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TOPIC OF INTEREST - "PULMONOLOGY"

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PULMONOLOGY

RESPIRATORY DISTRESS IN PRETERM NEONATES - A PRACTICAL APPROACH

**** Sridhar Kalyanasundaram***
***** Vidya Kanamkote Narayanan***

Abstract: *Respiratory distress syndrome is one of the most common morbidities faced by a preterm neonate. Many interrelated factors impact the approach to the management of respiratory distress. In this review, a practical and evidence-based approach to the management of preterm babies with respiratory distress, right from the delivery to the period when the respiratory distress gets resolved, is discussed*

Keywords: *Prematurity, Respiratory distress, Surfactant, Ventilation.*

With the major advances in neonatal intensive care over the past three decades, the survival of preterm babies has seen significant improvement. This applies to both the developed countries (where the threshold of viability has dropped from 24 weeks to even 22 weeks in some of the more advanced centers) as well as the developing countries such as India (where more extreme preterm babies between 24-26 weeks gestation are surviving).[1,2] Neonatal respiratory distress syndrome (RDS) is still a major cause of morbidity and mortality and impacts the outcome of a significant number of preterm babies. In this review, the focus is on a practical evidence-based approach to the management of this important condition.

Antenatal care and delivery room management

Good antenatal care can reduce the incidence of prematurity and this is an important area that needs more work in the developing world. Appropriate and timely use of antenatal steroids can reduce the severity of RDS due to surfactant deficiency. The first course is indicated in any situation where there is a high risk of preterm delivery between 24 and 34 weeks of gestation.[3] Careful identification of the risk of preterm delivery is important to avoid its use in situations where the risk of preterm delivery is low. Either betamethasone or dexamethasone can be used depending on local availability. A single repeat course of steroids can be considered if the baby is likely to be delivered (imminent delivery) before 32 weeks gestation, and more than 2 weeks have elapsed since the last dose (when given as part of the first course).[3] No further repeat doses are advisable. The use of antenatal steroids beyond 34 weeks and for elective LSCS at full term is not very clear. Though there is some evidence supporting a reduction in respiratory distress-related morbidity, there has been some concern related to long-term development.[4]

Attention to adequate preparation at delivery, preventing hypothermia, and delayed cord clamping are important. Hypothermia can affect the severity of the RDS. Measures to prevent hypothermia include maintaining the delivery room temperature between 24-25^{O}Celsius, using an overhead warmer, plastic bags to receive the preterm babies and using a thermal mattress. Delayed cord clamping will improve the hemodynamic stability of the preterm neonate by improving circulating blood volume and hemoglobin levels.[5] Hence one must ensure that the obstetric team is comfortable doing this (delay by 30-60 seconds, even if a preterm baby is not active or crying, as long as the cord pulsations are well felt with a fetal heart rate over 100 beats per minute). Delaying cord clamping until the lung expansion is achieved will likely be the emerging approach in the future. Current studies are looking into resuscitation measures provided at the mother's side to enable delayed cord clamping even in babies needing resuscitation at delivery. The results of these studies will inform us further on this aspect.

'In terms of respiratory support, ensure that the team follows the guidelines from the locally approved neonatal resuscitation program (NRP). It is better to use a T-piece device at resuscitation, as the pressure delivered as well as the inflation times are better regulated, and a reliable positive end-expiratory pressure (PEEP) can be delivered.[6]

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These can also be used to initiate continuous positive airway pressure (CPAP) at delivery using the face mask with a good seal. The team should be aware that the flow should be set at 10 liters/minute, and the flow must not be adjusted after the initial setup if the required pressure is achieved. They should also be aware that any increase in the flow will increase the delivered pressures,and this might increase the risk of lung injury.The fraction of inspired oxygen (FiO_2) for babies at or below 32 weeks gestation, needing support is initiated at 0.3 at birth, and titrated as required based on the age-appropriate saturation targets (as specified by NRP).[7] For babies born at over 32 weeks, resuscitation can be initiated in room air, and oxygen started as guided by the saturation. In any case, oxygen blenders are essential in the delivery room for the management of preterm babies.

If the preterm baby needs positive pressure ventilation as per NRP steps (due to apnea or low heart rate), bag and mask ventilation is started and if the baby is improving well with good respiratory efforts, CPAP is initiated in the delivery room using the T-piece device and face mask with a good seal, and later switched to the nasal prong CPAP at transfer using the transport ventilator. If the preterm baby needs intubation as part of the resuscitation process, it is better to transfer the baby to the neonatal intensive care unit (NICU) on a ventilator and consider the need for surfactant therapy, based on the pressure and oxygen requirement. Subsequent management will be based on the clinical picture.

Initial management of preterm babies with respiratory distress in NICU

Some important principles including the golden hour management guidelines[8] and guidelines for intraventricular hemorrhage (IVH) prevention[9] should be adhered to as well as measures to prevent infection.

It should be remembered that RDS is an evolving disease, so the picture at any point in time is likely to change depending on the progress of the condition as well as the response to the intervention. Because of this, continuous and careful evaluation at every step with appropriate and timely intervention is essential. There is good evidence showing that early surfactant therapy is better than the delayed surfactant therapy, though there is no clear evidence to support prophylactic surfactant therapy even inextremely pretermbabies.[10] When the preterm baby has respiratory distress and needs intubation (as part of the resuscitation process), surfactant is given once the baby is in the NICU (can be given in the delivery room if the clinical condition demands). There is clear evidence that even the extreme pretermbabies can be safely managed on non-invasive modes of ventilation, with close monitoring of the clinical condition and early surfactant therapy based on the met criteria.[11] The European consensus guidelines[2] suggest the fraction of inspired oxygen (FiO_2) of 0.3 at CPAP pressure of 6 cm H_2O as an indication for surfactant therapy.

The severity of RDS can be determined clinically using a combination of the FiO_2 needed to maintain normal saturation, assessment of the work of breathing, vital signs, and arterial blood gas picture. The main clinical parameters that suggest respiratory distress include tachypnea, grunting and retractions, the severity of each one of these can differ amongst these babies. The clinical scoring tools which help to assess the severity of respiratory distress include the Downe's and Silverman's scores of respiratory distress.[12] Though these could help in the objective assessment of the severity of respiratory distress, it is not essential to score if the experienced clinician can assess the severity based on overall clinical assessment. The other factors include the degree of aeration of the lungs on the chest X-ray and the PCO_2on the blood gas. In babies under 28 weeks gestation, hypercapnea related issues such as the risk of intraventricular hemorrhage (IVH) are worrisome, especially in the initial 72 hours of life. One should also remember that the source of blood gas, as a capillary blood gas sample will have a higher PCO_2than an arterial sample. Lung ultrasound is a very useful tool that could help to monitor the lung condition, and support decision-making.[13] It can be used fairly easily and one could consider introducing it after suitable training.

All these parameters can fluctuate rapidly based on the clinical condition and can be influenced by the efficiency of CPAP delivery. Expert neonatal nursing care is essential to ensure adequate pressure delivery with appropriate humidification of the inspired gases (if for any reason the humidifier is not turned on, the baby will get cold air with a high flow through the CPAP machine; this is not only very uncomfortable for the baby but it will also lead to worsening of the lung condition). Adequate thermoregulation and minimal handling must be ensured.

Normally, one can start with CPAP of 5-6 cm. There are three possibilities from this stage: 1) Baby stays stable on CPAP which is evident from improving respiratory distress and blood gas parameters and the FiO_2 stays below 0.3. In this case, the CPAP is continued and weaned according to unit practices. 2) If the baby has significant retractions, and respiratory acidosis with or without an abnormal chest X-ray and the FiO_2 more than 0.3 or approaching 0.3, surfactant therapy is initiated.[2]

3) If the baby has increasing distress but with good respiratory efforts, PCO_2 is borderline high but the FiO_2 is below 0.3, CPAP can be increased to 6 to 7 cm H_2O as maximum, and the clinical assessment repeated after 1-2 hours to decide on surfactant therapy.

It is better to avoid using relatively high pressures on CPAP or noninvasive positive pressure ventilation (NIPPV) before using surfactant therapy in RDS. In the first 2-3 days, when RDS is evolving, surfactant deficiency is the underlying factor, and the aim is to replace surfactant early as discussed above.[10] When high pressures are used on the stiff lung (with low compliance), it increases the risk of air leak, and the high pressure used could potentially increase the risk of other complications in the very preterm babies (including the increased risk of spontaneous intestinal perforation). In resource-limited settings, because surfactant is expensive, cautious use of higher pressures (CPAP or NIPPV) is considered, the increased risk of pneumothorax being a trade-off.

The target oxygen saturation is similar to any other preterm baby in the NICU, which is in the range of 90-94%.[2] During this acute phase, it would help make a timely (early) decision on surfactant requirement, if the FiO_2 is adjusted based on the saturation target closer to 94% than to 90%. For example, the baby might maintain 90-92% at 0.25 FiO_2 but would need closer to 0.3 FiO_2 to maintain 94% in such cases. The decision to give surfactant is not based on FiO_2 alone, as if the FiO_2levels do not meet the criteria but the baby has clinical findings suggestive of RDS including increased work of breathing, high PCO_2 on the blood gas and abnormal chest X-ray, surfactant would have to be administered. Lack of antenatal steroids, possibility of infection, birth asphyxia, features of persistent pulmonary hypertension (PPHN) etc., would add to the risk as well.

Once the decision has been made that the baby needs surfactant based on the above, the next decision is whether to go for less invasive surfactant administration therapy or if the baby needs to stay ventilated for a brief period. Though most are in favor of less invasive surfactant administration therapy, patient's conditionis important to avoid repeated intubation and procedures. A high PCO_2, recurrent apnea, hypotension or other hemodynamic instability, features of PPHN, infection or significantly increased work of breathing in a baby less than 1 kg are factors that would tilt the decision towards keeping the baby ventilated for a few hours after surfactant therapy.

If the baby is stable (this can be individualized according to unit guidelines, for example, weight over 1 kg, PCO_2 below 65 mmHg, FiO_2 below 0.6, no features of sepsis, and otherwise hemodynamically stable), we could go for less invasive surfactant therapy. Less invasive surfactant administration (LISA) and Intubate, Surfactant, and Extubate (INSURE) are the main treatment options.[14,15] Though LISA has been shown to have a clear-cut reduction in bronchopulmonary dysplasia (BPD) risk, the INSURE technique is more straightforward in terms of making sure the tube is in the right place using end-tidal CO_2 calorimetric detection as well as less leak, thus reducing the risk of surfactant wastage (an important factor in resource-limited settings). As long as the baby is extubated soon after surfactant, the pulmonary outcome is unlikely to be significantly different between INSURE and LISA.

If there are clinical concerns and the baby is kept intubated and ventilated after the surfactant dose, it should be aimed to extubate at the earliest possible. A similar approach could be used for further doses of surfactant as well, in case the baby's clinical condition suggests the need. Though premedication is preferred before elective intubation, it is still not clear whether we should consider premedication before less invasive surfactant therapy, as it might increase the chances of needing further support.[16] Once the surfactant has been administered and the baby is back on non-invasive ventilation, CPAP or NIPPV could be used as per the unit practice guided by FiO_2, blood gas, and work of breathing.

Respiratory management after stabilization

In case the baby is intubated and ventilated, the aim should be to extubateat the earliest possible, except in the tiniest babies under 26 weeks, where a few days of ventilation is preferred (higher risk of extubation failure with associated atelectotrauma which could worsen the overall outcome in these extreme preterm babies). If the baby is not successfully extubated by 7-14 days (the more preterm the baby, the wait can belonger), low-dose dexamethasone distress assessment and replacement therpy (DART protocol - low dose corticosteroids after first week of life to facilitate extubation in ventilator-dependent very preterm infants) can be considered.[17] Once extubated, the baby is usually maintained on CPAP or NIPPV and when the baby tolerates weaning pressure, HFNC therapycan be considered. In babies less than 32 weeks or those below 1.25 kg, maintenance of noninvasive ventilation is considered (NIV-either CPAP or HFNC at the lowest level tolerated till they reach 32 weeks of gestation and 1.25 kg weight). This approach, along with caffeine and a two-hourly tube feeding pattern (to reduce the risk of reflux that is possible in this group, when 3 hourly feeds is used with a higher volume) tends to reduce the intermittent

hypoxic episodes.[18] This is because as these small babies areprogressing with the feeds, reflux tends to overlap and whenever there is a slight reflux episode, they hold their breath with reflex laryngospasm. The lung de-recruits during this episode and the above suggested background pressure with NIV tends to recruit the lungs quicker in these tiny babies who would struggle otherwise. This is likely to prevent the persisting or prolonged intermittent hypoxic episodes (which can be linked to neuro development as well).[19]

Supportive management

Supportive treatment is very important in the successful management of preterm babies with respiratory distress.[2] Early loading dose of caffeine followed by maintenance caffeine is important. Avoiding hypothermia is essential. Antibiotics to cover early-onset infection are usually started in symptomatic preterm babies, but if markers are negative and the blood culture is negative, stopping by 36 hours is aimed in most cases. Appropriate attention to nutrition is important and if the weight and gestation would warrant the use of total parenteral nutrition (TPN), infusion through central lines would be considered as per unit policy. Excess fluid intake has been shown to increase the risk of BPD, patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC), so it is better to have fluid intake on the lower side as tolerated.[2] Trophic feeds with expressed breast milk (EBM) is aimed at the earliest possible in these babies, whether they are on invasive or non-invasive ventilation. If the baby is hemodynamically stable, feeds can be increased as per unit protocol to full feeds. Though PDA management is still controversial, in extreme preterm babies, there could be a beneficial impact of an early screening approach, with paracetamol or ibuprofen treatment if indicated.[19,20]

Conclusion

Though the above practical approach is suggested in the management of preterm babies with RDS, an individualized assessment and regular review of the clinical parameters are crucial to ensure a successful outcome. It is also important to have unit-specific guidelines that would cover all the aspects discussed here and together with regular quality improvement projects, would go a long way in ensuring evidence-based practice.

Points to Remember

- ***Respiratory distress syndrome (RDS) is a continuously evolving problem-and though the guidelines are important, an individualized care plan that is constantly reviewed based on the immediate clinical picture is essential to ensure optimal care. Early surfactant therapy will improve outcomes in preterm babies with RDS who need this treatment.***
- ***In babies who need surfactant therapy, the option to use the less invasive surfactant delivery methods, using LISA or INSURE is evaluated.***
- ***All units should strive for a standardized evidence-based approach to care for preterm babies, including the golden hour approach, IVH prevention, RDS management and infection prevention.***

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CLIPPINGS

National PReCePT Programme: a before-and-after evaluation of the implementation of a national quality improvement programme to increase the uptake of magnesium sulfate in preterm deliveries

Since 2015, the UK National Institute for Health and Care Excellence (NICE) has recommended administration of magnesium sulfate ($MgSO_4$) for fetal neuroprotection in very preterm deliveries (24-30 weeks' gestation). However by 2017, only two-thirds of eligible women in England were given $MgSO_4$, with wide regional variations.

The National PReCePT (Preventing Cerebral Palsy in Pre Term labour) was a quality improvement (QI) intervention in Maternity units (N=137) within NHS England and the Academic Health Science Network (AHSN) in 2018. This study aimed to evaluate the effectiveness and cost-effectiveness of the National PReCePT Programme (NPP) in increasing use of magnesium sulfate ($MgSO_4$) in preterm births.

The main outcome measures were $MgSO_4$ uptake post implementation and lifetime cost estimation. It was found that the average $MgSO_4$ uptake for babies born ≤30 weeks' gestation, in 137 maternity units in England, increased by 6.3percentage points to 83.1% post implementation. The health gains and cost savings associated with the NPP effectiveness generated a net monetary benefit of £866 per preterm baby and the probability of the NPP being cost-effective was greater than 95%.

This national QI programme was effective both in terms of implementation and cost saving. Research evidence can take decades to translate to clinical practice, as was the case for antenatal steroids. This study shows that national, network-supported QI programmes can accelerate uptake of evidence-based therapies and promote improvements in perinatal care. The PReCePT model may serve as a blueprint for future interventions in improvement of perinatal care.

Edwards HB, Redaniel MT, Sillero-Rejon C, Margelyte R, Peters TJ, Tilling K et al. National PReCePT Programme: a before-and-after evaluation of the implementation of a national quality improvement programme to increase the uptake of magnesium sulfate in preterm deliveries. Arch Dis Child: Fetal Neonatal Ed. 2023; 108:342-347.

