diseases, particularly pertussis (whooping cough), Hemophilus influenzae type b (Hib) disease, pneumococcal disease and influenza. Preterm and low birth weight infants have an even higher risk than full term infants of developing serious complications from vaccine preventable diseases. Infants born at less than 32 weeks gestation have significantly less IgG compared with those born at 32-36 weeks. Furthermore, IgG wanes more rapidly rendering preterm infants at increased and earlier risk for vaccine preventable diseases.[20]

Basic principles and vaccine administration

Birth weight and gestational age should not be taken into consideration for deciding about routine vaccination in preterm infants (except for hepatitis B vaccine). Hepatitis B vaccination should be modified in infants less than 2 kg based on maternal hepatitis B status. All routine vaccines have been found to be safe for use in preterm infants. There is adequate antibody concentration post vaccination in LBW infants for protection though the immunogenicity may be less. All well preterm infants should receive routine

Table I. Key nutrients from various enteral nutrition[19,20]

	Target intake	Breast milk (200 ml/kg/day)	Preterm formula (24 kcal/oz)
Energy intake (Kcal/kg/day)	128	134	129
Protein (g/kg/day)	3.5 to 4.0	2.0	4.3 to 4.6
Fat (g/kg/day)	5 to 7	7.8	5.6 to 7.0
Carbohydrates(g/kg/day)	12 to 14	13.2	12.9 to 13.6
Calcium (mg/kg/day)	150 to 220	50	210 to 234
Phosphorus (mg/kg/day)	75 to 140	26	117 to 129
Vitamin D (IU/day)	400	4	194 to 384
Vitamin A (IU/kg)	1000	780	960
Iron (mg/kg/day)	2-4	0.2	2.2

Table II. Nutrition supplementation for preterm infants[19,20]

Nutrient	Timing	Dose	Duration
Multivitamins (A,C,B_1, B_2,B_{12}, folicacid and Niacin)	On full enteral feeds (>100 ml/kg/day)	0.5- 1 ml / day	Till 1 year
Vitamin D	On full enteral feeds	800 – 1000 IU/day	Till 1 year
Iron	On full enteral feeds earliest by 2-3weeks postnatal age	2-3 mg/kg/day	Till 1 year
Calcium-Phosphorus (2:1)	On full enteral feeds	150/75 mg/kg/day	Till 40 weeks postmenstrual age
Human milk fortifier (human milk based)	On full enteral feeds with inadequate weight gain	Product recommendation1 sachet for 20-25 ml	Till weight 2 kg

vaccines as per national immunisation schedule based on their chronological age. Special vaccines against pneumococcus, rota virus and influenza are to be administered in addition due to increased incidences of these diseases in this high risk population. Vaccine dosages should not be reduced or divided when given to preterm infants. Majority of preterm infants produce adequate vaccine induced immunity against the disease with standard dose. The preferred site for intramuscular vaccines in preterm or low birth weight infants is the same as for full term infants, the vastus lateralis (anterolateral thigh). A 23-25 gauge x 16 mm needle inserted at a 90° angle to the skin is usually adequate.[21,22]

Recommendations for individual vaccine - Hepatitis B

Infants of hepatitis B negative mothers: Some studies suggest that infants weighing less than 2000g at birth have decreased seroconversion to hepatitis B vaccine. But by 4 weeks of age all infants, independent of gestational age and birth weight, are expected to respond to the hepatitis B vaccine and develop protection against the disease. Hence infants weighing less than 2000g at birth are vaccinated with HBV at 30 days chronological age or at the time of discharge whichever is earlier. Infants born to hepatitis B negative (HBsAg negative) mothers prematurely and/or

weighing less than 2000g are expected to be adequately protected against hepatitis B even if vaccination is started at 6 weeks of age and completes 3 doses.

Infants born to hepatitis B positive mothers: Infants born to HBsAg-positive (hepatitis B surface antigen-positive) mothers require hepatitis B immunoglobulin (HBIG) and a hepatitis B immunisation within 12 hours of birth. Thereafter a complete course of three hepatitis B vaccine doses are administered from 6 weeks of age irrespective of whether the infant had a birth dose of vaccine. Serology testing for hepatitis B infection (HBsAg) and immunity (antiHBs) is recommended at 9 -15 months of age for all infants born to hepatitis B positive mothers. If infant is HBsAg and anti HBs negative, reimmunise with three doses at 2 month intervals and retest.

Infants born to mothers whose hepatitis B carrier status is not known: Infants born to mothers whose HBsAg status is unable to be demonstrated as negative within 12 hours of delivery should also receive hepatitis B immunoglobulin (HBIG) and a hepatitis B immunisation regardless of their birth weight.[23]

Vaccine safety and monitoring

Vaccines in preterm infants have excellent safety profiles, comparable to those in full term infants, with the exception of a possible increase in apnea with or without associated bradycardia up to 48 hours post-immunisation.

Factors that have been identified as possibly being associated with an increased incidence of post-immunisation apnea include

i) Apnea within the 24 hour period before immunisation

ii) Severe illness at birth

iii) Chronological age less than 67 days, and/or

iv) Earlier gestational age in infants with a birth weight of less than 1500g.

An apneic episode following the first immunisation event is a significant risk factor for an apnoeic episode following the second immunisation event and may require monitoring for 48 hours. Immunisation should not be withheld or delayed.[23,24,25]

Points to Remember

- ***Intergrowth-21st charts can be used to assess preterm babies up to 64 weeks postmenstrual age after which they can be followed up with WHO MGRS 2006 charts.***
- ***Individualized feeding plan based on the infant's postnatal growth pattern is advisable.***
- ***Nutrient enrichment in the form of fortifiers in human milk fed babies or preterm formula in formula fed infants may benefit infants with or at risk of postnatal growth faltering.***
- ***Supplementation with calcium, phosphorus and multivitamins until 40 weeks term and vitamin D and iron until 1 year corrected age are recommended in exclusively human milk fed babies.***
- ***Complementary feeding is started at 4 months corrected age in growth appropriate infants and not later than 6 months corrected age in growth faltering infants.***
- ***All well preterm infants should receive routine vaccines as per National Immunisation schedule based on their chronological age.***
- ***Hepatitis B vaccination alone needs to be modified in infants less than 2 kg based on maternal hepatitis B status.***

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NEWS AND NOTES

IAP NEOCON 2020

National Neonatology Forum - Kerala

(Jointly Organized by NNF Kerala, IAP Thrissur and NNF Thrissur)

1st - 4th October, 2020

Lulu International Convention Centre & Hyatt Regency, Thrissur, Kerala

Conference Secretariat

Dr.Vishnu Mohan, Consultant Neonatologist,

Dept of Neonatology, Aster MIMS, Calicut - 673017

Mob: 9787304403, Email: regns.iapneocon2020@gmail.com

IAP-IJPP CME 2019

CLUES IN X-RAY DIAGNOSIS

Vijayalakshmi G

Everywhere we search for clues to help us in our quest for answers to various problems. There are many such pointers in radiology that will help one quickly analyse and come to the right conclusions.

Age of the child: Fig.1 is film of a just born baby with respiratory distress showing a patchy alveolar shadowing that could be congenital pneumonia. But as the baby is only a few hours old, one should consider transient tachypnea of the newborn which is only a delay in the normal expulsion of pulmonic fluid. Therefore a clearance in a repeat X-ray after 24 hours and improvement with supportive therapy confirms that it is just an unfolding physiological event.

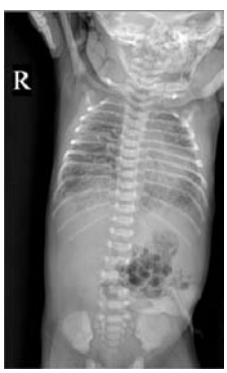

Fig.1. Transient tachypnea of newborn

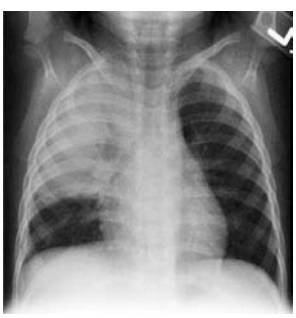

Fig.2. Consolidation - Right upper lobe

Air bronchogram: Fig.2 shows the air in the airways which stand out when the surrounding alveoli lose air either because they are collapsed and empty or filled with transudate or exudate. Therefore this sign is helpful to identify that the opacity is lung and not any other lesion. However, their presence is not absolutely essential to diagnose consolidation as the airways can also be filled with secretions or exudates.

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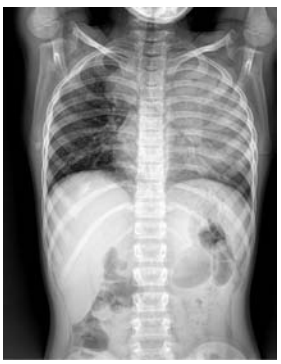

Fig.3. Sillhouette sign – Consolidation-left upper lobe. Note: Right mediastinal node.

Silhouette sign: Silhouette, in its real sense, denotes an outline of an object. In X-ray, the silhouette sign means a loss of outline. Hence, the medial edge of middle lobe consolidation is not seen separately but merges with the heart shadow. In Fig.3 the medial edge of the consolidated left upper lobe cannot be seen separately as it merges with the mediastinum.

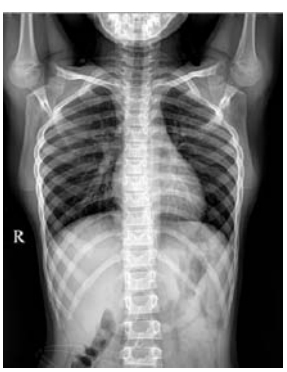

Fig.4. Lung hilum '>' sign

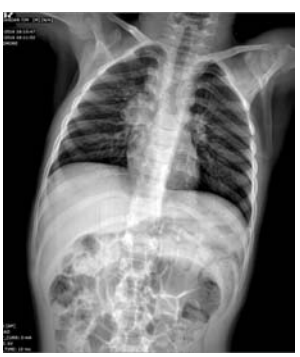

Fig.5.Hilar node - right side

Node in tuberculosis: Note that in Fig.3 there is also a bulge in the upper mediastinum on the right which is an enlarged mediastinal node. The presence of a node is a pointer to tuberculosis. Fig.4 shows the normal hilum on the right which is shaped like a 'greater than (**>**)' sign. The superior limb is formed by the superior pulmonary artery and vein while the inferior limb is formed by the inferior pulmonary vessels. A bulge obscuring this ">" shape is a hilar node (Fig.5).