PULMONOLOGY

RESPIRATORY DISTRESS IN TERM NEONATES - AN APPROACH

**** Sindhu Sivanandan***

Abstract: *Respiratory distress in a neonate manifests as tachypnea, chest retractions or grunting. In a term neonate the etiology of respiratory distress is more varied and includes transient tachypnea of newborn, respiratory distress syndrome due to surfactant deficiency, meconium aspiration syndrome, pneumonia, air-leak syndrome and congenital malformations. Early recognition of respiratory distress and prompt initiation of appropriate treatment improves outcomes.*

Keywords: *Respiratory distress, Term neonate, Meconium aspiration syndrome.*

Respiratory distress (RD) occurs in 5% of all neonates RD affects 30% of preterm and around 15-20% of term neonates.[1] One third of all neonatal intensive care admissions are due to RD. Management includes evaluating the neonate for the severity and cause of respiratory distress and prompt initiation of appropriate respiratory support.

Respiratory distress is diagnosed when atleast two of the following signs are noted; tachypnea (respiratory rate ≥60 per minute), subcostal/intercostal recessions and expiratory grunt. Other signs include the presence of nasal flaring, suprasternal retractions, decreased air entry on auscultation of the chest and hypoxia (oxygen saturation less than 90%). A neonate with severe distress may manifest with gasping, stridor (a sign of upper airway obstruction), apnea, bradycardia, poor perfusion or severe cyanosis. These are life threatening signs that require prompt intervention.

Etiology

The causes of RD in a newborn are varied with conditions arising from airway, lungs, chest wall, neuromuscular diseases, cardiac disorders and others (Box 1). According to the neonatal perinatal database

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Box 1. Common causes of respiratory distress in the newborn[3]

Upper airway disorders
Choanal atresia
Pierre Robin sequence
Tracheoesophageal fistula
Laryngo-tracheomalacia
Vocal cord paralysis

Pulmonary diseases
Transient tachypnea of the newborn (TTN)
Respiratory distress syndrome (RDS)
Meconium aspiration syndrome (MAS)
Pneumothorax
Persistent pulmonary hypertension of the newborn (PPHN)
Pulmonary hypoplasia
Congenital malformations of the lung
Congenital diaphragmatic hernia
Rarer causes: Surfactant protein deficiency syndromes and alveolar capillary dysplasia

Thoracic and muscular diseases
Chest wall deformity
Skeletal dysplasia
Muscular disease (myasthenia gravis)

Neurological conditions
Central nervous system damage (birth trauma, hemorrhage), meningitis, asphyxia
Medication (maternal sedation, narcotic withdrawal)
Spinal cord injury

Cardiac diseases
Congenital heart disease
Arrhythmia
Congestive cardiac failure
Cardiomyopathy

Others
Sepsis
Anemia
Polycythemia
Hypo and hyperthermia

(2002-03) common etiologies in term neonates were transient tachypnea of the newborn (46.7%), followed by meconium aspiration syndrome (MAS) (29%), respiratory distress syndrome (RDS) (3.7%), pneumothorax (3.4%) and pneumonia (2.1%).[2] Approximately 20% of these neonates required invasive ventilation and mortality was 25%.

Approach to diagnosis

History: Antenatal, and birth history and the time of onset of respiratory distress often give clue to the diagnosis (Table I).

Examination

Cranio-facial malformations, cleft palate, micrognathia, scaphoid abdomen and drooling of saliva should be looked for in a neonate presenting with respiratory distress. Presence of abnormal sounds can provide a clue to the diagnosis. *Stridor* is an inspiratory noise noted in upper airway obstruction such as laryngomalacia, Pierre Robin sequence, vocal cord palsy, laryngeal or subglottic edema, web, or stenosis.[5] *Grunting* is an expiratory noise produced due to the expired air flowing across a partially closed glottis. This generates an intrinsic positive end-expiratory pressure (PEEP) preventing alveolar collapse during expiration and maintains the functional residual capacity (FRC).

A chest wall shape that is rounded with increased anteroposterior diameter denotes hyperinflation and can occur with air-trapping conditions like MAS, TTN and pneumothorax. Auscultation helps to assess if breath sounds are heard equally and symmetrically in all areas, whether there is a prolongation of inspiratory or expiratory phase, and presence of added sounds like rales, rhonchi, wheeze, and stridor. Examination of the cardiac system is important as neonates with cardiac disease manifest tachypnea without significant retractions, may have poor perfusion, cyanosis and/or abnormal heart sounds or murmurs on auscultation.

Respiratory distress score: The severity of respiratory distress can be objectively assessed using the Silverman Anderson score[4] (Table II) or the Downes' Vidyasagar score[5] (Table III). The distress is graded as none (score=0) or mild (<3), moderate (4-6) or severe (≥7). Neonates with moderate distress need positive distending pressure like CPAP, while those with severe distress need intubation and mechanical ventilation. These scores are simple and can be easily used by nurses. The Silverman Score had good correlation with mortality and the Downes' score has good correlation with physiological parameters like arterial pH and blood gas tensions as well as mortality.

Oxygen saturation

Central cyanosis is bluish discoloration of the skin, mucous membranes and tongue. Visual estimation is often

Table I . Clue to the cause of RD

Predisposing condition/Time of onset	Respiratory problem
Maternal diabetes mellitus	TTN, RDS
Previous sibling with respiratory distress	RDS due to surfactant protein B deficiency
Polyhydramnios	Tracheo-esophageal fistula, neuromuscular disorders
Oligohydramnios	Pulmonary hypoplasia
Prolonged rupture of membranes, intrapartum fever or chorioamnionitis	Early onset sepsis/pneumonia
Meconium-stained liquor, fetal distress	Meconium aspiration syndrome, asphyxia
C-section without labor	TTN, RDS
Breech presentation, instrumental delivery	Trauma, Erb's with phrenic nerve palsy
Onset of respiratory distress shortly after birth	TTN, RDS, pneumothorax or air leak, MAS, congenital malformations
Delayed onset after birth	Pneumonia, congenital heart disease, air-leak, PPHN.

incorrect as deoxyhemoglobin level should be at least 2.5 g/dL in the blood for cyanosis to manifest. The polycythemic infants with high hemoglobin may manifest cyanosis when oxygen saturation is 88%, while anemic neonates may not appear cyanosed until saturation drops below 65%. Hence, pulse oximeter is an essential tool to identify hypoxia (SpO_2below 90%) (Fig.1). Oxygen saturation difference of more than 10% between pre-ductal (right hand) and post-ductal sites (leg) indicates probable right-to-left shunt through patent ductus arteriosus (PDA) in the setting of persistent pulmonary hypertension of the newborn (PPHN). Pulse oximeter is not a good tool to detect hyperoxia, as SpO_2 readings above 95% may occur with PaO_2 values of 80-300 mm Hg (sigmoidal oxygen dissociation curve). It is also not reliable below SpO_2<70%. ambient light, dyshemoglobinemia (methemoglobin and carboxyhemoglobin), low peripheral perfusion states and movement of limbs interfere with SpO_2 measurement.

The following are some of the common investigations that are performed in a neonate with respiratory distress.

1. **Transillumination:** A fiber-optic light source applied to the chest wall of the neonate in a darkened room can identify air leaks like pneumothorax, pneumomediastinum pneumoperitoneum and large emphysematous bullae. Bright transillumination suggests air collection.
2. **Chest radiography:** Chest radiography is the main diagnostic tool in a neonate with respiratory distress.

Table II. Silverman Anderson score for respiratory distress in neonates

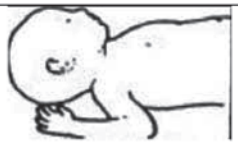
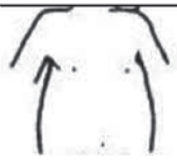
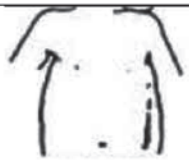
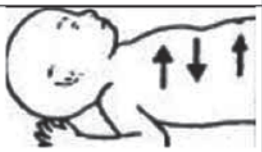
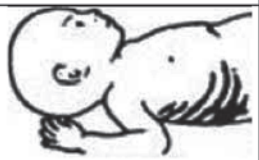
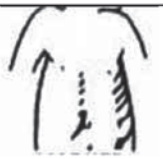
	Upper chest retraction	Lower chest retraction	Xiphoid retraction	Alar nasae flaring	Expiratory grunt
Observation	Observe the synchrony of the upper chest with abdomen movement during inspiration	observe the retractions between the ribs below the mid-axillary line	retraction below the xiphoid process	Observe the nasal flaring before the application of the nasal interface	
Score 0	 UC synchronized with the abdomen.	 None	 None	 None	 None
Score 1	 UC lags compared to the abdomen.	 Just visible	 Just visible	 Just visible	 Audible with stethoscope
Score 2	 see-saw movement of the chest and abdomen	 Marked	 Marked	 Marked	 Audible without stethoscope

Table III. Downe's score for grading severity of respiratory distress

Feature	Score 0	Score 1	Score 2
Cyanosis of lips and oral mucosa	None	In-room air	In 40% FiO_2
Retractions (intercostal, subcostal and suprasternal)	None	Mild	Severe
Expiratory grunt	None	Audible with stethoscope	Audible without stethoscope
Air entry	Normal	Decreased	Barely audible
Respiratory rate	<60	60-80	>80 or apnea

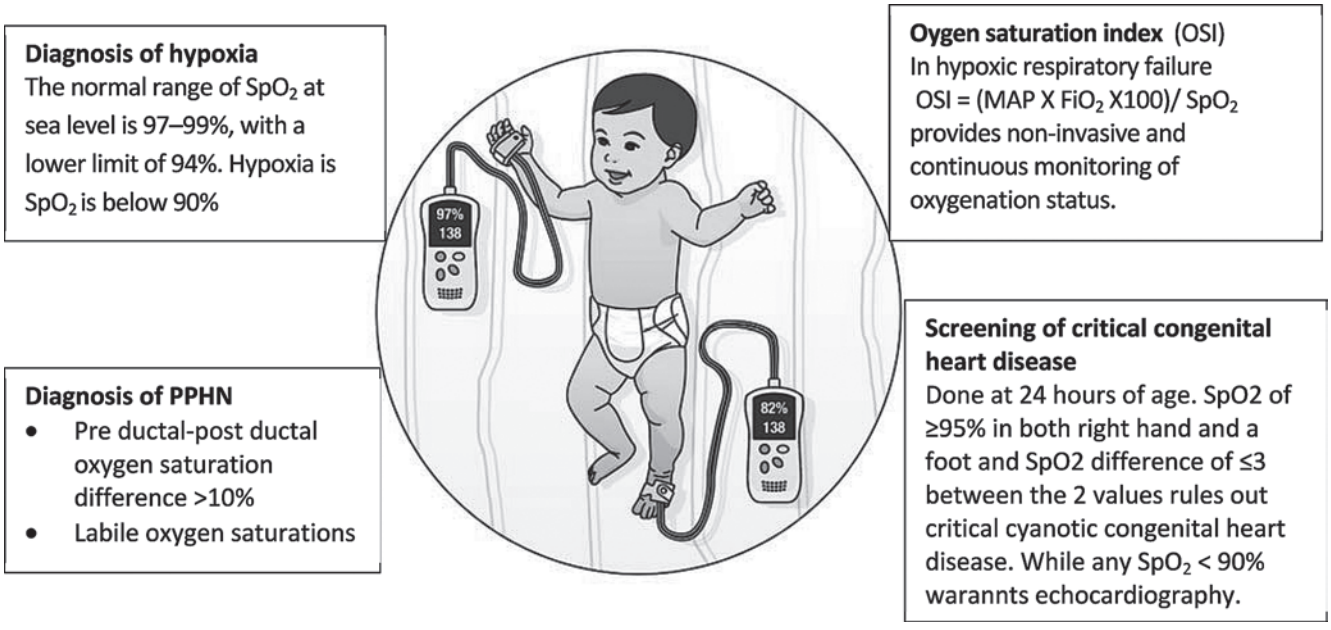


Fig.1. Uses and limitations of pulse-oximetry

The commonly taken view is antero-posterior while lateral and cross-table lateral views can be done for evaluation of air leaks, pleural effusions and placement of tubes or catheters.

3. **Ultrasound:** Ultrasonography is a bedside tool that can be used to diagnose many lung conditions such as TTN, RDS, pneumonia, pleural and pericardial effusions, pneumothorax, evaluation of mediastinal and thoracic masses, assess the position and movement of diaphragm as in eventration and diaphragmatic palsy.
4. **Arterial blood gas analysis (ABG):** ABG provides a snapshot of information about the patient's respiratory condition and must always be interpreted in the clinical context.

a. Normal values are pH 7.35-7.45, PaO_2 50-80 mmHg, PCO_2 35-45 mmHg, bicarbonate 20-24 mEq/L and base deficit of 3-5.

b. Respiratory failure is present when there is hypoxemia (PaO_2< 50), hypercarbia ($PaCO_2$> 60) and acidosis (pH<7.2).

c. Hypoxemia may result from both cardiac and respiratory causes

d. Hypercarbia is a better indicator of respiratory failure. Rising $PaCO_2$($PaCO_2$ >60) in the presence of falling pH (pH < 7.25) denotes failure of gas exchange and indicates the need for mechanical ventilation.

e. The goal of ventilation is not to make the blood gases normal but to keep them within acceptable target ranges.

5. **Hyperoxia test:** This helps to differentiate cyanotic heart disease from respiratory disorders. Arterial blood gas to estimate PaO_2 is obtained from the right radial (preductal) artery when the neonate is on room air. The ABG is repeated after providing 100% oxygen for 5 minutes (using an oxy-hood, CPAP or ventilator based on the respiratory support).
   - PaO_2<100 mm Hg: Denotes critical structural cyanotic heart disease - duct dependent and expressed as 'failed' hyperoxia test. It warrants immediate echocardiography and PGE1 therapy to keep duct open. Persistent pulmonary hypertension of the newborn (PPHN) can also result in a failed hyperoxia test. Unlike infants with a duct-dependent cardiac disease, those with PPHN show a pre-to-postductal saturation difference greater than 10% on pulse- oximetry (where shunting is at ductal level) and evince labile saturations when the neonate is agitated or with any clinical interventions (e.g. suctioning) whereas infants with cyanotic heart disease have fixed low oxygen saturations.
   - PaO_2>250 mm Hg: Expressed as 'passed' hyperoxia test and excludes fixed intracardiac right to left shunt lesions and primary pulmonary disease.
   - PaO_2 100-250 mm Hg: Possible cardiac disease with good mixing and increased pulmonary blood flow (Obstructive TAPVC).
6. **Oxygenation indices:** These indices give an idea about the severity of respiratory illness and are useful in instituting therapy and predicting death and adverse respiratory outcome. The commonly used oxygenation indices are
   a. **Alveolar-arterial oxygen pressure difference ($AaDO_2$).**

      This can be calculated using the formula: $AaDO_2 = (713 \times FiO_2) - (PaCO_2 / 0.8) - (PaO_2)$, where 0.8 indicates respiratory quotient on a mixed diet and 713 is derived from 760 mm Hg at atmospheric pressure at sea level - 47 mmHg (alveolar water vapor pressure). In healthy infants $AaDO_2$ is less than 20 in room air. In the face of hypoxia, if $AaDO_2$ is normal, it indicates alveolar hypoventilation or low inspired FiO_2. If $AaDO_2$ is increased, it may be because of ventilation-perfusion (V/Q) mismatch or shunt. If one were to increase the FiO_2 to 100% and observes an increase in PaO_2 then V/Q mismatch might be operating, while no change in PaO_2 means shunt lesion. The normal $AaDO_2$ is highly dependent on FiO_2 (for each 10% increase in FiO_2, $AaDO_2$ value increases by 5-7 points) and so the value should not be interpreted without the FiO_2

   b. **Oxygenation index:** OI = [mean airway pressure X FiO_2/ PaO_2 (mmHg)] X 100. An OI >15 indicates a ventilation-perfusion mismatch, and OI ≥40 is associated with a very poor prognosis with mortality approaching 80%. Infants with hypoxic respiratory failure with evidence of pulmonary hypertension and OI>25 may benefit from inhaled nitric oxide (iNO), and when OI exceeds 40, ECMO therapy is indicated.

   c. **Arterial-to-alveolar oxygen tension ratio (a/A ratio)**. The a/A ratio should be close to 1 in a healthy infant. A ratio of less than 0.3 indicates disturbances in oxygen transfer.

   d. **Oxygen saturation index (OSI):**OSI is calculated similar to OI, but SpO_2 replaces paO_2. The advantage is that it is non-invasive and allows continuous monitoring of oxygenation status.[6] The formula is = $MAP \times FiO_2 \times 100 / SpO_2$. OSI is validated as a reliable index for assessing the severity of the respiratory failure and lung injury in children. OSI correlates fairly well for OI values between 5 and 25 but has poor discriminatory values for OI >40. OI can be predicted from OSI (OI = 2 × OSI)
7. **Other investigations:** Sepsis screen and blood cultures are indicated when an infection is suspected. Blood sugar and electrolytes should be monitored. CSF examination is warranted in the presence of clinical sepsis or positive blood culture. Echocardiography should be done to rule out congenital heart disease and to evaluate PPHN.