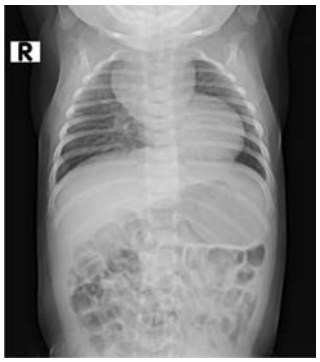

Fig.6.Thymus

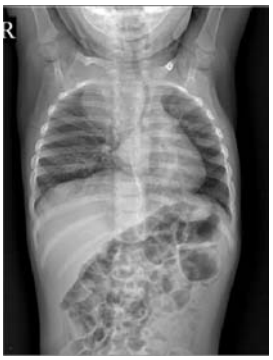

Fig.7.Mass - bronchogenic cyst

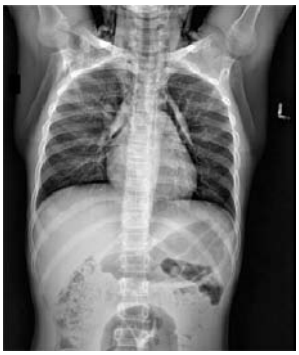

Fig.8. Spinnaker sail sign

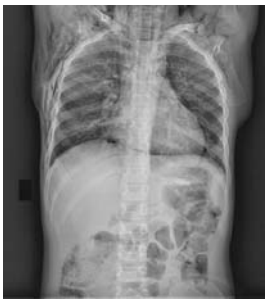

Fig.9.Continuous diaphragm sign

Thymus and mass: Fig.6 shows a lesion with a rounded shape on either side of the midline. This is the normal thymus. The thymus shape can be confusingly variable. It can bulge equally on either side of the midline or can be seen asymmetrically on both sides or it can be seen only on one side mimicking a mass. But the thymus will not shift the trachea. In Fig.7 the rounded mass on the right side shifts the trachea to the opposite side. Therefore it is a mass and needs further cross-sectional imaging. If in doubt, one can always use ultrasound for a quick answer. The normal thymus will have a uniformly echogenic appearance while a mass may show solid lesion or a cyst. Shift of normal structures denotes a space occupying lesion.

Thymus and pneumomediastinum: The X-ray in Fig 8 is that of a child who presented with respiratory distress. If one sees carefully, the thymus is lifted away from the heart - a sign of pneumomediastinum. The thymus shadow in children merges with that of the heart and hence termed as the cardiothymic shadow. When it is lifted away from the heart or is seen separate from the heart it means air has percolated into the mediastinum. This is called the 'Spinnaker-sail sign'. The 'Spinnaker-sail' is the colourful large sail in a yatch that billows out in the wind as it navigates downstream.

Fig.9 is pneumomediastinum giving rise to the continuous diaphragm sign where air insinuates between the heart and the diaphragm making the inferior border of the heart distinct from the diaphragm. Normally the heart shadow merges with the diaphragm. One can also look out for subcutaneous emphysema.

Bronchovascular markings: The presence of tissue architecture that is supposed to be in a particular location denotes the normalcy of that organ. An abscess in the liver is seen as a hypoechoic area replacing the normal echotexture of the liver. Similarly, the presence of bronchovascular markings means presence of lung. In pneumothorax there is absence of vascular markings in a black hemithorax. On the contrary, the presence of bronchovascular markings in a black hemithorax means the excess air is within the alveoli indicating emphysema.

The deep sulcus sign (Fig.10) may sometimes be the only sign of pneumothorax. In the supine position air in the pleural cavity tends to rise to the anterior and inferior portion of the thorax, first medially and then laterally. The costophrenic angle on the side of the pneumothorax is deep and projected more inferiorly than the costophrenic angle on the other side.

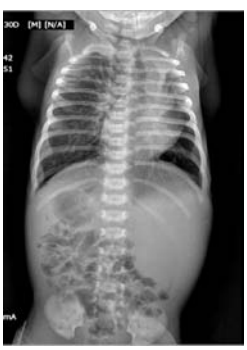

Fig.10. Deep sulcus sign

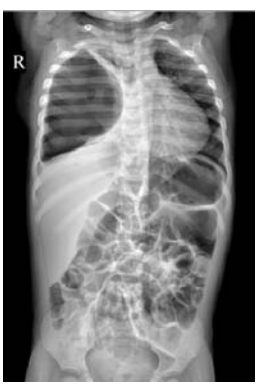

Fig.11. Grey colour of pyopneumothorax on right

Air is black while fluid is white. Pneumothorax makes the hemithorax black. Emphysema also makes it black. Fluid as well as mass makes the hemithorax white. A mixture of white and black i.e. grey is the colour of fluid mixed with air which is the case in pyopneumothorax (Fig.11). Recognition of this is important and placing an intercostal drainage tube as early as possible helps to save the child. The above are a few clues that will help you on the way to a correct and quick diagnosis.

DRUG PROFILE

ANTI-VIRAL DRUGS IN CHILDREN AND ADOLESCENTS

Jeeson C Unni

Abstract: *This article intends to make pediatricians familiar with antiviral drugs and provides specific recommendations for treatment of viral diseases. The antiviral drugs in clinical use are discussed in terms of their doses, routes of administration, mechanisms of action, established and potential efficacies and toxicities. Biologic response modifiers such as interferons, are mentioned.*

Keywords: *Children, Viral infections, Treatment*

Anti-viral drugs used commonly in children include: (i) Anti-herpetic agents, (ii) anti-virals for respiratory viral infections, (iii) anti-virals for viral hepatitis and (iv) anti-retroviral agents.

Anti-virals for herpes infection

The drugs used and their spectrum are given in Table I.

Acyclovir

It is used in treatment of herpes simplex infection of skin (genital, labial), neonatal HSV infection, HSV encephalitis and chicken pox and herpes zoster. In the immunocompromised individuals, it is used as prophylaxis for prevention of HSV infection.

Herpes labialis with gingivostomatitis[1]

Dose: Oral acyclovir - Gingivostomatitis - 1month - 2years 100 mg; 2-18years 200 mg 5 times daily for 7 days within 4 days of onset. Acyclovir may reduce duration of pain and time to healing for a first attack of herpes labialis compared with placebo; however, evidence is limited. There are no RCTs comparing topical antiviral versus placebo and no treatment.

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Table I. Anti-herpetic agents and indications

Drugs	Infections
Acyclovir	Herpes simplex virus -1 (HSV-1), HSV-2, varicella zoster virus (VZV) - Chicken pox, Herpes Zoster
Ganciclovir / Cidofovir	Cytomegalovirus (CMV)
Famciclovir (prodrug of Penciclovir - greatest bio-availability)	Herpes genitalis and Herpes Zoster
Foscarnet	Resistant HSV, VZV, CMV, HIV
Penciclovir (poor bio-availability - only for topical use)	Herpes labialis, CMV
Trifluridine (topical)	Herpetic keratoconjunctivitis

Prophylactic oral antivirals may reduce the frequency and severity of attacks compared with placebo, but there are no recommendations regarding the best timing and duration of treatment. Acyclovir, famciclovir and valaciclovir may reduce the duration of symptoms and the time to heal in recurrent attacks of herpes labialis. Limited evidence exists that topical antiviral agents may reduce pain and healing time in recurrent attacks.[2]

Treatment for recurrences: In adolescents - to shorten duration of episode - Valacyclovir (2,000 mg bid PO for 1 day), acyclovir (200-400 mg 5 times daily PO for 5 days) and famciclovir (1,500 mg once daily PO for 1 day). Long-term prophylaxis for frequent or severe recurrences are acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO).

Herpetic kerato-conjunctivitis[3]

The treatment of choice is application of acyclovir ointment 5 times daily and continued for at least 3 days after complete healing. Topical trifluorothymidine, vidarabine, idoxuridine or ganciclovir are also useful. Interferon monotherapy has a slight beneficial effect on

dendritic epithelial keratitis, but is not better than other antiviral agents. There are studies suggesting that a combined interferon-nucleoside therapy improves healing.

Children with HSV keratitis are at risk for recurrent keratitis and amblyopia. Prolonged systemic antiviral prophylaxis may help to prevent such consequences (one year of acyclovir / valaciclovir). Immune regulatory drugs, e.g. cyclosporine present an attractive alternative to managing HSV stromal keratitis, given the immune-mediated pathogenesis of stromal disease.

Herpes encephalitis[4]

IV acyclovir infusion: i) Neonate - 3months 20 mg/ kg 8th hourly for 21days, ii) 3 months-12 years 250 mg/ m^2 8th hourly for 21 days. Only limited studies are available in neonates and children. Poor prognosis and relapses despite treatment are not uncommon. It is necessary to confirm CSF negativity for HSV before stopping. Doubling of the dose is recommended in immunocompromised neonates and children.

Genital herpes

Acyclovir dose for adolescent 400mg tid; child - 10-20mg/kg/dose qid for 7 to 10 days and extended if healing is incomplete. Genital herpes is a recurrent, incurable viral disease. Treatment of the initial infection reduces the severity and duration of subsequent recurrent infections but has no effect on frequency of subsequent recurrent infections. Topical acyclovir has negligible or no clinical benefit.

For recurrent genital herpes - Adolescent 800 mg tid for 2 days during each episode (start within 1st day of onset or in prodrome). In HIV patients, imiquimod may be tried in episodic treatment of lesions thought to be acyclovir-resistant or nonresponsive. Valacyclovir and famciclovir are also effective but clinical experience is lacking.

Herpes simplex prophylaxis in immunocompromised (Post-transplant patients)

Oral acyclovir - 1 month to 2 years 100-200 mg 4 times daily and for children 2-18 years 200-400 mg 4 times daily.

Herpes simplex suppressive therapy

Oral acyclovir - Child 12-18 years 400 mg twice daily or 200 mg 4 times daily. Suppressive therapy reduces frequency of recurrences by 70%-80%. The dose may be increased to 400 mg thrice daily if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation). Therapy is interrupted every 6-12 months to reassess recurrence frequency-consider restarting after two or more recurrences.[5]

Acyclovir in varicella[6]

Antiviral therapy modifies course in both varicella and herpes zoster. In neonates, regardless of immune status and use of any immunoglobulins, IV acyclovir must be administered due to high risk of severe disease. Oral acyclovir is not recommended as absorption is variable. Healthy child -1month-12 years need not be treated. Adolescent should be treated within 24 hours. Immunocompromised children and those at special risk (severe CVS / respiratory disease /chronic skin disorder) should be treated for 10 days with at least 7 days of parenteral treatment. It is preferable to start therapy for varicella within first 24 hours of onset of illness.

Acyclovir in herpes zoster[6]

Systemic antiviral treatment can reduce the severity and duration of pain, reduce complications and viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7-10 days. Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.

Dose of acyclovir in chickenpox and herpes zoster infection

Oral: 1month - 2 years 200 mg; 2-6 years 400 mg; 6-12 years 800 mg 4 times daily for 5 days; 12-18 years 800 mg 5 times daily for 7 days (herpes zoster in the immunocompromised - continue for 2 days after crusting of lesions).

IV infusion: Neonate - 3 months - 10-20 mg / kg 8th hourly for at least 7 days; 3 months - 12 years - 250 mg/m^2; 12-18 years 5 mg/kg 8th hourly for 5 days. At all ages - double the dose in encephalitis or immunocompromised (given for 10-14 days in encephalitis, possibly longer if also immunocompromised). To avoid excessive dose in obese, IV dose is calculated on the basis of ideal weight for height.

Prophylaxis for varicella after delivery

IV infusion - Neonate 10 mg/kg 8th hourly and continued until serological tests (VZ IgM) confirm absence of virus.

If VZ immunoglobulin not indicated or not available, attenuation of chickenpox - Oral:1 month -18 years

10 mg/kg 4 times daily for 7 days starting 1 week after exposure. For IV infusion, reconstitute to 25 mg/ml with water for injection or normal saline then dilute to concentration of 5 mg/ml with normal saline or glucose saline and given over 1 hour or use infusion pump and central line to administer the 25 mg/ml solution over 1 hour.

Resistance to acyclovir occurs in the immunocompromised. If HSV lesions are unresponsive, worsening or if there is frequent recurrence the chances of acyclovir resistance is high. In such conditions, an attempt is to be made to isolate the virus for sensitivity testing. Foscarnet or cidofovir have been used in such situations with success.

Valaciclovir[7]

Used in herpes zoster in the immunocompromised and the dose for 12-18years is 1 g tid (PO) for 7 days (continue for 2 days after crusting of lesions).