Management of respiratory conditions

The basic principles of treatment include

- **Supportive care**

  All neonates with respiratory distress should be monitored in the NICU and supportive therapy forms the mainstay of care.

- Correct hypothermia
- Airway: Assess the airway for the presence of secretions. Suction, if needed and place a shoulder roll
- Breathing: Assess for respiratory distress using an objective scoring system. Check SpO_2. Intubate if respiratory distress is severe or neonate is apneic
- Circulation: Assess heart rate, blood pressure and urine output
- Check blood glucose level, and initiate intravenous fluids if distress is severe.

- **Respiratory support:** Respiratory support provided to the infant depends on the severity of respiratory distress, hemodynamic stability, presence of spontaneous efforts, the underlying condition, and the presence of complication, if any. The objective is to ensure adequate oxygenation and ventilation and thereby decrease the work of breathing. The options include non-invasive modes of heated humidified high frequency nasal cannula (HFNC), continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation
- **Oxygenation:** Preductal oxygen saturation should be monitored continuously using a pulse oximeter and FiO_2 should be titrated to achieve target SpO_2 of 91-95%.
- **Monitoring for and management of complications:** Infants with respiratory distress need to be monitored for worsening distress, hemodynamic instability, features of PPHN, acute kidney injury due to hypoxia and complications due to mechanical ventilation, etc. If any such complications develop, they should be managed appropriately.

Common respiratory disorders in term neonates

Transient tachypnea of the newborn (TTN)

TTN is due to ineffective clearance of fetal lung fluid after birth. In utero, the lungs are inflated and fluid filled. The lung fluid is derived from type II alveolar cells that actively secrete chloride (sodium and water follow the chloride into the alveoli). With the onset of labor, epinephrine levels increase and stimulate the amiloride-sensitive epithelial sodium channels (ENaC), leading to lung fluid absorption into the interstitium. When this process is delayed, TTN results.

Risk factors for TTN include prematurity (10% among 33-34 weeks of gestation, 5% among late preterm and less than 1% at term gestation), elective cesarean section before labor, male gender, maternal or family history of asthma, large for gestational age, and maternal diabetes.

Clinical features

Respiratory distress manifests shortly after birth with tachypnea, retractions and grunting. Lung hyperinflation may result in a barrel-shaped chest with pushed-down liver and spleen, making them palpable. Auscultation may reveal the presence of crackles. Chest radiograph shows retained fetal lung fluid in the fissures, perihilar streaking, relative cardiomegaly, and slightly hyper expanded lungs. While symptoms generally improve in 48 to 72 hours, chest X-ray findings may take up to a week to resolve.

Management

Neonates with respiratory distress should be transferred to NICU for continued monitoring. Silverman or Downe's scores should be continually monitored. Non-invasive respiratory support (CPAP) or oxygen administration (target SpO_2 between 91 and 95%) should be provided based on the degree of distress and oxygenation status. Neonates with persistent tachypnea (respiratory rate >80/min) or severe distress need gavage feeding; a few neonates might even require intravenous fluids. When RD scores are 7 or more, mechanical ventilation may be needed. Alternate diagnosis should be considered when the RD persists beyond 5 or 6 days (rule out congenital heart disease, pneumonia and congenital malformations), hemodynamic instability or risk factors for sepsis are present and when RD is severe with the need for mechanical ventilation (rule out PPHN and alternate pulmonary diagnosis). Management of TTN is supportive and drugs such as inhaled beta-agonist (salbutamol), inhaled epinephrine, corticosteroids, diuretics, and fluid restriction do not impact clinical outcomes.[7]

Prognosis

The prognosis of TTN is good with most neonates recovering within 3 to 7 days.

Prevention

Due to the high respiratory morbidity, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (AAP) have recommended deferring elective delivery until 39 completed weeks of gestation.

Meconium aspiration syndrome

Meconium aspiration syndrome (MAS) refers to respiratory distress in neonates born through the meconium-stained amniotic fluid (MSAF) whose symptoms cannot be otherwise explained. MSAF occurs in approximately 13% of normal pregnancies and about 5% of these infants manifest RD. Risk factors for MSAF include postmaturity (gestational age beyond 41 weeks), small for gestational age, oligohydramnios and fetal distress. Conditions causing fetal hypoxia such as placental insufficiency and cord compression lead to increased parasympathetic activity causing peristalsis and relaxation of the anal sphincter and in-utero passage of meconium. Fetal hypoxia also results in utero gasping efforts and aspiration of meconium.

Meconium aspiration results in lung injury by various mechanisms, including complete airway obstruction by particulate meconium resulting in atelectasis, partial airway obstruction resulting in air trapping, chemical inflammation by complement activation and cytokine production, inhibition of surfactant synthesis and function and increased pulmonary vascular resistance. Persistent pulmonary hypertension of the newborn (PPHN) often complicates MAS resulting in severe hypoxia and myocardial dysfunction.[8]

Clinical features

Meconium aspiration syndrome manifests shortly after birth with tachypnea, grunting, nasal flare, retractions and cyanosis. Most of these neonates are post-term and have meconium staining of nails, skin, and umbilical cord. They also have features of perinatal asphyxia due to fetal hypoxia that also precipitates in-utero passage of meconium. Examination shows a hyper inflated or barrel shaped chest due to air trapping and crepitations on auscultation. Chest X-ray shows bilateral heterogenous patchy infiltrates with areas of localized air-trapping. If the disease is predominantly associated with air-trapping, hyper-inflation and flattening of the diaphragm, is noted with pneumothorax and pneumomediastinum in severe MAS. If atelectasis is predominant bilateral consolidation is noted. Arterial blood gases reveal hypoxemia.

Management

All infants born through MSAF and manifesting respiratory distress should be transferred to neonatal intensive care unit. Normotherrmia and euglycemia should be ensured. Oxygen saturation and RD severity should be monitored. Mild distress may be managed with continuous positive airway support or heated humidified nasal cannula while 40% of MAS cases may need mechanical ventilation. Target preductal oxygen saturation is 91-95%. Both hypoxia and hyperoxia can exacerbate pulmonary arterial vasoconstriction and exacerbate PPHN.

Mechanical ventilation is challenging in MAS due to the heterogenous pathology-atelectatic areas require higher mean airway pressure (MAP) to recruit while hyper inflated areas pose a risk of pneumothorax. Therefore, the pressure values must be set individually- PIP should be sufficient enough to deliver a tidal volume of 4-5 ml/kg body weight with optimal positive end expiratory pressure (PEEP) of 4-6 cm H_2O to avoid alveolar hyper distention. The respiratory rates should be lower with adequate expiratory times to avoid air trapping. When MAP requirements exceed 12 cm H_20 high frequency oscillatory ventilation (HFOV) can be considered. In intubated infants with MAS and oxygen requirements more than 50%, surfactant therapy can be considered as it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO). However, surfactant therapy does not decrease the risk of mortality, chronic lung disease or risk of air-leak. Since the absolute volume of surfactant required in term neonates with MAS is more compared to smaller preterm infants with RDS, surfactant use in MAS should be considered on case-by-case basis. In severe MAS with oxygen index 15-25 and evidence of pulmonary hypertension, inhaled nitric oxide therapy should be started at an initial dose of 20 ppm after optimizing lung recruitment and hemodynamic support.

Prevention

Passage of meconium and its aspiration occurs in-utero and most interventions have proven to be not useful in randomized trials.[9] Before delivery, amnioinfusion (the infusion of isotonic solution into the amniotic cavity via a catheter) to thin the meconium, to decrease the risk of oligohydramnios, cord compression and meconium aspiration was practised. Amnioinfusion was shown to improve outcome (risk of MAS and perinatal mortality) only in settings where facilities for perinatal surveillance are limited. Intrapartum oropharyngeal suction before delivery of the body in cases of meconium-stained amniotic fluid is also not recommended. Similarly, elective intubation and tracheal suction in both vigorous and non-vigorous neonates born through MSAF does not alter the risk of MAS or neonatal mortality and is not recommended.

Prognosis

MAS is associated with a mortality of 5% to 25% due to the associated asphyxia and pulmonary hypertension.

About a third havepulmonary complication of pneumothorax/pneumomediastinum.PPHN and myocardial dysfunction are risk factors for mortality. Long term neurodevelopmental outcomes need to be monitored.

Pneumonia

Neonatal pneumonia due to infections can manifest as isolated pulmonary involvement or as a part of systemic sepsis.[10] Congenital pneumonia refers to onset of infection in fetal life with transfer of infection across the chorioamniotic membranes or transplacental route. Early onset pneumonia refers to onset within 72 hours of life due to ascending infection via vaginal route or acquired at the time of birth or shortly thereafter. Late-onset pneumonia manifests after 72 hours and is due to infection from the environment transmitted through caregivers. Risk factors for neonatal pneumonia include maternal group B streptococcus (GBS) carriage, chorioamnionitis, maternal fever, prolonged rupture of membranes, prematurity. The clinical manifestations of pneumonia resemble that of sepsis and include poor feeding, lethargy, apnea, hypo/hyperthermia and respiratory symptoms of tachypnea, retractions and grunting. CXR may show reticulogranular opacities, streakiness and atelectasis. The radiographic findings in GBS pneumonia may resemble RDS. Sepsis screen, blood culture and cerebrospinal fluid analysis must be considered in investigations.

Management includes supportive care and prompt initiation of empirical antibiotics. Generally, ampicillin and an aminoglycoside are the first line antibiotics for early onset pneumonia. Cefotaxime may be substituted for gentamicin when there is a strong suspicion of associated bacterial meningitis. If there is significant concern for herpes simplex virus, acyclovir should be started immediately. In hospital acquired pneumonia, the choice of antibiotic depends on local patterns of antibiotic resistance and severity of the disease. The empirical choice should include two antibiotics with cover for both Gram-negative and Gram-positive bacteria. Vancomycin should be added if methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected. The duration of therapy is 7-14 days with longer duration therapy if blood culture is positive.

Points to Remember

- ***The major signs of neonatal respiratory distress are tachypnea, chest retractions and grunting whereas cyanosis is a late sign.***
- ***The common causes of RD in a term neonate are transient tachypnea, meconium aspiration syndrome, pneumonia, air-leak syndrome and rarely surfactant deficiency.***
- ***Cardiac causes must be ruled out in any neonate presenting with respiratory distress.***
- ***Management involves supportive care, maintaining oxygen saturation targets through optimal respiratory support.***

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PULMONOLOGY

PNEUMONIA - MANAGEMENT UPDATE

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Abstract: *Pneumonia kills more children under the age of five years than any other disease. It is defined as infection of lung parenchyma and viruses are the most common infective cause. World Health Organization has revised the classification and treatment of childhood pneumonia at health facilities with the objective of providing appropriate treatment to more children. These revised guidelines will simplify the management of pneumonia at first level health facility and outpatient department and achieve better treatment outcomes. Oral amoxicillin is recommended as the first-line treatment for the treatment of both fast breathing pneumonia and chest in drawing pneumonia.*

Keywords: *Pneumonia, World Health Organization, Amoxicillin.*

Pneumonia is the single largest infectious cause of death worldwide in children under 5 years of age. The estimated death due to pneumonia was 740,180 children under the age of 5 in 2019, accounting for 14% of all deaths of children under five years of age and 22% of all deaths in children aged between 1 and 5, globally.[1] Pneumonia mortality is closely linked to poverty. More than 99% of cases of pneumonia in children are reported from low-and middle-income countries. India contributes to 20% of deaths due to pneumonia in the world.[2]

Etiology

Although the most common etiology is infectious, non-infectious causes like aspiration (of food or gastric acid, foreign bodies, hydrocarbons and lipoid substances), hypersensitivity reactions and drug or radiation can also cause pneumonia.

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Infective agents may enter the pulmonary system by aspiration, droplet infection or by hematogenous spread. Aspiration of oropharyngeal secretions may result in aspiration pneumonia due to virulent organisms such as *Streptococcus pneumoniae, Haemophilus influenzae type b (Hib)* and non-typeable *H. influenzae (NTHi)*. Droplet inhalation may result in pneumonia due to organisms such as legionella, mycoplasma, chlamydia and adenoviruses. Hematogenous spread of organisms to lungs may be associated with organisms such as Staphylococcus, as pulmonary circulation acts as filter for venous blood.

In community acquired pneumonia (CAP), child's age is the single most important predictor of the likely pathogen (Table I).[3,4]

Single most common infective cause of community acquired pneumonia in children between the ages of 1 month to 5 years is viral infections. Using molecular diagnostic techniques, virus can be identified in 40 to 80% of children with community acquired pneumonia. Among viruses, the most commonly identified to cause pneumonia in children are respiratory syncytial virus (RSV) and rhinovirus, especially in patients less than 2 years of age.[5]

Additionally, co-infection with either a virus and a bacterium or two or more viruses is common in children, with co-infection rate in infants being reported as high as 75%.[6]

Among bacterial causes, *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial pathogen in children of 3 weeks to 4 years of age, whereas *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are the most frequent bacterial pathogens in children aged 5 years and older. *Staphylococcus aureus* pneumonia is known to complicate illness caused by viral pathogen such as influenza or measles. Although, *S. pneumoniae, H. influenzae* and *S. aureus* are the major contributors to morbidity and mortality from bacterial pneumonia among children in developing countries; other causes that should be considered are HIV infection, *Mycobacterium tuberculosis*, atypical mycobacteria, salmonella, *Escherichia coli* and *Pneumocystis jiroveci*. Routine vaccination against *H. Influenzae* and

Table I. Common agents causing CAP according to age

Newborns	1-6 months	6-12 months	>1Year
• Group B streptococcus	• Viruses	• Viruses	• Viruses
• Enteric Gram-negative bacilli	• *S.pneumoniae*	• *S.pneumoniae*	• *M pneumoniae*
• RSV	• *H. influenzae*	• *H. influenzae*	• *S pneumoniae*
	• *S. aureus*	• *S. aureus*	• *C pneumoniae*
	• *M. catarrhalis*		
	• *Chlamydia trachomatis*		
	• *Ureaplasma urealyticum*		
	• *B pertussis*		

S.pneumoniae has significantly reduced the incidence of pneumonia caused by these agents. Certain immunocompromised states predispose children to pneumonia with unusual organisms, e.g. *Pseudomonas spp*. commonly seen in patients with cystic fibrosis.[5]

Factors that increase risk of pneumonia in children include overcrowding in household, lower socioeconomic status, low parental educational status, younger maternal age, exposure to indoor pollutants such as tobacco smoke and outdoor air pollution.[7] Lack of breastfeeding and malnutrition are also important factors contributing to increased risk of pneumonia in developing countries.[7]

Clinical features

Children with pneumonia can present with wide variety of symptoms like cough, fever, fast breathing, difficulty in breathing, chest pain, abdominal pain (common in lower lobe pneumonia) and headache. The signs may include chest retractions (intercostal, subcostal, sternal, suprasternal), nasal flaring, grunting, groaning and head bobbing. Auscultation may reveal bronchial breathing, rales, wheeze and decreased breath sounds. These signs and symptoms have variable sensitivity and specificity. Signs of severe illness like cyanosis, grunting respiration, dehydration, general danger signs like lethargy should be assessed in addition to vital signs and saturation.[8,9] There may be clinical pointers suggesting a particular etiological agent (Table II).

Age-specific criteria of the World Health Organization (WHO) are the most widely used, to diagnose and assess the severity of pneumonia. It recommends using "fast breathing" (tachypnea) and lower chest wall indrawing to diagnose pneumonia at the community level.[10] Since younger children have higher respiratory rate, the definition of fast breathing is different for different age groups (Table III). Respiratory rate should be counted for complete one minute while the child is afebrile and not crying.

Among all clinical signs, tachypnea is the most sensitive and consistent clinical manifestation of pneumonia. Auscultatory findings are not sensitive.[5] In infants less than 1 year of age, respiratory rate of 70/min or more can predict hypoxemia with a sensitivity of 63% and specificity of 89%.[11] WHO defined tachypnea in preschool children has a sensitivity of 74% and specificity of 67% to predict radiographically defined pneumonia.[12] Increased work of breathing, compared to fast breathing is more specific for the diagnosis of pneumonia. Without the danger signs, fast breathing alone was associated with radiological pneumonia and lobar pneumonia in 14% and 1% of the cases respectively.[13]

Acute onset fast breathing may be due to either respiratory or non-respiratory causes. Respiratory causes include asthma, bronchiolitis, viral croup, foreign body ingestion, pneumonia, pleural effusion, empyema and pneumothorax, while non respiratory causes include congestive heart failure, raised intracranial pressure, metabolic acidosis (e.g., DKA) and renal failure. A focused history and examination are imperative to rule out non-respiratory causes of fast breathing and to diagnose likely complications.