Treatment of herpes simplex: Oral - 12-18years 1st episode, 500 mg BD for 5 days; recurrent infection, 500 mg BD for 3-5 days (double dose for 5-10 days in immunocompromised or HIV positive).

Treatment of herpes labialis: Oral - 12-18 years initially 2 g, then 2 g 12 hours after initial dose.

Suppression of herpes simplex: Oral - 12-18 years 500 mg OD (immunocompromised or HIV positive 500 mg BD); interrupt every 6-12 months to reassess - consider restarting after 2 or more recurrences.

Prevention of CMV following solid organ transplantation (within 72 hours): Oral - 12-18years 2 g 4 times daily usually for 90 days.

Foscarnet[8]

CMV disease

Retinitis (ganciclovir resistant / immunocompromised patient): IV infusion - 1 month-18 years induction 60 mg/kg q8h for 2-3 weeks and then maintenance 60 mg/kg daily, increased to 90-120 mg/kg if tolerated. If disease progresses on maintenance dose, repeat induction regimen.

Mucocutaneous herpes simplex infection (acyclovir resistant / immunocompromised patient):

IV infusion - 1 month -18years - 40 mg/kg q8h for 2-3 weeks or until lesions heal. If central venous catheter is used can be given without dilution; if given through a peripheral vein it needs to be diluted to a concentration of 12 mg/ml with 5% glucose or normal saline and given over at least 1 hour (doses greater than 60 mg/kg given over 2 hours). Foscarnet is not to be used except for CMV retinitis and/or acyclovir resistant HSV in immune compromised child.

Ganciclovir[9]

It is the drug of choice for life or sight-threatening CMV infection in immunocompromised children. It is also used for prevention of CMV during immunosuppressive therapy following organ transplantation. Dose: 1 month-18 years initially (induction) 5 mg/kg q12h for 14-21 days as IV infusion for treatment or for 7-14 days for prevention; maintenance (for patients at risk of relapse of retinitis), 6 mg/kg daily on 5 days/week or 5 mg/kg daily until adequate recovery of immunity; if retinitis progresses - repeat initial induction treatment.

CMV infection of CNS

IV infusion dose - Neonate 6 mg/kg every 12 hours for 6 weeks. Close monitoring of full blood count is needed (severe deterioration may require correction and possibly treatment interruption).

Other rare indications

Oro-facial HSV reactivated after cosmetic facial laser resurfacing - Day before the procedure start oral valacyclovir/famciclovir. HSV infection in burns patients - Severe/life threatening - IV acyclovir. In HSV associated erythema multiforme (EM), antivirals not effective but long term herpes labialis prophylaxis prevents recurrences of EM.

Antivirals for respiratory viral infections

Influenza[10]

Oseltamivir / Zanamivir - these neuraminidase inhibitors prevent the release of new virions and their spread from cell to cell. They are effective against both influenza A and B. They are used for both prophylaxis and treatment. For treatment and post-exposure prophylaxis - Oseltamivir should be started within 48 hrs and zanamivir within 36 hrs of symptoms/exposure, respectively. In healthy individuals it reduces duration of illness by about 1-1.5 days. However, for severe influenza or in the immunocompromised children these drugs may be effective even after the ideal time for initiating therapy if viral shedding continues (unlicensed use).

Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic. Evidence suggests that some strains of influenza A have reduced susceptibility to oseltamivir, but retain susceptibility to zanamivir. Resistance to oseltamivir may be greater in severely immunocompromised children. Zanamivir should therefore be reserved for patients who are severely immunocompromised, or when oseltamivir cannot be used, or when resistance to oseltamivir is suspected. For those unable to use the dry powder for inhalation, zanamivir is available as a solution that can be administered by nebuliser or intravenously (unlicensed). Amantadine / rimantadine are no longer recommended.

Oseltamivir

Treatment of influenza: For children above 1year age - upto 16 kg - 30 mg, 16-23 kg - 45 mg, 23-40 kg - 60 mg and >40 kg - 75 mg orally every 12 hours for 5 days. For prevention of influenza: 13-18 years - 75mg (PO) once daily for at least 7 days after exposure or for upto 6 weeks during an epidemic.

Zanamivir - By inhalation of powder

Treatment of influenza: 5-18 years 10 mg BD for 5 days (10 days if resistance to oseltamivir suspected). Post-exposure prophylaxis of influenza- 5-18 years 10 mg once daily for 10 days. Prevention of influenza during an epidemic- 5-18 years 10 mg once daily for up to 28 days. There is a risk of bronchospasm with use of zanamavir. In addition, the US Food and Drug Administration recently approved peramivir, a novel neuraminidase inhibitor available for intravenous administration.

RSV bronchiolitis[11]

Ribavirin is a guanosine analog that inhibits a wide range of DNA and RNA viruses. It is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases. However, there is no evidence that ribavirin produces clinically relevant benefit in RSV bronchiolitis.

Palivizumab is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease; it should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation. Palivizumab is recommended for children under 9 months of age with chronic lung disease (defined as requiring oxygen for at least 28 days from birth) and who were born preterm and children under 6 months of age with hemodynamically significant, acyanotic congenital heart disease who were born preterm. Monthly doses of palivizumab (15 mg/kg per dose IM) during the RSV season to infants who qualify for prophylaxis in the first year of life are recommended.

Palivizumab should be considered for children under 2 years of age with severe combined immunodeficiency syndrome, children under 1 year of age who require long-term ventilation and children 1-2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension).

Ribavirin may also be used orally with peg interferon alfa / interferon alfa for the treatment of chronic hepatitis C infection; Lassa fever; and intravenously for the treatment of life-threatening RSV, parainfluenza virus, adenovirus infections in immunocompromised (unlicensed indications). Anemia and jaundice are adverse effects to be watched out for when ribavirin is administered.

Anti-virals for chronic viral hepatitis

The drugs used are i) interferons, ii) lamivudine - cytosine analog - HBV, iii) entecavir - guanosine analog - HBV - lamivudine resistance strains and iv) ribavirin - Hepatitis C (with interferons).

Chronic hepatitis B

Recommendations are still in evolution as no drug currently achieves reliably complete eradication of the virus. Treatment recommendations depend not only on effectiveness but also on many other factors such as adverse events, potential for viral resistance, cost, availability, patients' preference and values in the care setting.

Across all outcomes and in both HBeAg-positive and HBeAg-negative populations, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are the most effective agents for virologic suppression and of the two, TAF emerged as the treatment of choice with the most consistent performance.[12] It is a prodrug of tenofovir and has a better safety profile with respect to renal function and bone mineral density compared to TDF.

Prior to 2017, TDF and entecavir (ETV) were the recommended oral drugs for chronic hepatitis B infection. With TDF, renal complications (nephropathy and Fanconi syndrome) and osteomalacia have been reported, but no resistance has been detected to date. ETV has been associated with lactic acidosis and a low but slowly emerging resistance pattern.

Pegylated interferon-á (PEG-IFN) is a synthetic cytokine and is believed to act on the cell-mediated immunity. PEG-IFN treatment has the benefit of finite treatment duration, a higher rate of HBeAg and HBsAg seroconversion and no drug resistance. However, it is associated with more adverse events (flu-like symptoms, neutropenia, anemia, thrombocytopenia, depression, neuropathy and dermatological side effects) than any of the oral drugs. The need for parenteral administration also adds to the low preference and compliance. For these reasons, PEG-IFN is hardly used in clinical practice nowadays and is reserved for select cases. Certain combination strategies between a nucleos(t)ide and PEG-IFN have been shown to exhibit synergistic therapeutic effect resulting in greater viral suppression and higher rates of HBeAg loss and HBsAg loss.

Lamivudine - A study before the availability of oral nucleoside therapies of hepatitis B and long before the availability of the more potent agents with a higher barrier to resistance such as tenofovir and entecavir showed that lamivudine was found to have good activity, lowering HBV DNA levels in virtually all patients with subsequent improvements in serum enzyme levels and hepatic histology.[13] A major shortcoming, however, was the development of antiviral resistance after which HBV DNA levels generally rose and the biochemical and histologic features worsened.

Chronic hepatitis C[14]

WHO recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage. WHO also recommends the use of regimens having pan-genotypic direct-acting antivirals (DAAs) for the treatment of chronic HCV infection aged 18 years and above.

In adolescents aged 12-17 years or weighing at least 36 kg with chronic HCV infection, WHO recommends:

- Sofosbuvir / ledipasvir for 12 weeks in genotypes 1, 4, 5 and 6
- Sofosbuvir / ribavirin for 12 weeks in genotype 2
- Sofosbuvir / ribavirin for 24 weeks in genotype 3.

WHO recommends deferring treatment in children aged less than 12 years with chronic HCV infection. Treatment with interferon-based regimens should not be used. New highly effective short-course oral pan-genotypic DAA regimens are likely to become available for children less than 12 years of age in late 2019 or 2020. This will provide an opportunity to advance treatment access and cure to a vulnerable group that will benefit from early treatment.

Anti-virals for HIV infection[15]

The different classes of anti-retroviral drugs are given in Box 1. Antiretroviral therapy (ART) is used in Prevention of Mother To Child Transmission (PMTCT), Post Exposure Prophylaxis (PEP), Pre Exposure Prophylaxis (PrEP) and treatment of established case of HIV/AIDS.

Currently available ART does not eradicate virus or cure patient but only suppresses virus for extended periods and changes course of disease to a chronic process. Decisions about antiretroviral therapy for pediatric HIV are based on viral load/replication, CD4 count or percentage and clinical condition. In ART the reason for combining at least 3 antiretrovirals (ARVs) from at least 2 different classes is for its synergistic effect and to prevent the development of resistance which is likely in monotherapy.

Box 1. Antiretroviral drug – Classification

- NRTI (Nucleoside Reverse Transcriptase Inhibitors)
- NtRTI (Nucleotide Reverse Transcriptase Inhibitors)
- NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitors)
- PI (Protease Inhibitors)
- Entry Inhibitors
- Integrate Inhibitors

It is important to note that combination therapy increases the rate of toxicity. Complex drug-drug interactions exist among many of the antiretroviral drugs. Many protease inhibitor drugs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes. Inhibitory effect of ritonavir (a protease inhibitor) on the cytochrome P450 system has been exploited and small doses of the drug are added to several other protease inhibitors (lopinavir, tipranavir, atazanavir).

The preferred ART combination is two NRTI (to suppress replication in both active and resting cells) and one NNRTI or one protease inhibitor (to produce prolonged viral suppression).

Additional alternate regimens are triple NRTI (i.e., abacavir, zidovudine and lamivudine), boosted PI - lopinavir / ritonavir in combination with two NRTI or one NRTI and one NNRTI.

Prevention of Mother To Child Transmission (PMTCT): Zidovudine (ZDV)

ZDV is given orally to pregnant women in the dose of 100 mg five times per day. A combination antiretroviral (cART) containing ZDV should be preferred. Therapy should be started as early as 14 week gestation and continued during delivery and as long as the baby is exclusively breast fed or for the first 6 week of life (2 mg/kg q 6 hr PO). In the developed world, this decreases perinatal HIV transmission rate to <1%.

A short term regimen (300 mg BD from 36 week gestation and 300 mg every 3 hour during delivery) resulted in almost 50% reduction in transmission. Even if a mother receives no ART during gestation or delivery, a 6 week ZDV prophylaxis for the newborn as soon as possible after delivery and preferably within 6 hours of birth results in a meaningful reduction of transmission rate.

For full term infants, the dose of ZDV is 2 mg/kg q 6 h for 6 weeks while in preterm infants it is 1.5 mg/kg orally or IV q 12 h (if available) for the first 2 weeks and then increased to 2 mg/kg q 8 hour.

Prevention of Mother To Child Transmission (PMTCT): Nevirapine (NVP)

Oral nevirapine: One dose to women in labor and once to the newborn in the first 48 - 72 hour of life reduces perinatal transmission by 50%. It is effective because of the prolonged half-life of nevirapine and is a simple and highly cost effective regimen for developing countries. But if ART is required for children more than 6 months of age, a NVP based regimen was found to have a high failure rate.

Indications of ART

ART should be started before the immune system is irreversibly damaged. All infants, regardless of clinical or immunological must receive ART. In children between 36-59 months, treatment is initiated if CD4 <350 cells/mm^3 (15%) while in children more than 5 years old adult guidelines are followed. Treatment is started in adult and adolescents in WHO clinical stage 1 or 2 and a CD4 count $\leq$ 350 cells/mm^3 (initiate ART before CD4 drops below 200 cells/mm^3), WHO clinical stage 3 or 4 regardless of CD4 count, HIV and TB co-infection regardless of the CD4 count and HIV/HBV co-infection with evidence of active liver disease.

What to start [National AIDS Control Organisation (NACO) recommendation]

Pediatric formulations will be provided at all ART centres. The drugs supplied are fixed dosed combinations (FDC) available in India which are stavudine-based regimens (Table II). It has been recommended that in order to scale up the treatment for children, this will be used as long as zidovudine (AZT) - based regimens are available and also recommended globally as the preferred choice for children.

Choice of ART drug

In less than 2 years old exposed to nevirapine in mother or in infancy, boosted protease inhibitor (PI) based regimen (lopinavir/ritonavir, LPV/r) is started in view of concerns about persistence of resistant mutants to NVP.

Above 3 years with HIV TB co-infection, treatment is with two NRTI and Efavirenz (avoid nevirapine / rifampicin interaction); if efavirenz cannot be given, triple NRTI regimen is given.

Above 12 years with both HIV and hepatitis B infection, treatment is with tenofovir (TDF) + emtricitabine (FTC) / lamivudine (3TC) + NVP/EFV to provide the benefit of two potent drugs against hepatitis-B infection.

Table II. FDC in Pediatric HIV (India)

Formulation	Stavudine (d4T)	Lamivudine (3TC)	Nevirapine (NVP)
FDC 6 (baby tab)	6 mg	30 mg	50 mg
FDC 10 (tab)	10 mg	40 mg	70 mg
FDC 12 (junior tab)	12 mg	60 mg	100 mg
FDC 30 d4T (adult tab)	30 mg	150 mg	200 mg
FDC -30 AZT (adult tab)	300 mg	150 mg	200 mg

Efavirenz (EFV) not considered in less than 3 years age because of inadequate information on dosage and in adolescent girls due to its teratogenic potential in the first trimester of pregnancy.

Toxicity of ART drugs

Hematological side effects with AZT include anemia, neutropenia and thrombocytopenia.

Mitochondrial dysfunction with other NRTI drugs includes lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy. Lipodystrophy and other metabolic abnormalities are more common with stavudine (d4T) and protease inhibitors and to a lesser degree with other NRTI drugs. Abnormalities include fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, insulin resistance, diabetes mellitus, osteopenia, osteoporosis and osteonecrosis. Allergic reactions include skin rashes and hypersensitivity reactions which are more common with NNRTI drugs, but also seen with certain NRTI drugs, such as abacavir (ABC). In children with hepatic dysfunction of any etiology, NVP requires careful consideration because of its potential life threatening hepatotoxicity.

Conclusion

A review of drugs used to treat viral illnesses is needed as new recommendations are now available and drugs used previously are no longer used.

Points to Remember

- ***Among anti-herpes virus agents thorough knowledge of the prototype / 1st line drug, acyclovir is essential, as other Anti HSV drugs are rarely required.***
- ***Oseltamivir is the primary drug for treatment and prophylaxis of influenza.***
- ***Antivirals are used selectively for hepatic viral infections.***
- ***Pediatricians need to know about the indications, type of drugs, common side effects and follow-up in the treatment of HIV/AIDS.***

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ADOLESCENCE

HYPERPIGMENTED SKIN LESION

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Abstract: *Hyperpigmentation is the darkening or increase in the natural colour of the skin. Hyperpigmented skin lesions are a common occurrence in children. They maybe a separate entity or a manifestation of underlying systemic disease. A thorough knowledge and careful examination is needed for diagnosis and proper management of the conditions.*

Keywords: *Hyperpigmentation, Melanocytes, Congenital, Acquired, Epidermal and dermal melanosis*

Hyperpigmented disorders are commonly encountered dermatoses in children. Normal skin colour is determined by melanin in the melanocytes and to some extent by chromophores like hemoglobin and carotenoids.[1] Hyperpigmentation results from increased melanin production or due to deposition of exogenous materials like heavy metals and drugs in the skin.[2] These disorders can be classified as either congenital / acquired, circumscribed or diffuse, epidermal or dermal (Table I & II). Being the largest organ in the body, any deviation from normal colour of the skin results in cosmetic disfigurement and negative psychosocial impact in the child and parents.[3] Some common conditions seen are discussed in this article.

Congenital causes

Pigment demarcation lines (PDL): PDL are areas of abrupt transition from hyperpigmented to hypopigmented or normal skin colour. There are 8 groups of PDL

1. Anterolateral aspect of upper arm
2. Posteromedial aspect lower limb
3. Pre-sternal region of chest
4. Posteromedial aspect of spine
5. Line from mid third of clavicle to periareolar region
6. "V" shaped hyperpigmentation between temple and malar area in face
7. "W" shaped hyperpigmentation between temple and malar area in face
8. Band of hyperpigmentation from angle of mouth to lateral chin

Facial PDL pose cosmetic concerns where photoprotection, chemical peels (Glycolic acid peel) and laser (Q switched Alexandrite) have been tried with variable results.[4]

Café-au-lait macules: They are discrete tan coloured 2-20 mm macules / patches seen at birth or during childhood. Seen in 10-20% of normal individuals. Presence of 6 or more lesions measuring >5mm in someone <15 years old is a diagnostic marker for classic neurofibromatosis. They are not specific for neurofibromatosis but can be seen also in tuberous sclerosis, McCune-Albright syndrome, ataxia telangiectasia, Bloom syndrome, epidermal nevus syndrome, Russell-Silver syndrome.[5] They have no malignant potential and treatment is mainly cosmetic.

Ephelides / freckles: They are 2-3mm tan/ brown discrete macules on sun-exposed sites and sparing mucous membranes. They arise from childhood (2-4 years) and tend to fade in winter and increase in summer. The appearance of widespread freckles is associated with genodermatoses like Xeroderma pigmentosum. Photoprotection is the mainstay of treatment.

Lentigines: They are discrete 2-5mm brown to black macules seen in any site in skin and mucous membrane. If appears from childhood and shows no seasonal variation. Unilateral / Zosteriform lentigines is associated with segmental neurofibromatosis. Familial widespread lentiginosis is seen in LEOPARD Syndrome (Lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retarded growth and deafness), Peutz-Jeghers syndrome, Carney's complex, Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome and Cronkhite-Canada syndrome.[6]

Becker's nevus: It develops as unilateral pigmented patch on the shoulder, chest or back but any site can be involved.

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Table I. Hyperpigmentation – Congenital causes

Circumscribed	Physiological	Pigment demarcation lines
		Café-au-lait macules Speckled lentigenous nevus Becker nevus Lentigines Ephelides
	Nevoid conditions	Congenital melanocytic nevi Mongolian spots Nevus of Ota and Ito Blue nevus Incontinentia pigmenti
	Miscellaneous (rare)	Nevoid or whorled hypermelanosis Segmental pigmentation disorder
Diffuse	Idiopathic	Familial progressive hyperpigmentation
	Metabolic	Porphyria cutanea tarda Hemochromatosis Alkaptonuria Wilson's disease Gaucher's disease Niemann- pick disease

It is predominantly seen in adolescent boys. Hypertrichosis soon follows in the patch and the long, coarse hairs can sometimes extend beyond the patch. Associated conditions are smooth muscle hamartoma, unilateral breast hypoplasia, spina bifida and limb asymmetry. Q switched Ruby or NdYAG laser (1064nm) can be used for hypertrichosis and hyperpigmentaion.[7]

Congenital melanocytic nevi (CMN): It is found in 1% newborn infants as 1-5cm black coloured patch/plaque at any site over the body. Sometimes giant nevus >20 cm and nevi covering entire trunk "bathing trunk nevi" can be seen. Histology shows nest of nevus cells extending into the dermis. They may be junctional, compound or intradermal depending upon level of extension. The lifetime risk of malignant transformation is 4.5% to 10%. Small lesions can be excised followed by grafting. Lasers (Q switched Alexandrite/CO_2 laser) can be tried.

Mongolian spot: It is blue black macules or patch with indistinct margins seen at birth. Common site is lumbosacral area but aberrant locations such as face, extremities are seen. The characteristic colour of the lesion is due to Tyndall effect. They often regress spontaneously by 3-5 years and no treatment is needed. 3-4% are persistent with underlying metabolic disorders like Hunter's and Hurler's syndrome.[4]

Nevus of Ota and Ito: Unilateral blue black patch seen in the distribution of trigerminal nerve on the face. Also called as nevus fuscoceruleus ophthalmomaxillaris. The forehead, temple, periorbital area, cheek and nose are involved. Sometimes lesion can be bilateral. 50% are present at birth and the rest develop during puberty. Nevus of Ito is located in supraclavicular, deltoid and scapular region and is also called Nevus fuscoceruleus acromioclavicularis. Both Nevus of Ota and Ito are associated with Nevus flammeus (Portwine stain), cutis marmorata telangiectatia congenita and phakomatosis pigmentovascularis. Cosmetic camouflage and lasers (Q switched ruby, NdYAG, Alexandrite) are the treatment of choice.[8]

Incontinentia pigmenti: It is an X-linked dominant disorder characterised by linear vesicular eruptions at birth along the lines of Blaskcho. This is followed by verrucous lesions within a few weeks and swirled hyperpigmentation later which lasts for many years and is associated with ocular, CNS and skeletal abnormalities. Generally no treatment is needed.

Familial progressive hyperpigmentation: This disorder is characterized by bizarre pattern of hyperpigmented patches at birth that increases in size and number as the infant grows. No particular abnormality has been found for this pigment abnormality.[9]

Metabolic: Diffuse darkening is seen in various metabolic diseases. Photosensitivity and blistering are the predominant symptom in porphyria cutanea tarda. As age advances, blistering decreases and patients develops

Acquired causes (Table II)

Table II. Hyperpigmentation – Acquired causes

Circumscibed	Infections	Tinea versicolor Tinea nigra Confluent and reticulated papillomatosis
	Drugs	Fixed drug eruption
	Miscellaneous	Acquired nevomelanotic nevi Idiopathic eruptive macular hyperpigmentation Acanthosis nigricans
Diffuse	Physiological	Tanning
	Nutritional deficiencies	Kwashiorkor Vitamin B12 deficiency Folic acid deficiency Niacin deficiency Vitamin A deficiency
	Endocrine	Addison's disease Hyperthyroidism Cushing's disease
	Drugs	Sulphonamides Tetracyclins Antimalarials etc.
	Heavy metals	Silver, mercury, Arsenic, Gold
	Miscellaneous	Postinflammatory hyperpigementation Urticaria pigmentosa Carbon baby syndrome Bronze baby syndrome

atrophy, telangiectasia and dyschromia resulting in poikiloderma. Hemochromatosis is an iron storage disorder with diffuse hyperpigmentation of skin and mucous membranes. The juvenile form of hemochromatosis presents in childhood.[10] The pigmentation is due to melanin and not due to iron. Alkaptonuria is an inborn error of metabolism caused by lack of homogentisic acid oxidase. Dark urine in the diaper is the first sign in infants. Skin pigmentation appears later around eyelids, ear, nose cartilage, near tendons and nails. Correction of the underlying cause is the treatment.