Investigations

In a clinically stable child presenting in the outpatient setting, community acquired pneumonia (CAP) is a clinical diagnosis and no investigations are required. Investigations

Table II. Etiological types and characteristic differentiating features

Viral pneumonia	Streptococcal pneumonia	Staphylococcal pneumonia	Atypical pneumonia
• Follows short upper respiratory tract infection (URTI)	• More toxic	• Empyema	• More like viral pneumonia
• Gradual onset cough	• High grade fever	• Cellulitis/ abscess	• Wheezing
• Low grade fever	• Rapid progression	• Necrotizing pneumonia	• May not be sick (walking pneumonia)
• Less toxic look	• Lobar pneumonia	• Pneumatocele formation	• Diffuse lung involvement
• Wheeze may be associated (bronchiolitis like features)	• Gastrointestinal manifestations (lower lobe pneumonia)		
• Usually, bilateral affecting all lobes			
• Lasts 3-5 days and resolves spontaneously			

Table III. WHO age specific criteria for fast breathing

Age	Respiratory rate (breaths per minute)
< 2 months	60 or more
2 months up to 12 months	50 or more
12 months up to 5 years	40 or more

are required in sick children requiring hospitalization. The radiological, microbiological and biochemical (acute phase reactants) investigations can be used to evaluate a child admitted with pneumonia. Among the radiological investigations to evaluate pneumonia, the most useful one is chest radiograph. Chest X ray should not be routinely done in ambulatory patients with CAP.[14] It may be done in children with severe pneumonia when complications are suspected, if diagnosis of pneumonia is not clear, associated with severe acute malnutrition and post measles infections (Fig.1A to 1D). An infiltrate on chest radiograph may suggest the diagnosis of pneumonia. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing. Confluent lobar consolidation is typically seen with pneumococcal pneumonia. The radiographic appearance alone is not diagnostic, and overall clinical picture must be considered. Repeat chest radiographs at completion of treatment is not required in patients with uncomplicated pneumonia.[5]

Microbiological investigations are also routinely not indicated in patients with non severe pneumonia. These are needed in pneumonia severe enough to require admission to the paediatric intensive care units (ICU) or with complications, in those who fail to improve and who have progressive deterioration.[14] Available investigations include culture, polymerase chain reaction (PCR), immuno fluorescence and serology. Blood culture positivity is uncommon, especially when patients have received antibiotics. Nasopharyngeal secretions and nasal swabs may be used for viral detection using PCR and/or immuno fluorescence techniques. Serology may be used in both acute and convalescent phase of pneumonia if the likely etiologies include respiratory viruses, mycoplasma or chlamydia. In children with complicated pneumonia,

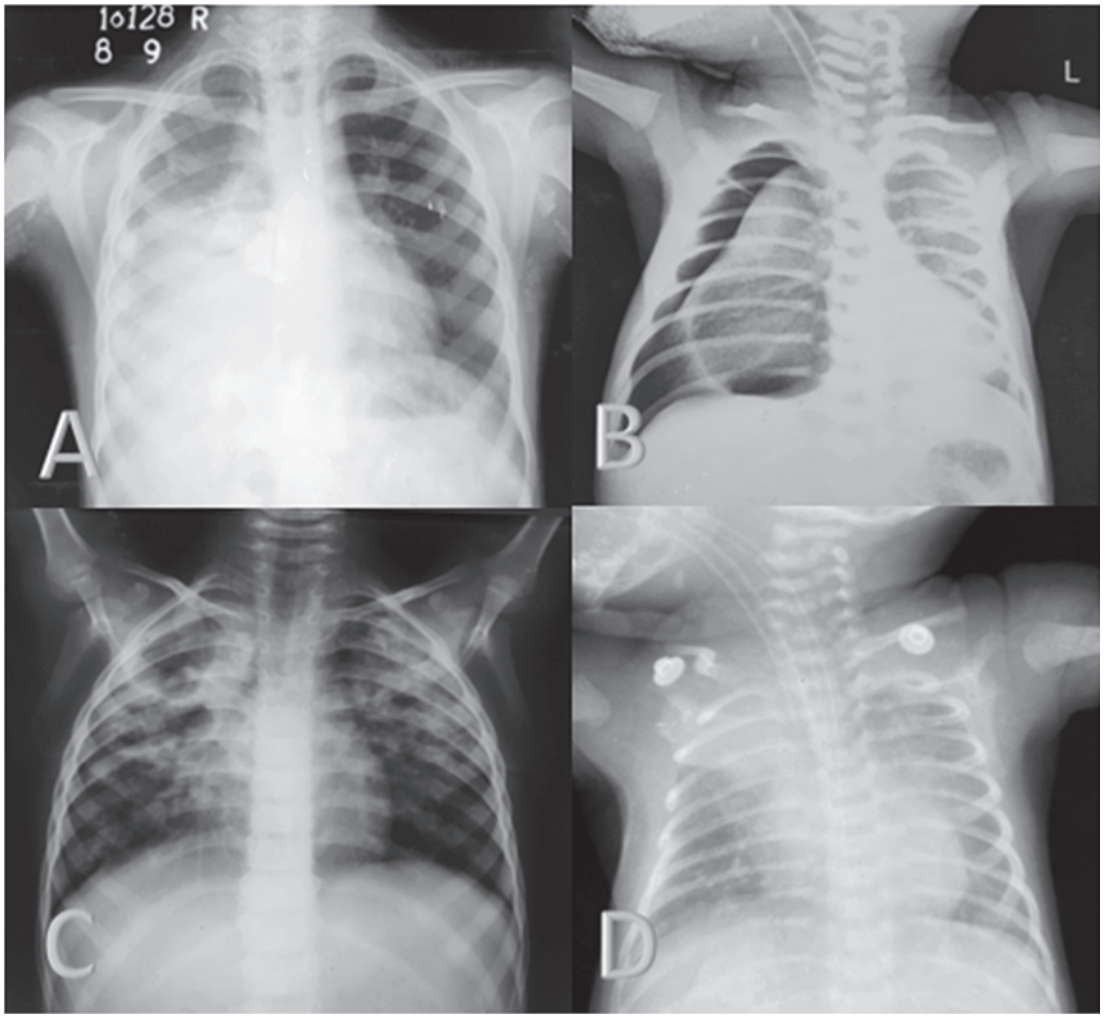

Fig. 1. (A) Right sided pleural effusion showing meniscus sign and costophrenic angle blunting. (B) Right sided tension pneumothorax with mediastinal shift to left. (C) Right upper zone cavitary lesion with areas of breakdown in the right middle zone and left upper and middle zone. (D) Right upper zone consolidation.

pleural fluid may be subjected to microscopy, culture, pneumococcal antigen detection and/ or PCR.

Acute phase reactants include procalcitonin, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), cytokines and white blood cell count. Without assessing the overall clinical picture, these reactants individually or in combination are of no clinical utility in distinguishing viral from bacterial infections and should not be tested routinely.[14]

Community vs hospital acquired pneumonia

Community acquired pneumonia (CAP):Acute infection of the pulmonary parenchyma in a previously healthy child, acquired outside of a hospital setting and not hospitalized within 14 days prior to the onset of symptoms.[4]

Hospital acquired pneumonia (HAP): Pneumonia acquired within a hospital environment that occurs 48 hours or more after admission.[4]

Changes in World Health Organisation (WHO) classification and treatment of pneumonia in children (2- 59 months).

The recommendations for the classification and management of pneumonia in health facilities have recently been modified.[15-18] The revisions have been based on new evidence in the last decade. The original guidelines classified the respiratory symptoms of children 2 to 59 months of age into four categories.[10] Evidence suggests that the majority of childhood pneumonia deaths are due to severe pneumonia/severe disease.[19] Thus the management of these severe cases

requires early identification, prompt referral and the availability of good-quality higher-level care. The revised classification included three categories instead of four, along with changes in admission criteria and choice of antibiotics (Table IV). The revised treatment recommendations are:[20]

Recommendation 1: Children with fast breathing pneumonia with no chest indrawing or general danger signs should be treated with oral amoxicillin, at least 40mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.

Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.

Recommendation 2: Children aged 2-59 months with chest indrawing pneumonia should be treated with oral amoxicillin, at least 40mg/kg/dose twice daily for five days.

Recommendation 3: Children aged 2-59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

- Ampicillin 50 mg/kg, or benzyl penicillin: 50,000 units per kg IM/IV every 6 hours for at least five days
- Gentamicin:7.5 mg/kg IM/IV once a day for at least five days

Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

Recommendation 4: Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.

For HIV infected as well as exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone (80mg/kg IM or I/V once daily) alone is recommended for use as second-line treatment.

Recommendation 5: Empiric co-trimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia.

Empirical co-trimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and exposed children over 1 year of age with chest indrawing or severe pneumonia

Indications for admission / referral

The following are indications for admission / referral to higher centre: age < 3 months, oxygen saturation (SpO_2) < 92%, severe respiratory distress, general danger signs, intermittent apnea and grunting, failure of outpatient department (OPD) treatment. General danger signs in a child with pneumonia include inability to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child or severe malnutrition.

Table IV. Revised classification and treatment for childhood pneumonia at health facility-2 months to 59 months

Age	Symptoms /signs	Diagnosis	Management
Child age 2-59 months with cough and/or difficult breathing	Cough and cold	No pneumonia	Home care advice
	Fast breathing and /or chest indrawing	Pneumonia	Oral amoxicillin and home care advice
	General danger signs*	Severe pneumonia or very severe pneumonia	First dose antibiotic and referral to facility for injectable antibiotic/ supportive therapy

**Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition*

Indications for transfer to pediatric intensive care unit (PICU) include shock, need for ventilatory support, oxygen saturation less than 92% on more than 50% FiO_2.

Treatment

The treatment will depend on the severity of illness, age of the child and clinical pointers to an etiology.

In children with pneumonia(non-severe), oral amoxicillin should be given for 3-5 days.

Co-amoxiclav is used as a second-line treatment in children, having failed on the first-line treatment. In children aged more than 2 months with severe pneumonia**,** the first line antibiotics are a combination of ampicillin and gentamicin administered intravenously. If there is improvement after 48 hours of IV antibiotics (ampicillin + gentamicin), antibiotics may be deescalated to oral amoxicillin to complete 7-10 days of total duration of antibiotics. If there is no improvement after 48 hours of first line IV antibiotics, complications of pneumonia like empyema or pneumothorax and other likely alternative diagnosis should be ruled out, before considering a diagnosis of drug resistance. Cloxacillin may be added if staphylococcus infection is likely. In cases of severe sepsis/ septic shock, vancomycin should be added.

In children less than 2 months of age with severe pneumonia, combination of intravenous ampicillin + gentamicin may be administered for 7-10 days. If there is no response in 48 hours, one can consider upgrading to a combination of IV cefotaxime/ceftriaxone + gentamicin, after ruling out complications of pneumonia and alternative diagnosis. The antibiotics may be given for a total duration of 7-10 days. Cloxacillin may be added if staphylococcus infection is likely. Clinical indicators which may suggest staphylococcal infections in pneumonia include rapid progression of the disease, presence of pneumatocele/ pneumothorax/ pleural effusion on chest X ray, large skin boils/ abscess/ infected scabies or post measles pneumonia.

If the likely etiology for pneumonia is viral**,** only symptomatic and supportive treatment should be given. Oseltamivir can be given if H1N1 infection is suspected, but it should be initiated within 3 days of symptoms.

Macrolides should not be used routinely for all cases of pneumonia. Likelihood of mycoplasma pneumonia is high if the onset is subacute or if there are extrapulmonary manifestations.

Supportive care

Limited evidence suggests that reduction of fever with antipyretics and external cooling methods may increase the blood oxygen saturation, although it may not indicate improved respiratory condition.[21] Intravenous fluids should be given if the child is dehydrated or unable to take orally or with impending respiratory failure. Oxygen should be started to maintain saturation above 92%. Bronchodilators should be used judiciously if there is presence of wheeze to decrease the work of breathing.[22]

Complications

Complications of pneumonia include pleural effusion, empyema, pneumothorax, lung abscess, bronchiectas is and pericarditis. Meningitis, suppurative arthritis and osteomyelitis are rare complications of hematologic spread. It is important to have a high index of suspicion for these complications, before considering change of antibiotics in children, not improving on first line antibiotics.

Discharge criteria

A child should be considered for discharge if the respiratory distress has resolved, there is no hypoxemia (oxygen saturation more than 90%), child is feeding well, and is able to take oral medications or completed a course of parenteral antibiotics. Additionally, parents should have understood the danger signs indicating the need to return to hospital, in case of worsening of child's clinical condition.

Points to Remember

- ***Pneumonia is the leading infectious cause of mortality in children aged less than 5 years globally.***
- ***Tachypnea is the most sensitive and consistent clinical sign of pneumonia.***
- ***Pneumonia is a clinical diagnosis in stable children who are being managed in outpatient settings and investigations are required only in sick children requiring admission.***
- ***As per the WHO revised classification, the respiratory symptoms of children 2 to 59 months of age are classified into three categories instead of four.***
- ***Oral amoxicillin replaces oral co-trimoxazole as first-line treatment of pneumonia.***

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NEWS & NOTES

PULMONOLOGY

ASTHMA - CURRENT GUIDELINES

**** Pallab Chatterjee***

Abstract: *Asthma is a common disease condition in children that leads to significant morbidity. The understanding of the disease has changed from a single disease to an umbrella term covering a group of diseases with similar symptoms as a result of different etiologies, phenotypes and endotypes. There is now a sea change in the initial management, which emphasizes on confirming the diagnosis before starting controller medications, avoidance of short-acting beta2 agonists alone and to use single maintenance and reliever therapy (SMART) in adolescents and adults. Add-on therapies like tiotropium and biological monoclonal antibodies have been approved for use in some children with severe asthma.*

Keywords: *Asthma, Phenotypes, Short-acting beta2 agonists, Tiotropium.*

As the understanding of asthma has changed from a single disease to an umbrella term covering a group of diseases with similar symptoms as a result of different etiologies, phenotypes and endotypes, there is now a sea change in the management of the disease, from a 'one-size-fits-all' concept to a more 'personalized' management of the disease.

Definition and diagnosis

Asthma is a heterogenous disease defined by history of respiratory symptoms (eg. wheeze, shortness of breath, chest tightness and cough) that vary over time and in intensity, together with variable expiratory airflow limitation.[1] Diagnosis is based on a typical history of characteristic symptoms and evidence of variable expiratory airflow limitation obtained from bronchodilator reversibility testing or other tests. A characteristic history of wheeze, chest tightness, shortness of breath and cough of varying intensity changing over time, usually at night and worsening with exercise, laughter, allergens, cold air and viral infections are features supporting a preliminary diagnosis of asthma. It is recommended to obtain and document evidence of asthma and confirm the diagnosis before starting controller therapy. This is to avoid inappropriate treatment or missing other diagnoses. In under-fives, asthma is more likely in cases of coughing or wheezing with exercise/crying/laughing or in the absence of respiratory infections and if they have a history of eczema or allergic rhinitis.[1]

Various tests that are recommended include demonstration of variable expiratory airflow limitation, demonstrating bronchodilator (BD) reversibility or responsiveness, a positive bronchial provocation test, excessive variability during peak expiratory flow (PEF) monitoring, excessive variation in FEV_1 between visits, or a significant increase in FEV_1 after inhaled corticosteroid (ICS) treatment. An increase in FEV_1 of >12% measured 10-15 mins after a 200-400 mcg of salbutamol from the pre-BD reading (having restricted short-acting beta2 agonists (SABA) for at least 4 hours and LABA for at least 24 hours) is considered significant. In resource limited settings, or where spirometry is not available or feasible, a daily diurnal variability over 2 weeks of the peak expiratory flow (highest of three readings) of >13% is considered significant. The diurnal variability is calculated as the day's highest minus the day's lowest PEF divided by the mean of the day's highest and lowest, where the PEF is measured twice a day and averaged over a week, using the same meter each time. The BD reversibility may be lost during viral respiratory infections and severe exacerbations and there may be a variation of up to 20% on using different PEF meters. A fall in FEV_1 by 12% and PEF by 15% after exercise or in between two visits is significant, though the latter has a good specificity but poor sensitivity. The exercise challenge is a non-specific indirect bronchial provocation test and is performed by running for 6-8 mins on a treadmill inclined at 5.5-10^0 with a rapidly increasing speed till a steady heart rate of 90-95% of the calculated maximum is reached and maintained for 4-6 mins at room temperature that should preferably be between 20 to 22 ^{0}C) with a relative humidity of ~40%. FEV_1 is measured immediately after and 3, 6, 10, 15 and 20 mins after running. The methacholine challenge test is

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a direct bronchial provocation test that should be performed in a competent laboratory with equipment necessary to handle severe bronchospasm, and they have a moderate sensitivity but limited specificity.[2]

The concentration of fractional exhaled nitric oxide (FeNO) is higher in asthma with type 2 airway inflammation and also in atopy, allergic rhinitis, eczema, eosinophilic bronchitis and intake of arginine containing food (like vegetables). It is lower during bronchoconstriction, viral respiratory infections and some asthma phenotypes (eg neutrophilic inflammation). The normal range is from 15 parts per billion (ppb) in early childhood to 25 ppb in adolescence, being slightly higher in males. A high FeNO above 40-50ppb is strongly suggestive of eosinophilic airway inflammation. Various other tests, like measurement of the interrupter resistance (Rint), airway resistance by the forced oscillation technique, plethysmographic specific airway resistance, induced sputum cytology, exhaled breath condensate (EBC), peak cough flow (PCF), whistle mouth pressure (Pmw) as a test of expiratory muscle strength[2], are not validated and not yet included in the current guidelines. Allergy testing by skin prick (SPT) or specific Immunoglobulin E (sIgE) does not indicate that the allergen is causing asthma symptoms and is positive in only a subset of asthmatic phenotypes.

Assessment of asthma

Asthma severity is defined retrospectively after giving treatment for a few months, Mild asthma is one which is controlled with as-required SABA/ICS-formoterol or low-dose ICS. Moderate asthma is one that is controlled with a low-to-moderate dose of ICS in a combination of long acting beta agonist (LABA). Severe asthma is poorly controlled despite a high dose of ICS and a second controller drug [like LABA or long-acting muscarinic antagonists (LAMA) or leukotriene receptor antagonist (LTRA)], with good compliance and technique and treatment of comorbidities.[1] However, for management, asthma should be classified as well controlled, partly controlled and uncontrolled.[1]

Management of asthma

Asthma management is not a 'one-size-fits-all' treatment and should be personalized and adjusted in a continual cycle of assessment, treatment and review to minimize symptoms and prevent exacerbations. Assessment includes confirmation of diagnosis, if necessary, symptom control and modifiable risk factors (including lung function), comorbidities, inhaler technique and adherence and patient / parent preference and goals. Adjustments include treating the modifiable risk factors and comorbidities (see below), non-pharmacological strategies (like allergen avoidance, etc), education and skills training and medications (according to the level of control). They should be reviewed at regular intervals for symptoms and exacerbations, growth monitoring and any side-effects of the medications, lung function and patient / parent satisfaction. Consider symptom control, risk factors for exacerbations and side effects, lung function, comorbidities, self-management skills and patient and/or caregiver goals, preferences and satisfaction.

Asthma medications are categorized as controllers, relievers, and add-on therapies:

- *Controllers* contain ICS, which reduce airway inflammation, control symptoms and reduce the risks of exacerbations, even in mild asthma and of asthma death. Treatment with ICS may reduce exacerbation-related declines in lung function. "Maintenance" therapies are controllers that are prescribed for daily use.
- *Relievers* (low-dose ICS-formoterol or SABA) are rapid-onset bronchodilators. They are used "as needed" (i.e. for quick relief of symptoms, including during exacerbations). Using ICS-formoterol as a reliever (often called an "anti-inflammatory reliever" or "AIR") also reduces the risk of severe exacerbations, compared with a SABA reliever, both with or without maintenance controller treatment. SABA or ICS-formoterol is also recommended before exercise if needed to prevent exercise-induced bronchoconstriction.
- *Add-on therapies* are mainly for patients with difficult-to-treat or severe asthma (see below). These include addition of long-acting muscarinic antagonists (LAMA), like tiotropium and biologicals like anti-IgE (omalizumab), anti IL-5 (mepolizumab), IL-5 receptor antagonist (benralizumab), anti IL-4 alpha (dupilumab) and anti-thymic stromal lymphoprotein (Tezepelumab). However, these are rarely needed in the regular day-to-day management of asthma and should be used only by specialized centers dealing with such situations. When choosing medications, consider local guidelines, regulatory approvals and affordability.[1]

Asthma control is defined as the extent in which the features of asthma are apparent or have been reduced or eliminated by controller treatment.[1] The treatment of a child with asthma is decided based on whether he or she is treatment naive or already getting treatment. Initial therapy of a child with asthma, who is not receiving any treatment,

is decided based on the frequency of daytime/nocturnal symptoms, activity limitation and risk of a future asthma attack. At follow-up, asthma control is assessed as controlled, partly controlled and uncontrolled. A child is labelled as well controlled if daytime symptoms have been less than twice a week, SABA usage less than twice a week, no night awakenings and no activity limitation. They are evaluated for risk factors for asthma flare-ups and treatment is optimized stepwise after ensuring correct asthma diagnosis, good compliance and inhaler technique (Figs.1 and 2). FEV_1 should be measured at the start of treatment, after 3-6 months of controller treatment to record the child's personal best lung function and then periodically for ongoing risk assessment.

Risk factors for exacerbations may be modifiable and non-modifiable. An important modifiable risk factor is having uncontrolled asthma symptoms. Additional potentially modifiable risk factors for flare-ups (exacerbations), even in patients with few symptoms include:

- Medications: High SABA use (associated with increased risk of exacerbations and mortality particularly if ≥1 x 200-dose canister per month), inadequate ICS, not prescribed ICS, poor adherence and incorrect inhaler technique
- Other medical conditions: Obesity, chronic rhinosinusitis, GERD, confirmed food allergy and pregnancy
- Exposures: Smoking, allergen exposure if sensitized and air pollution
- Context: major psychological or socioeconomic problems
- Lung function tests showing low FEV1, especially <60% predicted, high BD reversibility

Other major independent non-modifiable risk factors for flare-ups (exacerbations) include

- Ever intubated or in intensive care unit for asthma
- ≥1 severe exacerbation in last 12 months[1]

The updated stepwise management of asthma as per Global Initiative for Asthma (GINA) 2022 is summarized in Fig.1 and Fig.2.[1] The preferred step 1 treatment is low-dose ICS taken whenever SABA is taken and single maintenance and reliever therapy (SMART) is suggested for step 3 and step 4 in children. The change in step 1 management is based on two trials, the TREXA trial[4], done in 5-18 y of age and a pragmatic trial[5], done in 6-17 y of age. Overuse of SABAs (≥3 × 200-dose albuterol canisters per year) is associated with incrementally increasing risk of asthma exacerbations and mortality, including in patients treated with SABA alone. Regular use of SABA, even 2 to 4 times per day for 1-2 weeks, is associated with β2-receptor downregulation, loss of bronchodilator response, increased airway hyperresponsiveness and increased airway inflammation.[1] Importantly, from a cognitive and behavioural perspective, starting treatment with SABA alone trains the patient to regard it as their main asthma treatment, increasing the challenges for adherence with any subsequent advice to take ICS every day even when asymptomatic. Further, there is a risk of severe exacerbations with SABA-alone therapy, and there is a concern of poor compliance with daily ICS for mild asthma. By contrast, in mild asthma, as-needed ICS-formoterol decreases the risk of severe exacerbations requiring oral corticosteroid (OCS) by ≥60% compared with SABA alone[1], including in patients without elevated type 2 inflammatory markers, with a very small average daily ICS dose.

Regular daily use in SMART is defined as 1 to 2 puffs once to twice daily. As needed use in SMART is defined as 1 to 2 puffs every 4 hours as needed for asthma symptoms, up to a maximum of 12 total puffs per day for individuals aged 12 years or older.[6] In step 5, add-on therapy may be used like long-acting muscarinic antagonist (LAMA) or biological monoclonal antibody. Tiotropium, a LAMA, is recommended in children as add-on therapy.

Comorbid conditions such as allergic rhinitis, obesity, obstructive sleep apnea, dysfunctional breathing, gastroesophageal reflux, anxiety and stress should also be assessed and treated. Addressing allergen exposure, indoor and outdoor pollution and tobacco smoke exposure are essential steps in asthma management. The recent expert panel working group guidelines suggested multicomponent allergen specific mitigation interventions (e.g., air purifiers/ filters, pesticides, mattress covers, etc.) only for those asthma patients who had symptoms related to specific allergens (confirmed by history or allergy testing), not for all asthma patients.[6]

Stepping down to find the minimum effective dose

When good asthma control has been achieved and maintained for 2-3 months, consider stepping down to find the lowest effective step. Do not completely withdraw ICS, except if needed temporarily while confirming the diagnosis of asthma. Adults and adolescents with well-controlled asthma while on daily low-dose controller therapy can step down to either as-needed ICS-formoterol or to as-needed ICS + SABA taken together.[1]

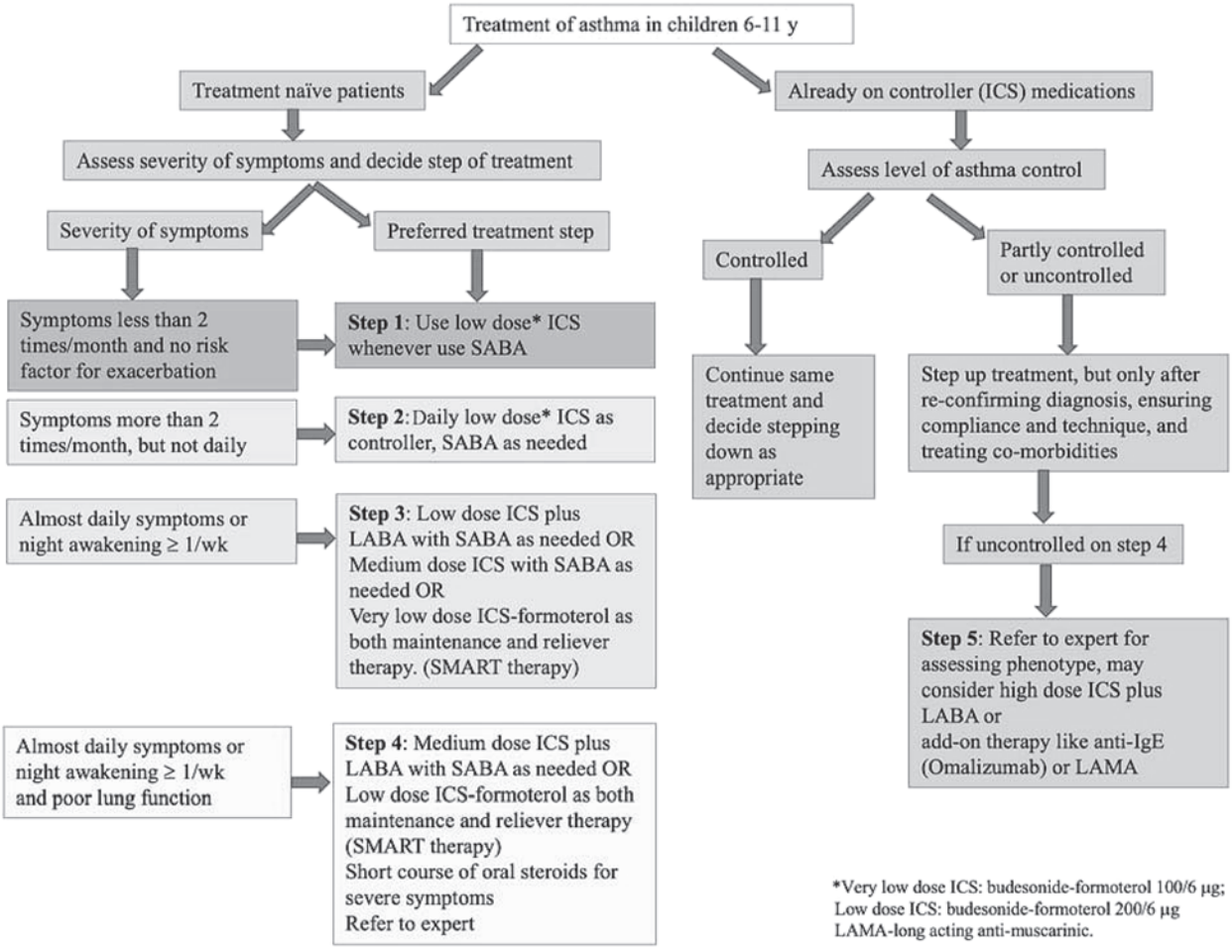

Fig.1. Updated asthma treatment as per GINA 2022 guidelines for children 5-11 y of age.

ICS - Inhaled corticosteroids; LABA Long acting beta-2 agonist; LAMA- Long acting muscarinic antagonist; SABA-Short acting beta-2 agonist. Diagram reproduced from Jat KR, Gupta A. Recent Advances in Long-Term Management of Asthma. Indian Journal of Pediatrics 2022; 89(4):378-386.

Management of exercise-induced symptoms

For patients with dyspnoea or wheezing on exertion, distinguish between exercise-induced bronchoconstriction and symptoms due to obesity, poor cardiopulmonary fitness, or alternative diagnoses such as inducible laryngeal obstruction. For patients with exercise-induced bronchoconstriction, prescribe ICS-containing controller treatment and advise sufficient warm-up before exercise.[1] Patients using as-needed ICS-formoterol as their reliever can use the same medication before exercise, if needed, and do not need a SABA inhaler.

Personalised asthma treatment

Asthma had various phenotypes (clinical presentations) and endotypes (distinct mechanistic pathways). The asthma clinical phenotypes include[7]:

(i) Allergic asthma: Asthma starting in childhood and it is associated with personal or family history of atopy. Sputum examination may reveal eosinophils and they respond well to ICS.

(ii) Nonallergic asthma: This asthma is not associated with allergy, and sputum profile may be neutrophilic, pauci granulocytic, or eosinophilic. These patients have a short-lasting response to ICS.

(iii) Late-onset adult asthma: This asthma presents first time in adults, mainly in women, and has an inadequate response to ICS.

(iv) Asthma with persistent airflow limitation: In some long-standing asthma, airway remodelling leads to fixed or incompletely reversible airway obstruction.

(v) Asthma with obesity: This asthma is associated with obesity; patients may have less eosinophilic inflammation but more asthma symptoms.

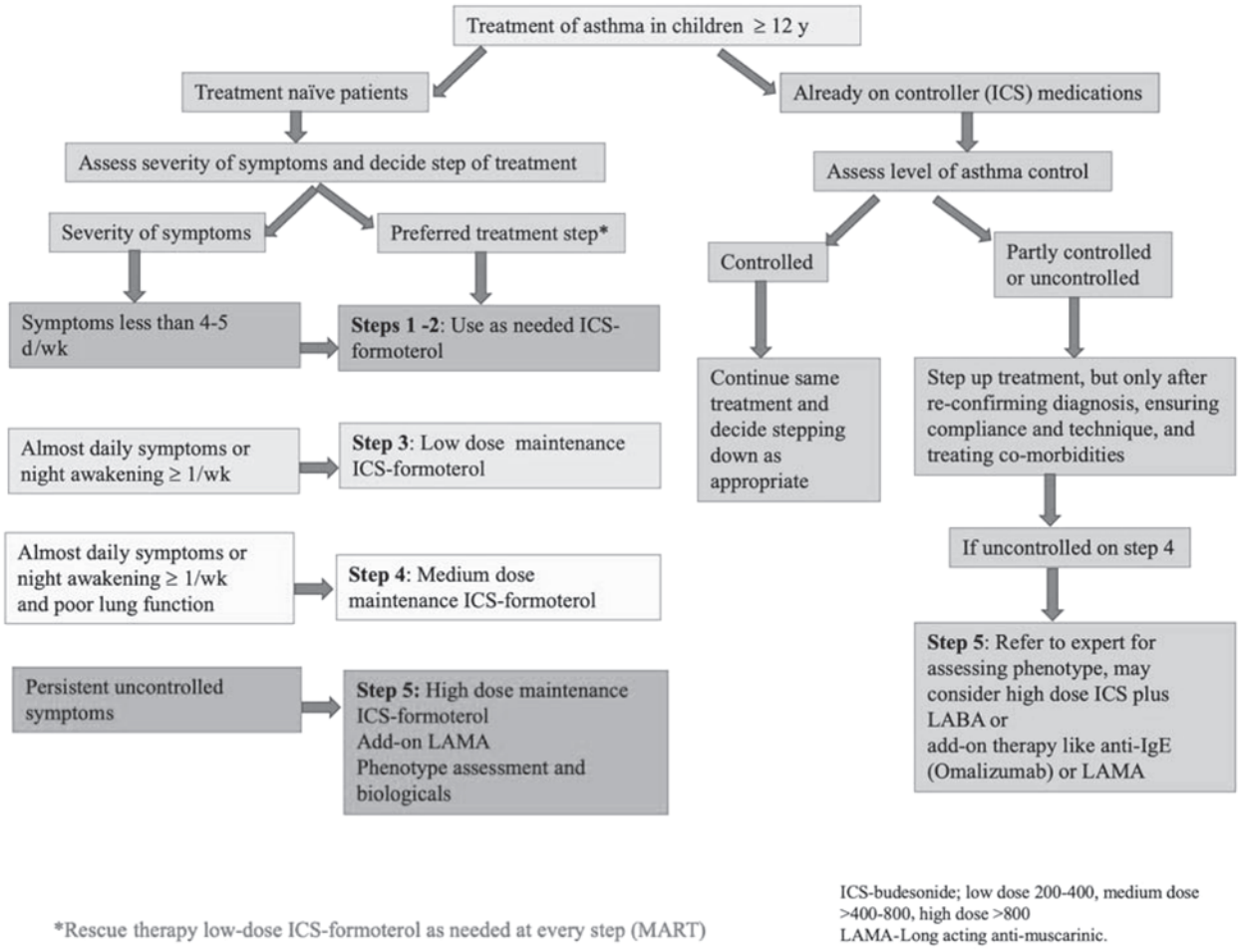

Fig.2. Updated asthma treatment as per GINA 2021 guidelines for children ≥12 y of age.