Tinea versicolor: The chromic variant of Tinea versicolor presents as multiple hyperpigmented uniformly scaly macules and patches in the face, upper chest, upper trunk and arms caused by Malassezia species. The scales are fine and branny and show yellow fluorescence in Wood's lamp examination. Diagnosis is by demonstration of oval spores and short hyphae in "Spaghetti and meatball appearance" in KOH mount of skin scrapings. Treatment includes topical antifungal creams 1% clotrimazole, 1% miconozole, Whitfield's ointment for localized and systemic azoles for florid lesions.

Fixed drug eruption (FDE): It presents as circumscribed pigmented patch with erythematous halo following intake of certain drugs and heals with residual pigmentation. On re-exposure, the lesions appear in the same site as that of old lesions and also at new sites. The common drugs implicated in children are sulphonamides, paracetamol, phenobarbitone, NSAIDs, tetracycline, etc. Oral and genital mucosal involvement is commonly seen. Discontinuation of offending drug is the treatment.

Acanthosis nigricans (AN): It presents as distinctive, velvetty hyperpigmentation in flexural areas. The inherited type (autosomal dominant) erupts during infancy and childhood. The other types seen are endocrine type (pituitary tumors/PCOS), idiopathic type, drug induced and pseudo AN type (obesity associated).[11]

Acquired nevonmelanocytic nevi (ANN): It presents as small 1-2 mm pigmented macule developing in early childhood particularly on the upper trunk, head and neck. Depending upon the location of nevus cells, they can be junctional, compound or intradermal. The nevi may darken, increase in size or number during puberty. Excision is the

treatment if needed. ANN has the risk of developing melanoma.

Nutritional: Pigmentation is a common feature of nutrition deficiency states. In Vitamin A deficiency, there is brown pigmentation in the elbows and knees. Vitamin B12 can cause diffuse melanosis along with pancytopenia. Niacin deficiency causes pellagra with hyperpigmented eczematous skin in photoexposed / frictional site as the initial manifestation. Usually, the pigmentation persist even after correction of the nutritional deficiency.

Endocrine: In Addison's disease, there is increased pigmentation in the areas unexposed to skin like palmar creases, nipple, areola and axilla. There is pigment line in gums. This is due increased adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH). Associated hypotension, tachycardia, hypoglycemia, weight loss may be seen. Diffuse pigmentation has been reported with hyperthyroidism but rare.

Heavy metals: Argyria (silver) presents as localized or widespread bluish-gray or slate coloured pigmentation. Face, forearm, hands and mucous membrane are predominantly affected. Chronic exposure to mercury results in acrodynia (pink disease) in infants and children with slate gray pigmentation in skin. Arsenic excess can cause rain-drop pigmentation predominantly in the trunk. Chrysiasis (gold) presents as bluish gray or purplish pigmentation mainly around the eyes and mucosa are spared.

Postinflammatory hyper pigmentation: This condition presents as circumscibed patches of hyperpigmentation in the areas of previous dermatoses. Diaper dermatitis, insect bites, trauma, papulosquamous disorders like psoriasis, lichen planus, immunobullous disorders, infections, morpheoa are the common dermatoses resulting in post inflammatory hyper pigmentation in children. Usually no treatment is needed and lesions fade away in several months but for cosmetic significance depigmenting creams and spot peeling agents can be tried.

Carbon baby syndrome: Carbon baby or universal acquired melanosis is a condition of unknown etiology in which child develops diffuse pigmentation at 3-5 months of age and becomes jet black in 3-4 years. Histology shows increased melanin in the entire thickness of epidermis.

Bronze baby syndrome: This disorder shows generalized gray-brown pigmentation in neonates undergoing phototherapy for hepatocellular dysfunction. During phototherapy, the porphyrin compounds undergo photodestruction results in brown substance being deposited in skin. The condition is benign and no treatment is needed.

Conclusion

Most of the hyperpigmented disorders in children are benign while few may be marker of underlying life-threatening systemic disorder or a genetic disorder. A detailed history regarding the age of onset and progression and thorough physical examination for other associated features often leads to diagnosis in most of the conditions. Treatment is cause oriented ranging from topicals to lasers. Proper counseling about the condition to the parent and child is needed to avoid unnecessary anxiety.

Points to Remember

- ***Pigmentation disorders are common dermatoses seen in children.***
- ***Nevoid conditions are more common than other causes.***
- ***Skin pigmentation can be the sole manifestation of underlying systemic and genetic diseases sometimes.***
- ***Treatment is mainly for cosmetic concern in many cases and lasers are useful.***

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ADOLESCENCE

MEDIA USAGE IN ADOLESCENTS

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Abstract: *Current generation is growing in media driven world. However, as adolescent brain is still developing and have poor self-control, they can fall prey to the ill effects of media. It is important for pediatricians and parents to advice adolescents regarding safe use of media. This article gives an insight into media usage among adolescents and a quick guide to pediatricians in handling adolescents with media related problems in their office practice.*

Keywords: *Media use, Cyberbullying, Sexting, Media history, Digital boundary.*

In this technology driven era, the millennial are using digital media more than anyone could ever imagine. Adolescents, normatively have immature self-control, self-regulation and cognition as compared to adults and are most vulnerable to ill effects of media.

Using media, adolescents are able to easily access information and entertainment and stay connected with friends and family. Popular social media of 2019 in India are listed in Box 1 along with the percentage of individuals who use them.[1]

Current scientific evidence has linked increased media use to decreased outdoor and physical activities, decline in academic performance, problematic internet use, difficulty in making and maintaining social relations, sleep disturbance, issues surrounding online safety, compromised privacy and cyberbullying.

Digital citizenship is defined as appropriate and responsible behaviour while using technology. Education about digital citizenship is important and encompasses learning to respect others and to protect oneself and others online.

Box 1. Social media usage in India 2019

Facebook - 88.05%

Pinterest - 3.78%

YouTube - 3.65%

Instagram - 2.44%

Twitter - 1.82%

LinkedIn - 0.09%

The growth in interactive media platforms and their rapid adoption by young people is an indication of the compelling nature of social media tools, such as Instagram and Snapchat. Adolescents, who are highly attuned to peer relationships, find the social component of many of these platforms very rewarding. About 76% of teen-aged respondents in a recent Pew Research Center (a nonpartisan American think tank based in Washington DC) survey reported that they use social media.[2]

In 2018, three online platforms other than Facebook including YouTube, Instagram and Snapchat were used by majority of the adolescents. Overall, 84% of teens revealed that they currently have access to a game console at home and 90% said that they play video games of any kind (whether on a computer, game console or cell phone).[3] Excessive screen time can be due to online TV series as over a period of time the pattern to access media has changed with mobile phone screens replacing TV screens for entertainment.[4] Technology addictions are more common among single parent and lesser in nuclear and joint families. Psychiatric distress was seen more in mobile phone users as compared to those with internet addiction.[5]

Effects of media on adolescent health

Digital media usage has both advantages and disadvantages.

a) Adverse effects of media

Social media use is associated with experiences of online harassment, short sleep hours, delay in time to fall

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Box 2. Health hazards of media use

Behavioural problems

Obesity and postural problems

Poor sleep hygiene

Body image issues

Academic underachievement

Online dating and relationship issues, trafficking

Internet addiction

Substance abuse

Sexting, cyberbullying

Depression and suicide

FOMO (Fear of Missing out)

Nomophobia

asleep, sleep disruption and body image issues among girls and boys. Adolescents, being constantly online have sleep patterns affected which has negative impact on their mood.[6] Anger due to peer rejection in early adolescence but not in young adults leads to increased viewing of antisocial media content.[7] Adolescent victims of bullying who regulated their anger through maladaptive strategies (e.g. other-blame, rumination) showed higher levels of cyberbullying themselves.[8] Traditional media as an information source was not significantly associated with sexual risk behaviour outcomes, suggesting that social media platforms may offer special avenues for influencing sexual health behaviours (and potentially other health outcomes) not offered by traditional media sources. The adverse effects of media usage in adolescence are listed in Box 2.

A few important terms associated with digital hazards are explained below.

Cyberbullying: When internet, cell phones or other devices are used to send or post text or images intended to hurt or embarrass another person, it is termed cyberbullying. It is a form of online harassment where the derogatory remarks spread quickly and are known to become 'viral'. It is the most common online risk for all teens and could be devastating. It may result in severe psychological trauma. Several victims of cyberbullying are driven to suicide.

Box 3. Benefits of digital media

Access to knowledge

Emotional support and connectedness

Strengthening relationships

Self- identity

Awareness regarding health related issues

Self-expression

Community building and participation

Mobile health e.g. vaccination reminder apps, fitness apps, suicide helpline

Table I. Basic guide for eliciting media related history from parents

Television / Mobile screen	Time spent watching / watching with or without family member / discussion about the shows / TV installed in bedroom / TV watching rules/demands to buy products seen in advertisements.
Movies / Videos	Type of movies or videos being watched/any restrictions/nightmares or trouble after watching movies
Music	Type of music/discuss about the lyrics that parent object/any restriction on certain type of music
Video games	Familiarity with type of video games played / check on game's rating before buying / permission for downloading violent games / restriction on time spent playing video games
Internet	Access to individual computer / talking about the best use of the internet / aware of different websites visited / using any software to block visiting inappropriate / pornographic web sites
Books	Time spent reading books / providing variety of reading materials / discussing about the books read
Any other concerns	Use of tobacco or alcohol / body image or sexuality / display of aggressive behavior or foul language

Table II. Practical tips on setting digital boundaries

Digital apps / Procedures	Advantages
Apps that show the time spent online	Gives accurate time spent on each apps on daily basis
Apps that restrict access to social media sites	To restrict the time, spent online, these apps which prevent accessing social media sites after usage for a fixed duration. Also notification can be set up which pops up after certain amount of time is spent online
Use silent mode	Whenever working on something very important or during academic work this mode is used so that attention is not diverted and thereby time is well utilized
Turn off notifications	Helps indirectly in designating particular time to look at each app. Eagerness to check in to apps during notifications is controlled.
Curating digital timelines	Follows accounts that make the teens feel good and unfollow any accounts that fill them with guilt or dread whenever they pop up. Mutes the posts if they cannot unfollow.
Privacy settings	Determine those who might be able to see and share the messages that one posts.
Hiding phone	Taking phone out of the pocket and off the coffee table or study table or hiding it in the bag, or even in a drawer, can stop teens from reaching for their phones without intention
Use a watch	To check the time, use a watch there by the pull to use mobile to check time is reduced. This helps reducing mindless scrolling.
Set time aside	Setting time aside to scroll through apps and to respond helps teens to limit use of media devices
Set expectations	Letting friends and family know that teen is reducing screen time and might not reply as quickly as before will ensure their cooperation and encourage them to reduce screen time
Turn off devices before bedtime	To get a sound sleep, to turn phone off 1 hour before going to bed and to leave it outside the bedroom.