ICS- Inhaled corticosteroids; LABA Long acting beta-2 agonist; LAMA- Long acting muscarinic antagonist; SABA- Short acting beta-2 agonist. Diagram reproduced from Jat KR, Gupta A. Recent Advances in Long-Term Management of Asthma. Indian Journal of Pediatrics 2022; 89(4):378-386.

Two types of asthma endotypes had been described: T-2 (type 2) high and T-2 low.[8] T-2 high inflammation is characterized by high eosinophils, high immunoglobin E (IgE) and increased fractional exhaled nitric oxide (FeNO). It results from increased activity of IL-4, IL-5 and IL-13.

Therefore, biologicals active against IgE and these T-2 high interleukins may be helpful for severe asthma. In personalized asthma treatment, asthma management is tailored to symptom control and treatment of modifiable risk factors for asthma attack or poor asthma control and considering asthma phenotype/endotype and patient/ parent's preferences

Uncontrolled, difficult-to-treat and severe asthma

Uncontrolled asthma is defined as poorly controlled asthma in the form of frequent daytime symptoms or rescuer use, night awakening or exercise limitation or having ≥2 per year exacerbations or ≥1 per year severe exacerbation requiring hospital admission.[1] Difficult-to-treat asthma is defined as uncontrolled asthma despite a medium to high dose of ICS and another controller medication or maintenance oral steroids (GINA step-4 or step-5 treatment). It may be due to incorrect diagnosis, poor compliance, poor inhaler technique, or comorbidities in the majority.

Severe asthma is defined as poorly controlled asthma despite a high dose of inhaled corticosteroids (ICS) along with a second controller drug with good compliance and technique, and treatment of comorbidities. Severe asthma is sometimes called severe refractory asthma and it accounts for a subset of difficult-to-treat asthma. Severe asthma accounts for about 5%-10% of overall asthma.

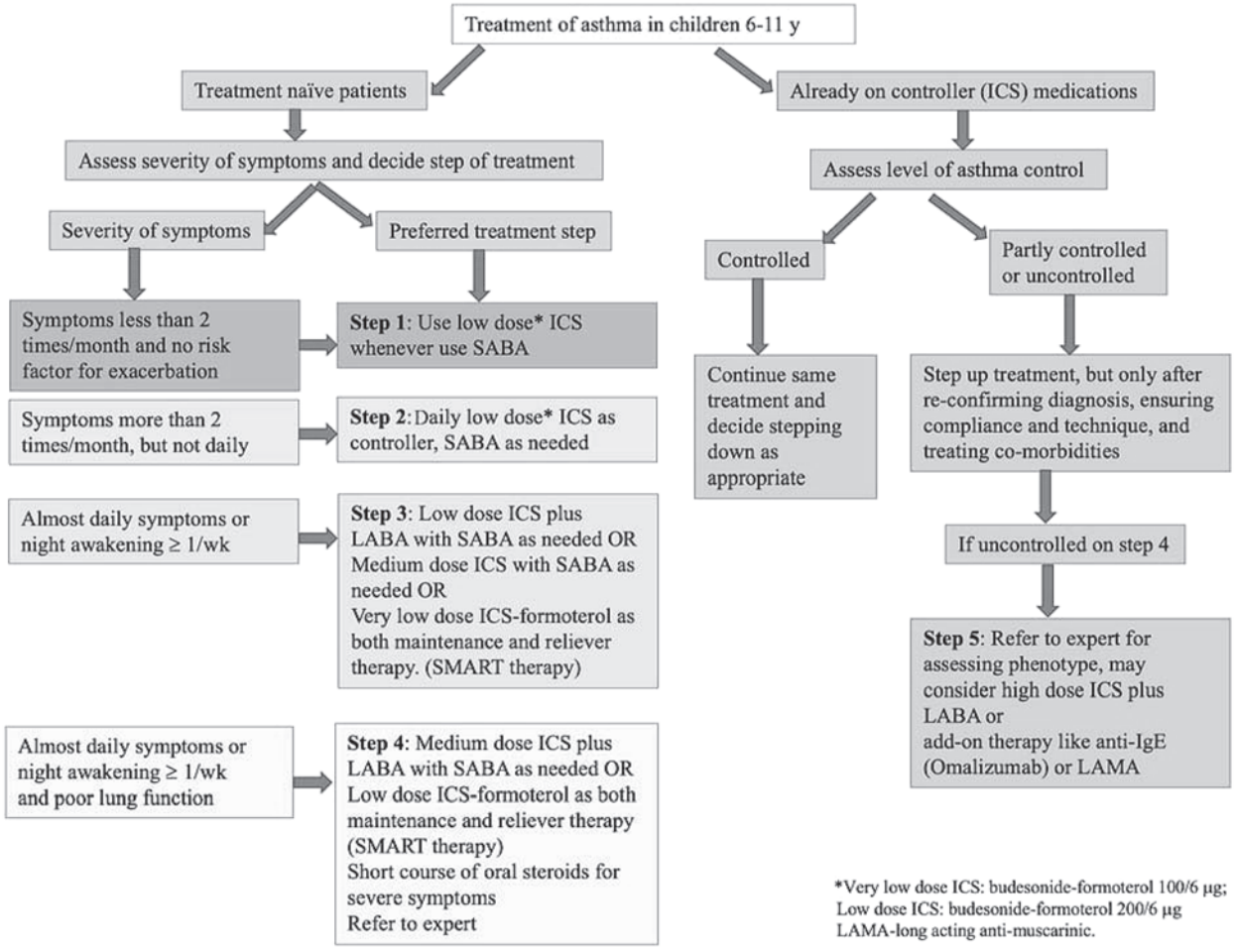

Fig.3. Management of severe asthma based on GINA 2022 guidelines.

LAMA Long-acting muscarinic antagonist. Diagram reproduced from Jat KR, Gupta A. Recent Advances in Long-Term Management of Asthma. Indian Journal of Pediatrics 2022; 89(4):378-386.

Severe asthma in children should be managed by a multidisciplinary team at a specialized centre by experts in Pediatric pulmonology using pediatric-specific guidelines. The children with severe asthma should be evaluated for the clinical or inflammatory phenotype to decide on add-on therapy. The assessment includes atopy (eczema, allergic rhinitis), blood eosinophil levels, FeNO, sputum eosinophils, total IgE, aspergillus-specific, or other allergens-specific IgE and chest radiograph or HRCT chest. An algorithm for the management of severe asthma is summarized in Fig.3.[3] Type 2 airway inflammation is characterized by blood eosinophils ≥150/µL, FeNO ≥20 ppb, sputum eosinophils ≥2%, allergic asthma or requiring oral maintenance steroids.[1] If Type 2 response is there, consider biologicals as per eligibility and give a trial for at least 4-6 months. If there is a good response to biologicals, titrate the other therapy and decide the duration of it. However, these cases should best be managed in higher centers with experience in handling such children.

Asthma exacerbations or 'flare-ups'

Asthma exacerbations represent acute or subacute worsening in symptoms and lung function from the patient's usual status. In some cases, a patient may present for the first time during an exacerbation. All patients should be provided with a written Asthma Action Plan. Action plan recommendations for responding to worsening asthma depend on the patient's usual therapy.

Patients prescribed as-needed ICS-formoterol as their reliever, either alone or in MART, should increase their as-needed doses as symptoms increase. Those on a maintenance ICS-containing controller should increase to a high dose temporarily (e.g. for 1-2 weeks).

Assess exacerbation severity from the patient's mental state, degree of dyspnoea, vital signs, oxygen saturation, and lung function (PEF or spirometry) while starting treatment with repeated administration of SABA (in most patients, by pressurized metered-dose inhaler and spacer) and controlled flow oxygen (sufficient flow to maintain oxygen saturation at 93-95% for adults, 94-98% for children 6-11 years), if available. Repeated administration of salbutamol (up to 4-10 puffs every 20 min for the first hour) is effective for rapidly reversing airflow limitation.[1] Avoid nebulization except for life-threatening asthma; delivery of rapid-acting β2-agonist via a pressurized metered-dose inhaler and spacer or via a dry-powder inhaler is as effective in patients with moderately severe acute asthma and avoids the risk of disseminating infectious particles. Current evidence does not support the routine use of intravenous β2-agonists in patients with severe asthma exacerbations. Start OCS early after presentation with prednisolone 1-2 mg/kg (maximum, 20 mg in children 0-2 years, 30 mg in children 3-5 years and 40 mg in children 6 years and above) or dexamethasone 0.6 mg/kg/day for 3-5 days. Tapering is not needed if administered for <2 weeks. Review response of symptoms, vital signs, oxygen saturation and lung function after 1 h (or earlier if worsening). Give ipratropium bromide only for severe exacerbations. Consider intravenous magnesium sulphate for patients with severe exacerbations not responding to initial treatment.

Diagnosis and management of asthma in children below 5 years of age

Recurrent wheezing occurs in a large proportion of children 5 years and younger, typically with viral respiratory infections. Recognising when this is the initial presentation of asthma is difficult. In young children with a history of wheezing, a diagnosis of asthma is more likely if they have any of the following:

- Wheezing or coughing that occurs with exercise, laughing, or crying, particularly in the absence of an apparent respiratory infection.
- Allergic sensitization, eczema, allergic rhinitis or food allergy or asthma in first-degree relatives.
- Clinical improvement during 2-3 months of controller treatment and worsening after cessation.

It is particularly important in this age group to consider and exclude alternative causes of wheeze, cough and breathlessness.

Wheezing episodes in young children should be treated initially with inhaled SABA, regardless of whether the diagnosis of asthma has been made. A trial of controller therapy (e.g. for 3 months) should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe (GINA). The response to treatment should be reviewed before deciding whether to continue it. If the response is absent or incomplete, reconsider alternative diagnoses. The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered-dose inhaler and spacer, with a face mask for children younger than 3 years and a mouthpiece for most aged 3-5 years. Children should be switched from a face mask to a mouthpiece as soon as they can demonstrate good technique.

The treatment steps are as follows:

Step 1

Provide inhaled SABA for relief of wheezing episodes. A need for SABA more than twice a week on average over 1 month indicates the need for a trial of controller medication. NAEPP recommends In children aged 0-4 years with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections, starting a short course of daily ICS at the onset of a respiratory tract infection with as-needed SABA for quick-relief therapy, as opposed to as-needed SABA for quick-relief therapy only.[6]

Step 2

The preferred option is regular, daily, low-dose ICS plus as-needed SABA, given for at least 3 months. Regular montelukast is less effective than low-dose ICS and parents/caregivers should be counselled about potential neuro behavioural adverse effects, as in a safety-related warning from the US Food and Drug Administration.

Step 3

The preferred option is to step-up to double the low ICS dose. However, before doubling the dose, one should check for concomitant or alternative diagnoses, check and correct inhaler technique and adherence and ask about risk factors such as exposure to allergens or tobacco smoke. ICS-LABA is not recommended in children <4 years old, as there are insufficient data about efficacy and safety.

Step 4

Refer the child for expert advice if symptoms and/or flare-ups persist, or at any time if side effects of treatment are observed or suspected, or if there are doubts about diagnosis.

Primary prevention of asthma

The development and persistence of asthma are driven by gene-environment interactions. For children, a "window of opportunity" to prevent asthma exists in utero and in early life, but intervention studies are limited. Current advice and recommendations for preventing asthma in children, based on high-quality evidence[1] or consensus, include the following:

- Avoid exposure to environmental tobacco smoke during pregnancy and after birth.
- Encourage vaginal delivery where possible.
- Where possible, avoid the use of paracetamol and broad-spectrum antibiotics during the first year of life
- Identification and correction of vitamin D insufficiency in women with asthma who are pregnant, or planning pregnancy, may reduce the risk of early-life wheezing episodes, but not asthma.
- Allergen avoidance strategies directed at a single allergen have not been effective in preventing asthma.

Multifaceted strategies may be effective, but the essential components have not been identified. Breast-feeding is advised for its general health benefits.

Over the past 2 years there have been many advances made in the understanding of the natural course, risk factors, mechanisms and optimal treatment of asthma. As we have noted above, many findings have opened novel avenues for prediction of disease progression and intervention. A greater understanding of the mechanisms underlying responses and nonresponses to novel therapeutics and across asthma phenotypes also would be beneficial. Regarding difficult-to-treat asthma or severe therapy resistant asthma, the majority of asthma in children can be controlled with conventional treatments and pediatric studies investigating the efficacy of newer once daily combined ICS/LABA preparations (eg., Fluticasone furoate-vilanterol) and SMART regimens are an urgent unmet need. If undertaken carefully, there is potential to effectively manage the majority of children with difficult-to-treat asthma with these newer approaches. It is important to remember, there are a group of children in whom all attempts to optimize therapy adherence may not work and the only way to keep these "refractory" children safe may be prescription of a biological, as a steroid-sparing therapy, that can be administered as directly observed therapy in hospital.[9]

Points to Remember

- ***Asthma is diagnosed by typical history with characteristic symptoms and evidence of variable expiratory airflow limitation obtained from bronchodilator reversibility testing or other tests.***
- ***Risk factors for exacerbations may be modifiable and non-modifiable and an important modifiable risk factor is having uncontrolled asthma symptoms.***
- ***The preferred step 1 treatment is low-dose ICS taken whenever SABA is taken, and SMART (single maintenance and reliever therapy) is suggested for step 3 and step 4 in children as per GINA 2022 guidelines.***
- ***The children with severe asthma should be evaluated for the clinical or inflammatory phenotype to decide on add-on therapy.***
- ***Primary prevention strategies include encouraging vaginal delivery where possible, avoidance of exposure to environmental tobacco smoke during pregnancy and after birth, and it also includes avoiding the use of paracetamol and broad-spectrum antibiotics during the first year of life.***

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CLIPPINGS

Antiseizure medication at discharge in infants with hypoxic-ischaemic encephalopathy: An observational study

This retrospective study aimed to assess variability in continuation of antiseizure medication (ASM) at discharge and to evaluate if continuation of ASM at discharge is associated with death or disability among infants with hypoxic-ischaemic encephalopathy (HIE) and seizures.

The study enrolled infants with HIE who survived to discharge and had clinical or electrographic seizures and were treated with ASM from three National Institute of Child Health and Human Development Neonatal Research Network Trials of therapeutic hypothermia from 22 US centres.

Patients who were discharged on ASM were taken as cases and those whose ASM was discontinued at discharge served as control. The outcomes were death or moderate-to-severe disability at 18-22 months. Multivariable logistic regression evaluated the association between continuation of ASM at discharge and the primary outcome, adjusting for severity of HIE, hypothermia trial treatment arm, use of electroencephalogram, discharge on gavage feeds, Apgar Score at 5min, birth year and centre.

302 infants were enrolled of which 61% were continued on ASMs at discharge. Electroencephalogram was done in 92% of the cohort. Infants with severe HIE comprised 24% and 22% of those discharged with and without ASM, respectively. The risk of death or moderate-to-severe disability was greater for infants continued on ASM at discharge, compared with those infants discharged without ASM (44% vs 28%).

The study concluded that in infants with HIE and seizures, continuation of ASM at discharge may be associated with a higher risk of death or disability at 18-22 months of age.

Sewell EK, Shankaran S, McDonald SA, Hamrick S, Wusthoff CJ, Adams-Chapman I National Institute of Child Health and Human Development Neonatal Research Network, et al. Antiseizure medication at discharge in infants with hypoxic-ischaemic encephalopathy: an observational study. Archives of Disease in Childhood - Fetal and Neonatal Edition 2023; 108:421-428.

NEWS & NOTES

OOTY NEOCON 2023

Workshop 20th October 2023

REGISTRATION TARIFF

Category	Up-to 15th September	Upto 10th October	On Spot Registration
Consultants	6490	7080	7670
PG students	5900	5900	6490
Nurses	3540	3540	4130

PULMONOLOGY

BRONCHIOLITIS - RECENT UPDATE

**** Hema Gupta Mittal***
**** Sonia Bhatt***

Abstract: *Bronchiolitis is a common respiratory illness in infants which contributes considerably to hospitalization There are many variations in practice in diagnosing, monitoring and managing bronchiolitis. The focus of this review is on updates on various diagnostic and treatment recommendations which will be helpful to practicing pediatricians. Bronchiolitis is a clinical diagnosis. No recommendation exists for routine use of laboratory / radiological investigations. Most guidelines recommend fluid management and oxygen and supportive care as mainstay of treatment. Evidence suggests no benefit with the use of salbutamol, glucocorticoids and antibiotics. Parental education and counselling remain essential.*

Keywords: *Bronchiolitis, Hypertonic saline, Steroids, Adrenaline, Oxygen therapy, Heated humidified high flow nasal cannula.*

Bronchiolitis in infants contributes to considerable morbidity and mortality not only in developed nations but also in developing countries. There are variations in practices both in the diagnosis and management of this disease. This article focuses on existing guidelines and recommendations across the world.

Definition, burden and epidemiology

Bronchiolitis previously was defined as "a viral lower respiratory tract infection characterized by obstruction of small airways caused by acute inflammation, edema and necrosis of the epithelial cells lining the small airways along with increased mucus production that typically presents with a first episode of wheezing before the age of 12 months".[1] Later the American academy of pediatrics (AAP) guidelines defined bronchiolitis as "a constellation of clinical signs and symptoms occurring in children younger than two years, including a viral upper respiratory tract prodrome followed by increased respiratory effort and wheezing," excluding children with recurrent wheezing.[2] Bronchiolitis is broadly defined as a clinical syndrome of respiratory distress that occurs in children <2 years of age and is characterized by upper respiratory symptoms (eg, rhinorrhea) followed by inflammation of the small airway/bronchioles, resulting in symptoms of respiratory distress along with wheezing or crackles.[3] Common essential feature in these definitions is that the first episode of viral-triggered wheezing in children under age two years is considered as bronchiolitis.

Viral infections have been identified as the most common etiological agents for bronchiolitis. *Respiratory syncytial virus* (RSV) is the most common virus attributing to bronchiolitis in children. It has been estimated that RSV infects more than 60% of all infants during the first year of life.[4,5] The estimated global burden of RSV-caused infections in under 5 children was reported being approximately 33 million (range: 21.6-50.3 million), with 3.2 million hospitalizations (range: 2.7-3.8 million) and 120,000 deaths (range: 94,000-149,000) annually[6, 7] with increasing intensive care admissions.[8,9] Exact prevalence data from India is not available however in various studies high rate of RSV-associated lower respiratory tract infections (LRTI) has been found in pre-term and term infants beyond six months of age extending up to two years of life.[10]

Other viruses causing bronchiolitis are rhinovirus (RV), parainfluenza virus, metapneumovirus (MPV), influenza virus, human bocavirus and adenovirus.[11] At present evidence on whether coinfections may lead to severe disease is contradictory.[12]

Clinical manifestations and outcome

Bronchiolitis usually presents as mild, self-limiting condition in most infants, but in some may progress to severe respiratory distress and respiratory failure . It usually

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begins with symptoms of upper respiratory tract infection with cough, rhinorrhea, fever and followed by difficulty in breathing and feeding. Low oxygen (O_2) saturation levels, apnea, lethargy, dehydration and fever are common in bronchiolitis. Clinically there will be tachypnea and dyspnea with, crackles and/or wheezing on ausculatation.[13]

The symptoms usually peak between 3-5 days of illness and improvement occurs in 7-14 days, with 90% of infants having a resolution of cough within 2-3 weeks. The underlying causes for variable course are poorly understood and may be disease severity, comorbidities, genetic predisposition and immunological/ inflammatory responses.[14]

Risk factors for serious illness include gestational age <37 weeks, failure to thrive, chronic lung disease, congenital heart disease, age at presentation<10 weeks, breast fed for <2 months, associated neuromuscular diseases or immunodeficiency, environmental and social factors.[15,16] Several clinical scores are available to guide treatment.

Pediatric early warning score (PEWS) which is a reliable score for predicting clinical deterioration in pediatric patients can be used in predicting deterioration in infants with bronchiolitis too.[17] Others include Wang Bronchiolitis Severity Score (WBSS), Kristjansson Respiratory Score (KRS), mTAL score and Global Respiratory Severity Score (GRSS). Most of the scores use vital parameters and the clinical conditions.[18]

Criteria for hospitalization include low oxygen saturation (<90-92%), moderate-to-severe respiratory distress, dehydration and presence of apnea. Children with pre-existing risk factors should be carefully assessed.[19,20]

Differential diagnosis

In a child presenting with fever and crackles, bronchopneumonia is an important differential diagnosis. Viral-induced wheeze or early-onset asthma in older infants and young children should be thought off if they have persistent wheeze without crackles or recurrent episodes of wheeze in the background of personal or family history of atopy.[13,14] Viral myocarditis is a close mimic of bronchiolitis. Disproportionate tachycardia, lethargy, forehead sweating, muffled heart sound and gallop should raise the suspicion of myocarditis and if chest skiagram shows cardiomegaly, echo cardiogram needs to be done.[13,14]

Outcome and sequel

The most common sequelae is the development of recurrent wheezing or asthma later in childhood. Although, the reported risk varies from 20% to 60% in infants with severe bronchiolitis (particularly infants <6 months of age).[21,22] Asthma may occur with increased frequency in infants with atopy or family history of atopy. Other rare complication include development of bronchiolitis obliterans.[23,24]

Recommendations on investigations

As bronchiolitis is a clinical diagnosis no investigation is required in majority of infants.[15-17,19,25-27]

- Blood tests: Complete blood count and blood cultures are not recommended and have no role in management unless there is a clinical suspicion of sepsis.[15-16]
- Arterial blood gas analysis: Is indicated only in severe respiratory distress or respiratory failure who need intensive care treatment.[15,16,19]
- Chest X-ray (CXR) : Is done not to diagnose bronchiolitis but to identify mimics and complications as well. Chest radiographs can reveal hyperinflation, atelectasis or infiltrates, which may not reflect disease severity or help in management.[28]
- Lung ultrasound: Lung ultrasound is not routinely indicated in bronchiolitis but may help to identify complications in bedside.[29,30]
- Virological testing: Use of nasopharyngeal swab or aspirate for respiratory viruses are not routinely indicated in diagnosis and management of bronchiolitis. These may be done in admitted children for cohorting, decreasing antibiotic use and epidemiological surveillance. The Real-time polymerase chain reaction (RT- PCR) remains the gold standard diagnostic test. High costs of these tests may prevent their routine used in resource poor settings.[15,16,19]
- Urine microscopy and culture : Indicated if there is a clinical suspicion of urinary tract infection.[16,31,32]
- Pulse oximetry: Guidelines do not recommend continuous saturation monitoring though it may be needed if disease severity increases. Indicated in all children along with clinical monitoring and not a routine.[15, 16, 19]

Recommendations on management

I. Indications for hospitalization and discharge

a. Child with bronchiolitis without respiratory distress can be managed at home with counselling and education of parents about signs of worsening.

Hospitalization is recommended in those with, inability to maintain adequate hydration, having O_2 saturation persistently below 92% and those infants with risk factors for severe disease (prematurity, BPD, congenital heart disorder, cystic fibrosis, neuromuscular disease, Down syndrome). Rapid deterioration,[15-17,19] poor oral intake, respiratory rate >70/minute, infants < 3 months and low confidence level of caretakers are other indications for hospitalisation.[17]

b. Criteria for discharge include child's ability to maintain saturation above 93% in room air without respiratory support, able to take oral feeds adequately, and general condition of child becoming stable.[15-17,19]

II. Treatment recommendations

Treatment recommendations are mainly supportive and are aimed to control respiratory and systemic symptoms.[33-37] Following are the evidence-based recommendations in the management of bronchiolitis

a) Clearing the nasal cavity: Nasal suction is not routinely recommended in older infants. A superficial nasal suction may be done in young children with nasal block which may help to improve the nasal airway patency and to some extent oxygen saturation. Deep nasal suction is not recommended routinely.[15-17,19]

b) Respiratory support and oxygen therapy: Oxygen support is recommended to those children with hypoxia whose saturation is persistently below 92%. The levels of O_2 saturation used as a guide for starting supplemental O_2 therapy ranges from <90% to <95% among guidelines.[15-19] It may be administered through a simple nasal prongs or non-rebreathing mask depending on the level of hypoxia

Heated humidified high flow, nasal cannula (HHHFNC) therapy: Heated humidified high flow oxygen via nasal cannula should be considered as modality of choice in those with hypoxia and moderate to severe retractions.[15-16]. Evidence shows that HHHFNC can improve respiratory scores, respiratory rate and o_2 saturation faster than standard low flow oxygen therapy and may reduce the frequency of infants going in for respiratory failure. Also HHHFNC treatment has been shown to reduce the need for intubation and invasive ventilation if started in emergency room in those with severe respiratory distress on presentation.[25] It has to be noted that HHHFNC does not modify the disease pathology but is only a better way of administering oxygen and reducing the energy expenditure of the body by its heated humidified supply of oxygen at supraphysiological flow.

c) Continuous positive air pressure (CPAP) (Nasal): This modality of non-invasive respiratory support is frequently used . It generates a positive end-expiratory pressure (PEEP) which counteracts airway resistance and prevents atelectasis.[38]

In general, the hypoxemia can be treated with low-flow oxygen administered via nasal prongs at rates of up to 2-3 L/min, or by HHHFNC therapy.[39] Initial high-flow rate of 2 L/kg/min in HHHFNC improves respiratory mechanics and breathing effort. Oxygen supplementation should be continued till child is able to feed and maintain saturation above 93%.[15,16]

d. Hydration maintenance: Feeds may be given by nasogastric or orogastric tube if they are not able to take adequate fluids orally. Intravenous isotonic fluids may be started in those children who do not tolerate nasogastric or orogastric feeds or have severe disease or impending respiratory failure.[19]

Chest physiotherapy: Chest physiotherapy need not be given except in those with comorbidities(e.g., spinal muscular atrophy, severe tracheomalacia) to improve mucus clearance.[15,17,19]

Medications

- Inhaled B2 Agonist-:These are not recommended in treatment of bronchiolitis. Salbutamol (albuterol) in infants does not improve O_2 saturation, duration of symptoms or length of hospital stay and there is a potential risk of harm.[11-14]

- Nebulized adrenaline: Nebulized adrenaline is being used in majority of centres as first line therapy for moderate to severe bronchiolitis. It can reduce the edema of the mucosa in nasal cavity. Due to its short duration of action and potential adverse effects, nebulized adrenaline is not recommended.[15-17,19]

- Nebulized and systemic steroids*:* Both treatments do not prevent hospital admission, do not affect the length of stay in hospital and do not improve short and long-term outcomes in patients with bronchiolitis.[40-42] Using nebulized and systemic corticosteroids alone or in combination with other therapies (epinephrine or bronchodilators) in treating acute bronchiolitis is not recommended.[15-17,19]

- Nebulized 3% hypertonic saline: Multiple randomized trails and systematic reviews on usage of nebulized 3% saline in bronchiolitis in infants have concluded insignificant reduction in severity or duration of hospital stay.[43,44] Based on currently available evidence,

nebulized 3% saline is not presently being recommended in treatment of bronchiolitis.[15-17]

- Combined bronchodilator and corticosteroids also do not have any proven efficacy.[17]
- Antibiotics: The use of antibiotics in bronchiolitis is not recommended except in cases with a strong suspicion or clear evidence of a secondary bacterial infection.[15-17] There is no data supporting benefits with the use of macrolides in children with bronchiolitis.[45,46].
- Antivirals and other therapies: Antivirals (ribavirin) is not recommended by guidelines for management of bronchiolitis.[15-17,19]
- Other therapies: Medications like montelukast, inhaled DNase, inhaled furosemide, inhaled ipratropium bromide, magnesium sulphate, helium, surfactant and methylxanthine in children with acute bronchiolitis are not supported by the current evidence.[15-17,19]

Evidences of various treatments in bronchiolitis are summarized in Table I.

III. Preventive strategies

Certain preventive strategies should be followed to reduce the prevalence, morbidity and severity of bronchiolitis. These may include:

- Environmental prophylaxis: Exposure to tobacco smoke must be discouraged.[47] Frequent handwashing

Table I. Summary of evidence of various treatments in bronchiolitis[15-17,19]

Treatments	Indications	Evidence quality recommendation / Strength
Supportive treatment	Recommended	Evidence Quality: A Recommendation Strength: Strong
Oxygen therapy	Recommended *(when SpO_2<92%)*	Evidence Quality: A Recommendation Strength: Strong
HFNC	Recommended when standard subnasal supplemental O_2 fails in infants who are hypoxic. *(It should not be used as a primary treatment modality)*	Evidence Quality: B Recommendation Strength: Moderate
Nebulized hypertonic saline solution Inhaled	Not Recommended	Evidence Quality: B Recommendation Strength: Strong
Bronchodilators	Not Recommended	Evidence Quality:A Recommendation Strength: Moderate
Chest physiotherapy	Not Recommended	Evidence Quality: B Recommendation Strength: Strong
Nebulised adrenaline	Not Recommended	Evidence Quality: A Recommendation Strength: Strong
Nebulised steroids	Not Recommended	Evidence Quality: A Recommendation Strength: Strong
Systemic steroids	Not Recommended	Evidence Quality: B Recommendation Strength: Strong
Antibiotics	Not Recommended *(Except in case of strong suspicion or clear evidence of a secondary bacterial infection)*	Evidence Quality: B Recommendation Strength: Strong

and decontamination of hands using alcohol solutions by parents or caregivers and other household contacts are recommended. Cleaning of solid surfaces using water and disinfectants or sodium hypochlorite is strongly supported. Sharing kitchen utensils and personal effects must be avoided.

- Exclusive breastfeeding for at least six months should be encouraged.[48,49]
- Prophylaxis with monoclonal antibodies:
  - ❖ The only currently licensed immunoprophylaxis for RSV is the monoclonal antibody (mAb) palivizumab produced by recombinant DNA technology and targeting the fusion (F) protein of the virus. Palivizumab effectively reduces hospitalization and prevents lower respiratory tract infections in preterm infants. It is administered via intramuscular injection once each month during the RSV season for five doses (i.e. 15 mg/kg).
  - ❖ A newer mAb, nirsevimab, has been recently approved. It offers protection of 5 months, enabling coverage of the entire RSV season with a single intramuscular dose. In a recent study, Nirsevimab reduced medically attended RSV-associated LRTI by 70% and RSV hospitalization by 78% versus placebo in healthy preterm infants.[50,51]

Palivizumab prophylaxis during RSV season (November-March) is recommended as follows.[15-17,19]

a. Infants of gestational age < 29 weeks and age <12 months

b. Infants of 29-35 weeks gestational age and age < 6 months

c. Infants diagnosed with BPD (during their first year of life)

d. Infants with hemodynamically significant congenital heart disease

e. Immunoprophylaxis can be considered for infants with cystic fibrosis, Down syndrome, congenital diaphragmatic hernia, neuromuscular diseases and immunodeficiency

Points to Remember

- ***Bronchiolitis is a common condition in infants and children under 2 years of age and diagnosed on the basis of history and clinical examination.***
- ***Respiratory syncytial virus remains the most common cause.***
- ***It may be mildly symptomatic or lead to a severe disease with fulminant course and respiratory failure.***
- ***The mainstay of treatment remains supportive in the form of humidified oxygen therapy, adequate hydration and proper nutrition.***
- ***There is no role of nebulised drugs (salbutamol, adrenaline, steroids, magnesium sulphate), antibiotics, azithromycin, antivirals or chest physiotherapy in routine management.***
- ***In severe bronchiolitis with respiratory failure, HHHFNC and other non invasive respiratory support have been successful in reducing the need for invasive ventilation.***
- ***Preventive strategies includes hand hygiene and immunoprophylaxis in preterm infants.***

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PULMONOLOGY

MANAGEMENT OF CHILDHOOD TUBERCULOSIS

**** Kalpana S***

Abstract : *The National Strategic Plan 2017-2025 has set an ambitious target of elimination of tuberculosis by 2025. In India, an estimated 3.33 lakh children in the 0-14 years' age group become ill with tuberculosis each year which contributes to 28% of global childhood tuberculosis burden. Improving the diagnostic and treatment strategies in children will contribute in a major way in controlling this menace. Investigations for the diagnosis includeboth radiological and microbiological. Treatment includes preventive strategies , treatment of drug sensitive and drug resistant tuberculosis.*

Keywords: *Cartridge based nucleic acid amplification test, Treatment regimen, Preventive therapy.*

Managing tuberculosis in children is a challenge as the diagnostic and treatment approaches employed in adults are not directly translatable to the pediatric population. Newer molecular diagnostics like cartridge based nucleic acid amplification have revolutionized case diagnosis. Newer treatment regimens have been proposed that can significantly shorten the treatment duration. This article focuses on the diagnostic modalities and treatment strategies in the management of tuberculosis.