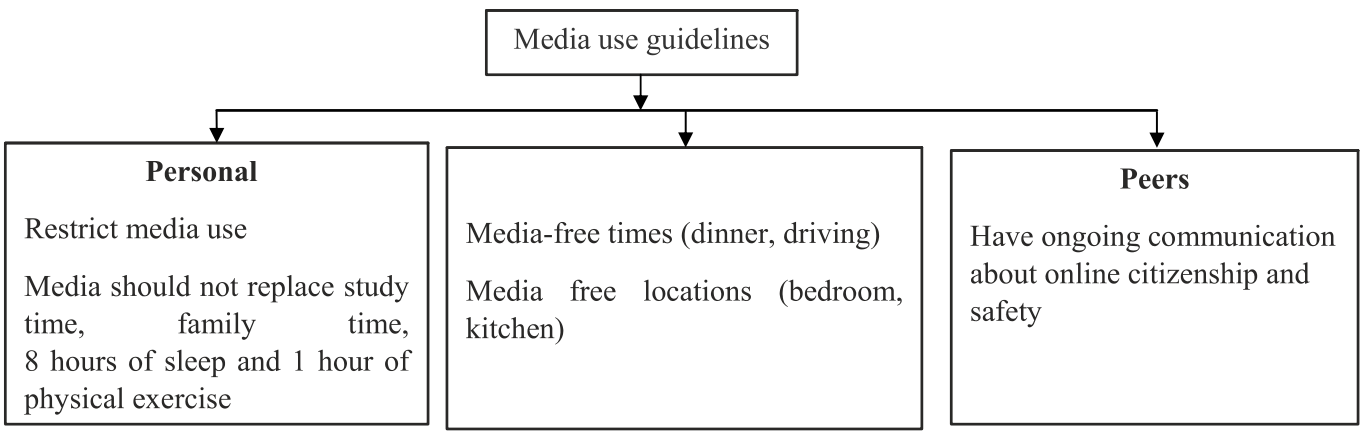

Fig.1. Media use guidelines

Sexting: Sending, receiving or forwarding sexually explicit messages, photographs or images is termed sexting. It is very dangerous as the adolescents can be blackmailed into recording of videos showing pornography and even sex trafficking. Sexting is a crime under 'Protection of Children from Sexual Offences (POCSO) Act'.

Internet gaming disorder (IGD): It is the excessive or uncontrolled internet gaming activity, leading to negative consequences in the psychosocial functioning of an individual. As IGD has been considered to be a significant public health issue, the Diagnostic and Statistical Manual has stated that it is akin to an alcohol use disorder.[9] Suggested nine criteria for IGD as proposed in DSM-5 are as follows: (i) preoccupation (ii) withdrawal symptoms (iii) tolerance (iv) unsuccessful control (v) impaired decision-making (vi) rewarding deficit (vii) escape (viii) deceit about internet gaming and (ix) impaired function. Similar criteria are used to define other addictive behaviours such as substance use disorder or gambling disorder.

Focusing on likes: is the need to gain "likes" on social media. This can cause teens to make choices they would otherwise not make, including altering their appearance, engaging in negative behaviors and accepting risky social media challenges.[10]

FOMO (Fear of missing out): It is a pervasive apprehension that others might be having rewarding experiences from which one is absent. This social anxiety is characterized by a desire to stay continually connected with what others are doing.

Nomophobia: It is a psychological condition where people fear of being without mobile phone or being unable to use phone for some reason, such as the absence of signal or running out of battery power.

Phantom vibration syndrome: It is the perception that one's mobile phone is vibrating or ringing when it is not ringing. In a study done in medical students, it was found that 60% felt phantom vibrations and 42% felt phantom ringing.[11]

b) Benefits of media

There are numerous advantages of media, if it is used in moderation. These are listed in Box 3.

Teens who struggle with social skills, social anxiety or who do not have easy access to face-to-face socializing might benefit from connecting with other teens through social media. Teens in marginalized groups - lesbian, gay, bisexual, transgender, transsexual, queer (LGBTQ) teens and teens struggling with mental health issues - can find support and friendship through the use of social media. When teens connect with small groups of supportive teens via social media, those connections can be the difference between living in isolation and finding support.

Role of pediatrician

Anticipatory guidance should be provided during a clinical encounter with an adolescent. Details of eliciting media history is listed in Table I.[12]

If there are issues with overuse of social media or mobile phones, then parents and the adolescent should be counselled for setting up digital boundaries and thereby decrease time spent on media. A few practical tips are enumerated in Table II. The screening tool for internet addiction is Young's internet addiction test and for IGD is problematic online gaming questionnaire. Psychotherapeutic interventions for media addiction include cognitive behavioral therapy (CBT) and motivational enhancement therapy.[13,14] Whenever there are features of associated mental disorders like depression and ADHD, appropriate screening, therapy and/ or referral to psychiatrist should be advised. Parents should be encouraged to talk about using media appropriately early in childhood and build a relationship of trust surrounding social media. This would improve communication between parent and adolescents regarding issues of media usage. Adolescents should be made aware about safe use of media not only in schools, colleges and community centers but also through radio, TV talks and articles in print media. Media use guidelines are outlined in Fig.1.[15]

Conclusion

Adolescents of today are known as digital natives as they are born in a world full of digital devices and media messages. Healthy media use in adolescence promotes socio emotional wellbeing and enhances knowledge. Excessive and unmonitored media usage can result in poor physical and mental health. Pediatricians should give anticipatory guidance and screen for media related health issues during adolescent health visits. Timely counselling and therapy will promote digital citizenship and prevent adverse health consequences.

Points to Remember

- ***Adolescent media usage has become an integral part of present day lifestyle.***
- ***Awareness regarding benefits versus ill effects (cyberbullying, sexting) is the need of the hour.***

- ***Education about staying safe in the digital world.***
- ***Pediatricians should give anticipatory guidance.***
- ***Parents need to talk regarding the healthy media use to their adolescents.***

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CLIPPINGS

Association between Screen Media Use and Academic Performance among Children and Adolescents - A Systematic Review and Meta-analysis.

In this systematic review and meta-analysis of 58 cross-sectional studies, television viewing and video game playing (but not overall screen media) were inversely associated with the academic performance of children and adolescents. In addition, the negative association between these screen-based activities and academic performance seemed greater for adolescents than for children. This study suggests that education and public health professionals should consider screen media use supervision and reduction as strategies to improve the academic success of children and adolescents.

Adelantado-Renau M, Moliner-Urdiales D, Cavero-Redondo I, Beltran-Valls MR, Martínez-Vizcaíno V, Álvarez-Bueno C. Association Between Screen Media Use and Academic Performance Among Children and Adolescents: A Systematic Review and Meta-analysis . JAMA Pediatr 2019; 173(11):1058-1067. doi:https://doi.org/10.1001/ jamapediatrics.2019.3176.

RADIOLOGY

THE DILATED COLLECTING SYSTEM-1

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The ultrasound of a normal kidney shows a central area that is bright due to the presence of echogenic fat. The renal pelvis and calyces lie in this area and are not seen unless there is accumulation of urine that will distend the pelvicalyceal system (PCS). In the same way the normal ureter also is not seen unless it is distended with urine. So, an obvious visible collecting system is a feature indicating some pathology even if the actual abnormality is not made out. Most often a calculus in the mid ureter is not visualised due to bowel gas and also the inability to compress abdomen and displace the gas because of pain or obesity. The presence of colic along with dilated PCS and upper ureter can be taken as indicative of a mid ureteric calculus even if it is not seen. Though CT will identify calculi with high accuracy, it carries the disadvantage of ionising radiation. Rarely do CT scans change the management of calculi as majority of them spontaneously resolve. Hence ultrasound is the primary imaging modality in suspected calculi and CT can be reserved for those who do not improve with conservative management. Calculi are the commonest cause of obstruction. Fig.1 shows a calculus at the pelviureteric junction (PUJ). It is a hyperechogenic focus with posterior shadowing. The pelvis and calyces are dilated and appear black.

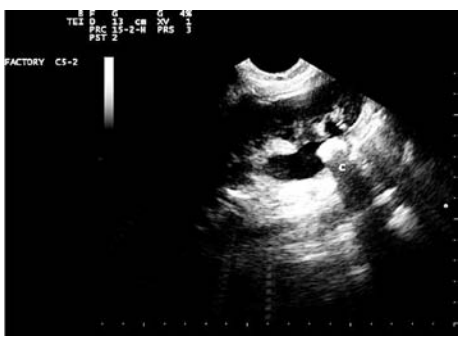

Fig.1. Calculus at PUJ. Note the after shadow(C)

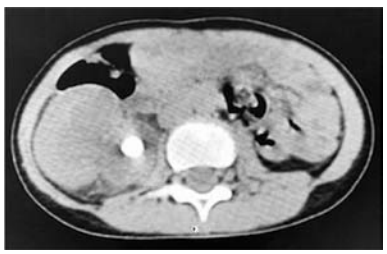

Fig.2. CT abdomen – PUJ calculus (right)

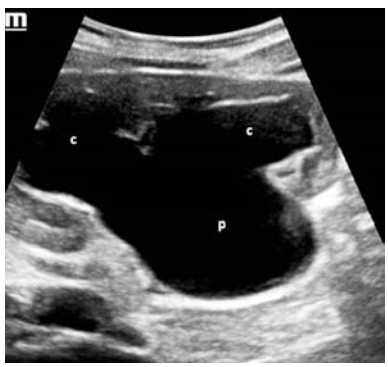

Fig.3. USG-PUJ obstruction - Coronal section (P- pelvis, C- calyx)

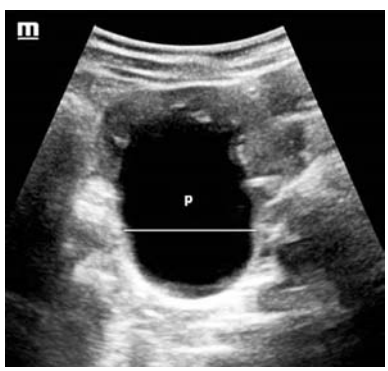

Fig.4. USG-PUJ obstruction - Cross section (P- pelvis)

The calculus in CT appears opaque just as in an X-ray. Fig.2 shows a calculus at the PUJ. In CT the Hounsfield unit (HU) is a value that quantifies the amount of x-rays that can pass through that tissue. The radiodensity of water is defined as 0, fat has a negative HU and blood

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Table I. Antenatal hydronephrosis - Classification

Trimester	Antero-posterior diameter of pelvis		
	Mild	Moderate	Severe
Second	4 to 6 mm	7 to 10 mm	> 10 mm
Third	7 to 9 mm	10 to 15 mm	> 15 mm

and other tissues have a positive HU. In the past decade CT has been used to predict the type of stone and determine the appropriate mode of treatment, so that HU has now become a part of clinical guidelines. A HU of less than 600 responds well to Extracorporeal Shock Wave Lithotripsy (ESWL) while a HU of more than 1000 is associated with poor ESWL success. A HU of less than 600 is also associated with poor success of percutaneous nephrolithotomy (PCNL) as PCNL uses fluoroscopic guidance and stones less than 600 HU are not well seen with fluoroscopy. Consequently residual stones may not be visible and may not be extracted.

Another common cause for PCS dilation is PUJ obstruction (Fig.3) which is now increasingly recognized because of antenatal ultrasound. Proper guidelines have been formulated for the management of these children so that renal damage is prevented. The antero-posterior diameter (APD) of the dilated pelvis is used to quantify the degree of dilation (Fig4). Antenatal hydronephrosis is present, if the APD is $\geq$ 4mm in second trimester and $\geq$ 7mm in the third trimester and classified as mild, moderate and severe (Table I). The higher the grade, more the likelihood of postnatal hydronephrosis and need for surgery. Spontaneous resolution or stabilisation is usual with the mild grade and quite common with moderate grade.

Another common renal anomaly is the duplex kidney characterised by two separate pelvicalyceal systems with complete or partial duplication of ureters. It can be

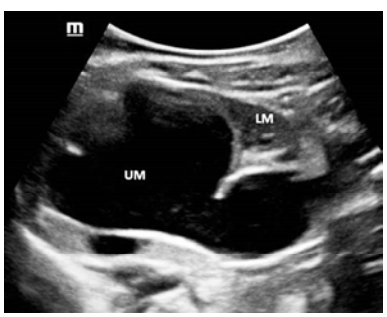

Fig.5. USG - Duplex collecting system (LM- lower moiety, UM- upper moiety)

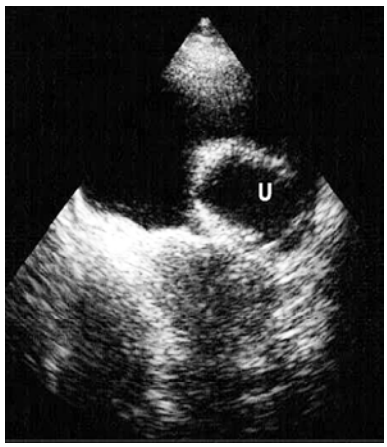

Fig.6. USG - Ureterocele (U)

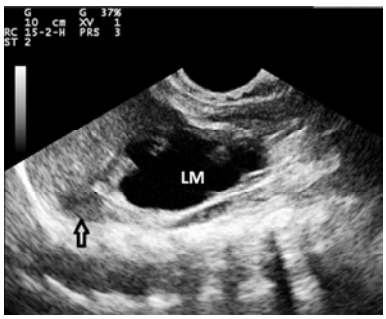

Fig.7a.USG-PUJ obstruction of lower moiety

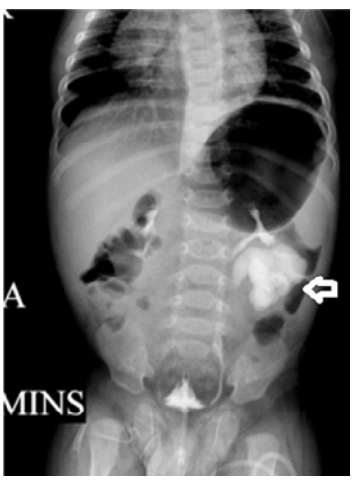

Fig.7b. IVU-PUJ obstruction of lower moiety

unilateral or bilateral and if uncomplicated remains asymptomatic. However, they are frequently complicated by dilation of the collecting system. The upper moiety ureter ends ectopically caudal and medial to the lower moiety or in the vagina, urethra or seminal vesicle and is prone for obstruction and non-excretion or dysplasia of that moiety. Fig.5 shows a dilated PCS and ureter of upper moiety. The parenchyma is also thinned. The terminal part of the ureter may be dilated to form a ureterocele (Fig.6). PUJ obstruction of the lower moiety is another presentation (Fig.7a and 7b).

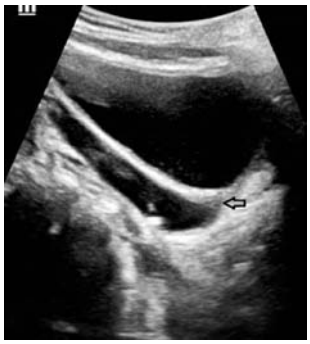

Fig.8a. USG-Primary megaureter Note the beaked appearance of terminal ureter

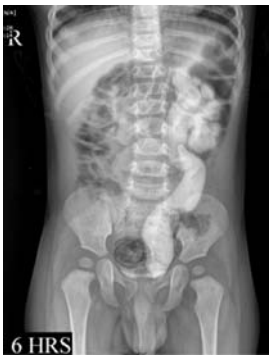

Fig.8b. IVU-Primary megaureter

Another common renal anomaly is the duplex kidney characterised by two separate pelvicalyceal systems with complete or partial duplication of ureters. It can be unilateral or bilateral and if uncomplicated remains asymptomatic. However, they are frequently complicated by dilation of the collecting system. The upper moiety ureter ends ectopically caudal and medial to the lower moiety or in the vagina, urethra or seminal vesicle and is prone for obstruction and non-excretion or dysplasia of that moiety. Fig.5 shows a dilated PCS and ureter of upper moiety. The parenchyma is also thinned. The terminal part of the ureter may be dilated to form a ureterocele (Fig.6). PUJ obstruction of the lower moiety is another presentation (Fig.7a and 7b).

NEWS AND NOTES

CASE REPORT

MORE THAN WHAT MEETS THE EYE – INVASIVE FUNGAL INFECTIONS IN TWO IMMUNOCOMPETENT CHILDREN PRESENTING AS LYMPHOMA

*Meena S
*Shivani P
*Venkateswaran VS
*Dharaani J
*Ramya Uppuluri
*Revathi Raj
**Annapoorneswari
**Parmar HV

Abstract: *Invasive fungal infections are rare in children, seen almost exclusively in immunocompromised patients. We report two immunocompetent children who presented with clinical features suggestive of lymphoma and were diagnosed to have conidiobolomycosis and pheohyphomycosis on tissue biopsy. They were treated with liposomal amphotericin B and voriconazole respectively and are now in remission with a median follow up of 6 months. These two cases are reported in view of the rarity and to highlight the importance of tissue biopsy and multi-disciplinary approach.*

Keywords: *Immuno-competent, Invasive fungal infection, Tissue biopsy*

Invasive fungal infections are rare in children with high incidence among children with primary immune deficiency disorders, those undergoing treatment with chemotherapy, immunosuppressive therapy and post hematopoietic stem cell transplantation. Invasive candidiasis and aspergillosis are the most common life threatening fungal infections reported in children.[1] We present two children with clinical features suggestive of lymphoma where tissue biopsy confirmed the diagnosis of invasive fungal infection.

* Department of Pediatric Hematology and Blood and Marrow Transplantation

** Department of Histopathology, Apollo Cancer Institute, Chennai.

email: drmeenas1986@gmail.com

Case Report 1

A six year old boy from eastern India presented with cough of one month duration associated with episodes of hemoptysis. On examination, he was well nourished with no lymphadenopathy or organomegaly but with decreased air entry in the right posterior lung fields. His blood counts, renal and liver parameters were normal. High Resolution Computed Tomography (HRCT) chest revealed an ill-defined mass in the posterior mediastinum compressing the lower lobe of the right lung, surrounding the lower branch of pulmonary artery (Fig.1). Suspecting lymphoma, CT guided biopsy was performed. Histopathology of the lung tissue was reported to have epitheloid cell granulomas with inflammatory infiltrates rich in eosinophils. Fungal elements were found along with Splendore Hoeppli phenomenon (asteroid bodies). It is characterised by

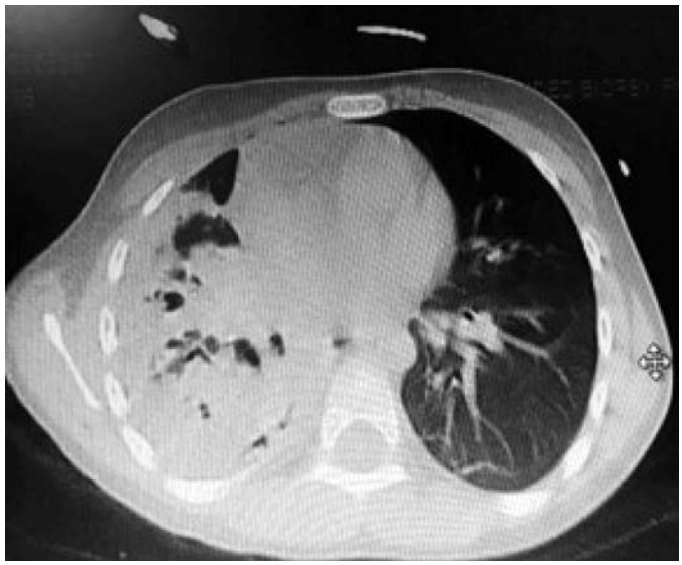

Fig.1. CT chest showing ill defined mass in the posterior mediastinum compressing the lower lobe of the right lung

microorganisms (fungi, bacteria and parasites) surrounded by radiating intensely eosinophilic material (Fig.2). The eosinophilic material has been described to be due to deposition of antigen – antibody complexes and debris from the host inflammatory cells. Fungal cultures were negative (fungal cultures of tissue biopsy is generally negative with positivity ranging from 15-25%). The histopathological

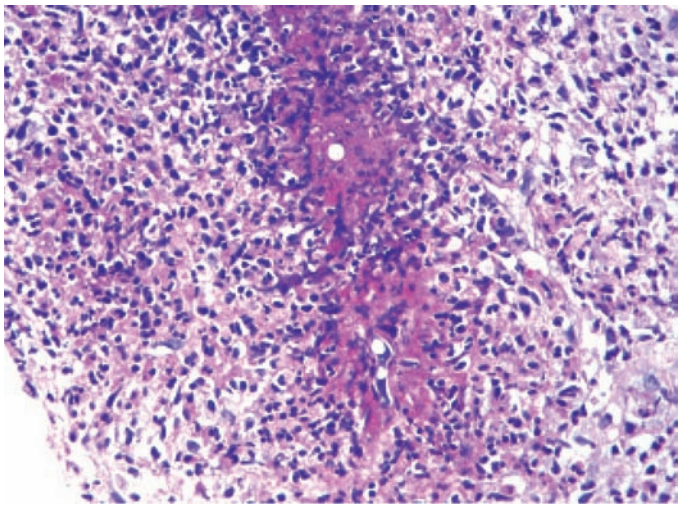

Fig.2. Fungal elements with Splendore Hoeppli phenomenon suggestive of conidiobolomycosis

features of Splendore Hoeppli phenomenon with the characteristic fungal hyphae were suggestive of conidiobolomycosis. Infectious disease experts were consulted and he was treated with liposomal amphotericin-B at a dose of 5mg/kg/day for 4 weeks with regular renal and liver function monitoring followed by oral posaconazole for 3 months. He was extensively worked up for immune deficiency including whole exome sequencing which were normal. He is now 9 months post treatment and serial imaging revealed complete resolution of the lesion and the child is doing well.

Case Report 2

A five year old girl presented to the pediatric neurologist with complaints of sudden onset right sided facial twitching. She is developmentally normal and with no significant past or family history. Her systemic examination was unremarkable. MRI brain revealed contrast enhancing lesions in the frontal cortex (Fig.3) suggestive of neurotuberculosis. She was started on

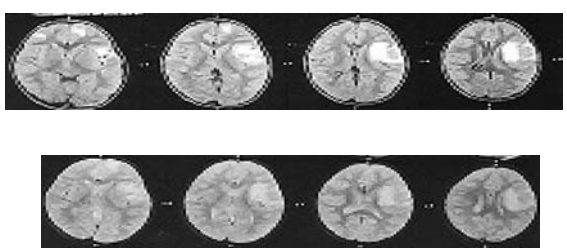

Fig.3. MRI shows ill defined hyperintense lesion over the frontal and parietal region

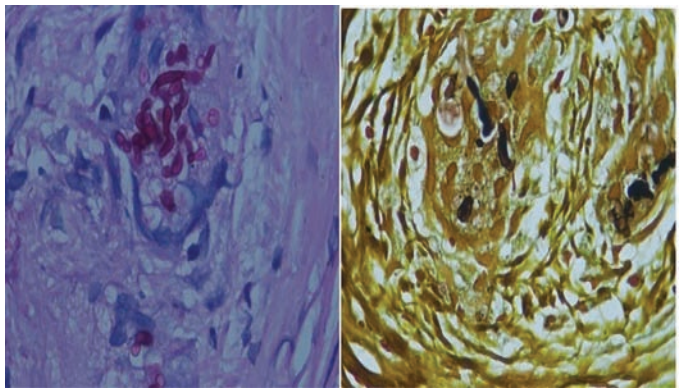

Fig.4. Fungal elements resembles phaeohyphomycosis

antituberculous therapy and anticonvulsants. Chest X-ray and ultrasound abdomen were performed to rule out disseminated tuberculosis which revealed mediastinal widening and suspicious hypodensities in the liver. Whole body PET CT was performed which revealed metabolically active lesions in the left frontal cortex, liver, mediastinum and retroperitoneal nodes suggestive of lymphoma. Histopathology from the ultrasound guided biopsy of liver lesion revealed fungal elements with features consistent with pheohyphomycosis (Fig.4). She was worked up for underlying immune deficiency and all evaluation including gene mutation analysis were normal. She was treated with intravenous voriconazole at a dose of 7 milligram/kilogram/dose twice dialy for 2 weeks in consultation with infectious disease specialists, followed by oral voriconazole for 3 months. Follow up imaging was suggestive of significant reduction in the size of the lesions. She has been continued on oral voriconazole and is now 5 months on follow up and clinically well.

Discussion

The annual incidence of invasive fungal infections including aspergillosis has been reported to be 0.4%.[2] The burden has increased in recent times with increase in the number of immunocompromised patients.[3-5] Risk factors include post high dose chemotherapy namely children diagnosed to have relapsed leukaemia, acute myeloid leukaemia, post hemopoietic stem cell transplant (HSCT), graft versus host disease, immunosuppressive therapy, PIDs particularly chronic granulomatous disease, HIV, profound neutropenia, aplastic anemia and associated cytomegalovirus infection.[6-7] An associated mortality rate of 58% has been reported, most likely as a result of delay in diagnosis. Its an emerging infection even in immunocompetent individual and must be considered in our spectrum of differential diagnosis. A high index of

suspicion with a multi-disciplinary team approach including radiologists, microbiologists, pathologists, infectious disease specialists and pediatricians is the key to early diagnosis and treatment so as to provide optimal care for these children.

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CLIPPINGS

Minimally invasive surfactant therapy (MIST) failure: risk factors and outcome

A retrospective cohort study was performed in two tertiary neonatal intensive care centres in the Netherlands. Infants born between 24 weeks' and 31 weeks' gestational age (GA) (n=185) with MIST with poractant alfa (100-200mg/kg) for respiratory distress syndrome were included. MIST failure was defined as need for early mechanical ventilation (<72 hours of life). 30% of the infants failed CPAP after MIST. In a multivariate logistic regression analysis, four risk factors were independently associated with failure: GA <28 weeks, C reactive protein ≥10 mg/L, absence of antenatal corticosteroids and lower surfactant dose. Infants receiving 200mg/kg surfactant had a failure rate of 14% versus 35% with surfactant dose <200mg/kg. Furthermore, MIST failure was independently associated with an increased risk of severe intraventricular haemorrhage.

Janssen LC, Van Der Spil J, van Kaam AH, et al Minimally invasive surfactant therapy failure: risk factors and outcome. Archives of Disease in Childhood - Fetal and Neonatal Edition 2019; 104:F636-F642.

NEWS AND NOTES

PEDICON 2020

57th Annual Conference of the Indian Academy of Pediatrics

Date: 9th - 12th January, 2020

Venue: Brilliant Convention Centre, Indore

Conference Secretariat:

Dr.V.P.Goswami, Chief Organizing Secretary, PEDICON 2020

Email: info@pedicon2020.com; Phone: +91 93722 75650; website: www.pedicon2020.com

AUTHOR INDEX

SUBJECT INDEX

Dr.Mehta's Hospitals

7th DNB PEDIATRICS OSCE WORKSHOP & MOCK EXAM

Organised by: The Department of Pediatrics, Mehta Multispeciality Hospitals India Pvt. Ltd.

"Intensive OSCE Training"

Venue: Hotel Savera, Dr.Radhakrishnan Salai, Mylapore, Chennai

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Dates: 14th - 16th February, 2020

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Email: drm1@mehtahospital.com / drm2@mehtahospital.com

NEWS AND NOTES

POSICON 2020: 26th Annual Conference of the Paediatric Orthopaedic Society of India

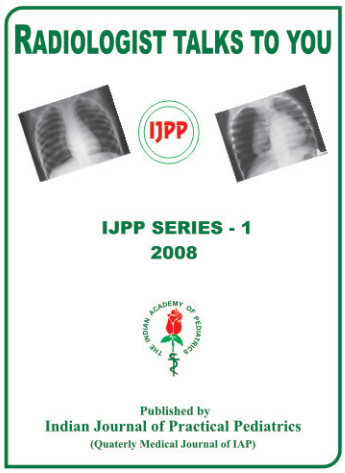
Date: 9th – 12th January, 2020

Workshop Venue: Live Surgery Workshop - 9th & 10th January, 2020 - Ganga Hospital, Coimbatore.

Conference Venue: 11th & 12th January, 2020 - Hotel Radisson Blu, Coimbatore.

Contact No. : 914222485000; landline: 0422 - 4345130

Email: posicon2020@gmail.com



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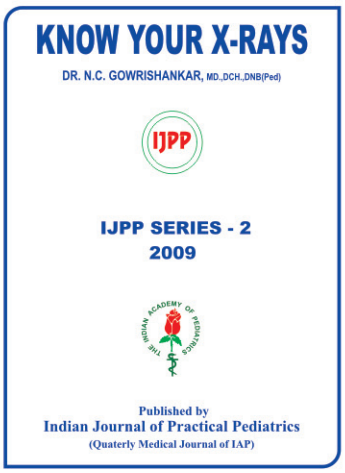

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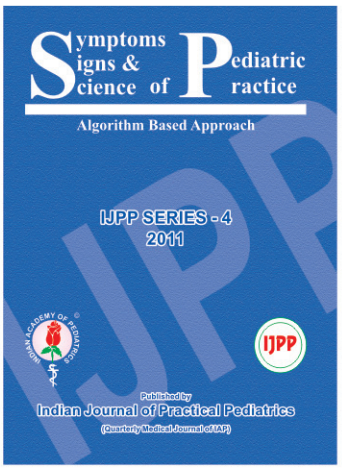

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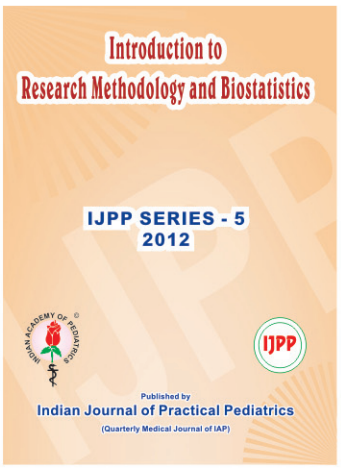

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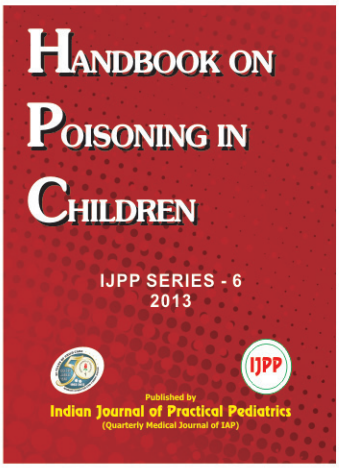

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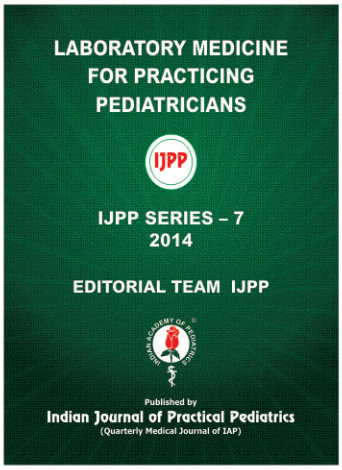

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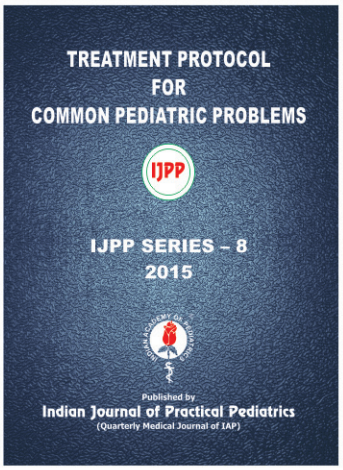

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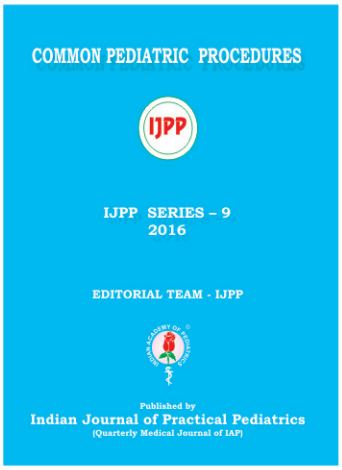

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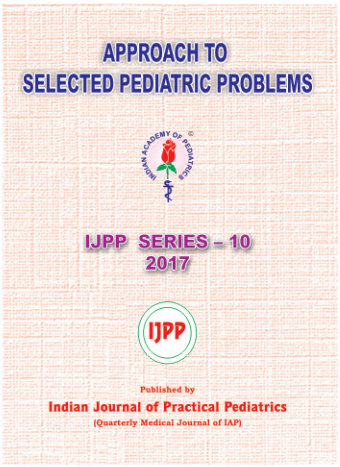

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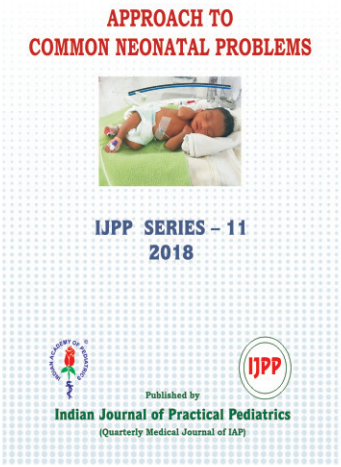

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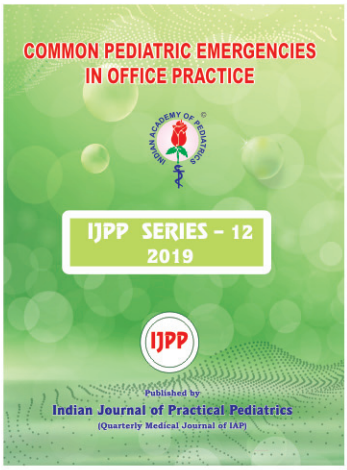

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Organised by

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&

IAP Respiratory Chapter, TN.

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