I. Investigations

Chest X-ray: X-rays still remain the first line of investigation in children with symptoms of presumptive tuberculosis. The algorithm recommended by National tuberculosis elimination programme (NTEP) for children recommend classifying X-rays as those that are suggestive of TB like milliary pattern, fibrocavitory disease and hilar or mediastinal lymphadenopathy or X-rays with nonspecific findings - like consolidations, non-homogenous or ground glass opacities and thin walled cavities.[1]

The importance of characterizing X-rays lies in the fact that symptomatic children with radiological findings suggestive of tuberculosis can be subjected to nucleic acid amplification tests (NAAT) like GeneXpert or Truenat upfront. Children with presumptive symptoms whose chest X-ray is not suggestive of TB must be given a course of antibiotics and if they do not improve clinically and radiologically, are subjected to further evaluation by NAAT. Antibiotics like linezolid and fluroquinolones should not be used, as they have anti TB action and may show a temporary improvement in symptoms.

The interpretation of chest X-rays (CXR) remains an important skill and the impact of rotation, phase of respiration, exposure, motion artefacts and confounders like thymic shadows should all be taken into account during interpretation.

However, despite the high sensitivity when interpreted by experienced radiologists, CXR has its challenges, mostly due to its modest specificity and high inter and intra-reader variability.

In a rapid communication in 2020, WHO recommended computer assisted detection (CAD) software for the automated interpretation of chest radiograph.[2] This technology may be used as an alternative to human reader interpretation of plain digital CXR for TB screening and triage among adults and adolescents more than 15 years of age. Such machine learning and deep learning technologies in CAD might also be utilized for interpretation of X-rays in younger children in the near future.

Microbiological diagnosis: Obtaining representative samples is the corner stone of getting a microbiological diagnosis.

Resting gastric juice (RGJ)/Gastric lavage (GL): This is the preferred method of collection of sample used in children who cannot produce a representative sample either by expectoration or induced sputum. Ideally gastric aspiration on each of two consecutive mornings should be performed. This is the number that seems to maximize the yield. The samples can be pooled for NAAT. RGJ is preferably done in hospitalised children. Gastric aspiration is generally not an aerosol-generating procedure.

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The following points need to be adhered while performing RGJ

- Performing the test properly usually requires two people (one doing the test and an assistant). The child should fast for at least 4 hours (3 hours for infant) before the procedure.
- After collection of gastric juice, add an equal volume of sodium bicarbonate solution to the specimen (in order to neutralize the acidic gastric contents and so prevent destruction of tubercle bacilli). This is a critical step especially if the contents are being subjected to cultures.
- If it is likely to take more than 4 hours for the specimens to be transported, place them in the refrigerator (4-8 °C) and store until transported.
- RGJ may be done as an ambulatory procedure with some loss in yield.

Sputum induction: Sputum induction does not require overnight hospitalization and can be performed in an out-patient setting. The yield from one induced sputum (IS) sample has been found to be equivalent to three GL samples.[3] This has shifted clinical practice to include IS as a diagnostic procedure in young children and infants with suspected pulmonary tuberculosis (PTB). The safety of IS in infants and young children is now well established with thousands of procedures having been performed with no documented serious adverse events. Recent studies have shown that this procedure can safely be performed even in young infants. Samples have been successfully collected from children as young as 1 month of age.[3] It is important to note that, unlike gastric aspiration, sputum induction is an aerosol-generating procedure.

Expectorated sputum: Expectorated sputum sampling can be performed in older children and adolescents. The procedure is as follows: Instruct the child to take two deep breaths, holding the breath for a few seconds after each inhalation and then exhaling slowly. Ask him to breathe in a third time and then forcefully blow the air out. Then, breathe in again and proceed to cough. This should produce sputum from lower respiratory tract. The sputum container is held close to the lips and sputum is spit into it gently after a productive cough.

Nasopharyngeal aspirate (NPA):Nasopharyngeal aspiration is an attractive diagnostic procedure, requiring minimal facilities and training. Since passing a nasal cannula elicits a cough reflex in many children, NPA may be regarded as a form of sputum induction. The New WHO Consolidated Guidelines for Management of Tuberculosis in Children and Adolescents, 2022 recommends the use of Xpert MTB/RIF Ultra in nasopharyngeal aspirate in addition to gastric lavage and sputum for the diagnosis of pulmonary tuberculosis.[4] Two drops of sterile saline are instilled into each nostril and the nasopharynx is suctioned using a sterile catheter with a mucus trap.

Stool sample: The WHO guidelines also recommend the use of stool as an alternative to other specimens including gastric lavage (GL), sputum and nasopharyngeal aspirate (strong recommendation, moderate certainty of evidence).

A Cochrane meta-analysis reported that sensitivity and specificity of Xpert MTB/RIF Ultra (Ultra) in stool specimens as 53% and 98%, respectively, while in GL, it was 64% and 95%.[5] Ultra is more sensitive than Xpert for stool and GL is more sensitive than stool for diagnosis of childhood TB. While stool is easier to collect as compared to other specimens, it needs special processing techniques. Adoption of stool for TB diagnosis by NTEP is limited by the need to retrain the personnel in processing techniques, lower sensitivity, and nonavailability of Ultra.

Bronchoalveolar lavage: Broncho alveolar lavage (BAL) is a less popular sample, as it is an invasive procedure and also the yield seems to be lower than multiple gastric aspirates.

Microbiological diagnosis must be attempted in all cases of presumptive tuberculosis. The preferred number of samples for microbiological diagnosis is given below.

- Smear for acid fast bacilli - 2 samples
- WHO approved NAAT - 1 sample
- Culture - 1 (pooling of samples can increase the yield)
- CSF - Amount of CSF that can be safely collected: In the neonate, 2ml in total can be safely collected and in an older child 3 to 6 ml can be sampled depending on the child's size. If the sample obtained is very minimal, the sample be processed for Xpert MTB/RIF rather than culture.
- Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB, using any method. A pleural biopsy is the preferred sample. The sensitivity of Xpert MTB/RIF in pleural fluid is very low.

Nucleic acid amplification tests (NAATs)

The pros and cons of the currently available NAATs approved under NTEP are given in Table I.

Table I. Nucleic acid amplifications tests under NTEP

Truenat® MTB-RIF Dx	XpertMTb /Rif
Both use PCR to detect Mycobacterium tuberculosis (M.Tb) and rifampicin sensitivity	
Developed an Indian firm - Molbio	Cephaid, USA
• Requires a 2 step process - DNA extraction and then addition to the chip	• Fully automated
• Technician time - 20 - 30 min	• Technician time – 5 min
• Portable, battery operated, direct connectivity with mobile interface for data sharing	• Requires continuous power supply, airconditioning, data sharing is through a computer
• Limit of detection - 105 colony-forming units (CFU)	• Detects 112 CFU (with Xpert Ultra-16 CFU)

Specimens that can be processed by either Xpert MTB/RIF/Xpert MTB/RIF Ultra include GL, sputum, nasopharyngeal aspirate, stool and BAL. Other samples that can be processed include CSF, lymph node aspirate and biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens.

In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB.

Xpert MTB /RIF ULTRA™: The limit of detection of Ultra is lower (16 CFU per ml compared with 112 CFU per ml with Xpert).[6] Initial assessments have shown better performance in specimens containing low number of bacilli like those from Human Immunodeficiency Virus (HIV) positive persons, pediatric specimens and extrapulmonary specimens especially CSF. Rifampicin resistance is also detected more accurately. In the 2022 WHO guidelines, it is recommended that for children as well as people living with HIV who are being evaluated for pulmonary tuberculosis (PTB), and for persons being evaluated for extra pulmonary tuberculosis (EPTB), the "M. tuberculosis complex (MTBC) detected trace" Ultra result should be considered as bacteriological confirmation of TB. Unfortunately, as there are more Truenat machines in NTEP than Xpert machines, there are practical hurdles in upgrading to Xpert Ultra in India, but when available it should be used in preference to Xpert MTB/RIF, especially for extrapulmonary TB/TB meningitis.

AFB smear: Smear is less preferred as a single test for diagnosis of TB for several reasons, mostly because of its poor sensitivity (10%) in paucibacillary TB and no significant increase in yield even with fluorescent microscopy.

Universal drug sensitivity testing: We are currently moving into an era of drug sensitivity based treatment of tuberculosis. Universal drug sensitivity is now recommended for all cases of tuberculosis. "Universal" refers to drug sensitivity testing for all cases of presumptive tuberculosis and not for all the anti Tb drugs used.

- This is mainly by testing for rifampicin resistance for all cases if access to a body fluid or tissue specimen is available by Genexpert or Truenat.
- It also aims at testing for INH resistance
    - This is possible by using Line probe assay (FL- LPA). However due to technical difficulties we can do LPA only in cases with a smear positive sample.

MTB culture: Both solid cultures by Lowenstein Jensen medium and automated liquid cultures like Mycobacterium growth indicator tube (MGIT) can be utilized. MGIT is now available through NTEP lab network with a turnaround time of 2-3 weeks. Under the universal drug testing strategy, if molecular testing is negative, MGIT should be sent.

Urine Lipoarabinomannan (LAM): Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests for TB. Currently, the urine lateral flow LAM assay (LF-LAM) strip-test-Alere LAM-is the only commercially available urinary LAM test.

In inpatient settings, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children in the following situations:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) (strong recommendation); or
- with advanced HIV disease or who are seriously ill (strong recommendation; moderate certainty in the evidence about the intervention effects)
- irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm3

Line probe assay (LPA): Line probe assay (eg. Hain test, MTBDR plus™, MTBDRsl™) cannot be used as a primary diagnostic test in pediatric presumptive TB as it can be performed only on smear positive specimens. The use of LPA in pediatric samples comes in the rapid detection of drug resistance in culture samples. LPA detects presence of MTB and detects resistance to rifampicin (R) and isoniazid (H) (First line LPA). It can also detect resistance to fluoroquinolones and second line injectables (SLI). LPA can help in deciding the regimen for drug resistant tuberculosis (DRTB); short vs. long drug resistant TB regimens. For e.g. the shorter regimens can be used only if we can demonstrate that there is no fluoroquinolone resistance. Interpretation of LPA results is given in Table II.

Mantoux and IGRA: Both detect TB infection. Mantoux is still preferred due to its cost effectiveness. WHO guidelines recommend either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) be used to test for TB infection. IGRA is preferred in children more than 5 years of age to detect infection and Mx is preferred in children < 5 years.

C-Tb: May replace conventional Mx in the near future. Modified Mantoux technique is a similar technique,except that instead of PPD, it uses Mtb specific antigens ESAT 6 and CFP 10. Hence false positive results with atypical Mycobacteria and BCG vaccination is avoided. An induration >5mm reaction is taken as positive.

II.Treatment

TB Preventive therapy

Removing the age barrier for TB preventive therapy is one of the huge steps taken by NTEP 2022 towards TB elimination. The term “Latent TB infection” has been replaced by “TB infection.”

Target population for preventive therapy

- Should be given to all children < 5 years of age, who are household contacts of bacteriologically confirmed pulmonary TB, even if TB infection testing is unavailable
- May be given to all children > 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB, who are found not to have TB disease by an appropriate clinical evaluation
- People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or hematological transplant, long term steroids/ immunosuppressive therapy should be systematically tested and treated for TB infection
- Systematic TB testing and treatment can also be considered for health care workers in countries with high TB burden

Table II. Interpretation of line probe assay

No mutation detected	Drug sensitivity testing (DST) as required
gyrA MUT 3C, 3D, 3B	Resistance to levofloxacin and high level resistance to moxifloxacin (Mfx)
gyrA MUT 1,2,3A, gyrB mut 1,2	Genotypic low level resistance, Mfx can be used in higher doses but should be correlated with phenotypic DST at clinical break point
rrs mutation	Resistance in SLI
eis mutation	Kanamycin resistance detected, amikacin can be used
rpoB mutation	Rifampicin resistance
inhA	Low level INH resistance, INH can be used in higher doses
KatG	High level INH resistance

- Infants and children living with HIV should be started on tuberculosis preventive therapy(TPT) even if they are symptom screen negative
- Newborn born to mothers with TB disease
- Post treatment to children living with HIV (CLHIV) - all CLHIV who have completed treatment for TB disease should receive a course of preventive therapy after completion of course of ATT.

TB preventive therapy options that are available include

- 6 or 9 months of daily isoniazid, or
- 3-month regimen of weekly rifapentine plus isoniazid,(in children more than 2 years) or 3-month regimen of daily isoniazid plus rifampicin.
- 1-month regimen of daily rifapentine plus isoniazid or 4 months rifampicin daily are other alternatives.
- Preventive therapy is also now offered to household contacts of drug resistant pulmonary cases (Table III).

Treatment of drug sensitive TB

- Current regimen for all new cases and retreatment cases (i.e. treatment after failure, recurrent and treatment after loss to follow up, if found to be drug sensitive) include 2 months of daily isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of daily isoniazid, rifampicin and ethambutol (2HRZE + 4 HRE). In case of CNS TB and osteoarticular TB, continuation phase should be extended to 10 months. The dose of the various first line anti TB drug is given in Table IV.

Fixed drug combinations (FDCs) are preferred as they are safe, permit convenient dosing and reduce the risk of missing one or more of the combination drugs and thereby reduce the risk of emergence of resistance. The pediatric formulation consists of 50mg isoniazid along with 75mg rifampicin and 150mg pyrazinamide in a single FDC along with 100mg ethambutol. The adult formulation consists of 75mg isoniazid, 150mg rifampicin, 400mg pyrazinamide and 275mg ethambutol.

The number of FDCs for the various pediatric weight bands is given in Table V.

Routine pyridoxine supplementation is offered to all children receiving either ATT or IPT.

Dose of pyridoxine is as follows

- 10mg daily
- If on DRTB regimen 50-100mg depending on drugs included in regimen (higher doses are required if the regimen contains cycloserine)
- If there is evidence of pyridoxine deficiency - 50mg daily

Table III. Preventive therapy for contacts of drug resistant TB

Drug resistance of index case	Preventive therapy	Duration
Fluoroquinolone sensitive MDRTB	daily levofloxacin	6 months
INH monoresistance or poly resistance	daily rifampicin	4 months
Rifampicin resistance and INH sensitive	daily isoniazid	6 months

Table IV. Dose of first line antituberculous drugs

		Range mg/kg/day	Average mg/kg/day	Maximum dose (mg)
Rifampicin	R	10-20	15	600
Isoniazid	H	7-15	10	300
Pyrazinamide	Z	30-40	35	2000
Ethambutol	E	15-25	20	1500
Streptomycin	S	15-20	20	1000

Table V. No. of FDCs for pediatric weight bands (0- 18 years)

Weight Band (Kg)	No. of FDCs
4 -7	1P + 1E
8 – 11	2P+2E
12- 15	3P+3E
16-24	4P+4E
25-29	3P+3E + 1A
30 -39	2P+2E +2A

Newer TB treatment regimens

There is constant research to reduce the duration of TB therapy all over the world. WHO in its' consolidated TB guidelines 2022 has given a key recommendation pertaining to shortening of therapy from 6 months to 4 months for non severe TB (strong recommendation, moderate certainty of evidence) in children aged 3 months to 16 years.

Non-severe TB : Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.

This is based on the results of the SHINE trial- a noninferiority, open-label trial, which randomized children below 16 years from 3 countries in Africa and India with symptomatic, non severe, smear-negative and presumably, drug-sensitive tuberculosis to 6-months regimen of 2HRZ(E) and 4HR(E) or 4-months regimen of 2HRZE and 2HRE. Treatment success was reported in 97.1% in the 4-months regimen versus 96.9% in the 6-months regimen. The rates of drug-related adverse events were similar. While shortening of the drug regimen will result in reducing drug costs and improving compliance, there are concerns about adoption of the shorter regimen in the Indian setting. The trial was conducted with intense review and monitoring by experts, which may be difficult to replicate in field setting. The classification of disease into severe and non severe may be flawed due to errors in the interpretation of the chest radiograph. Note: children with severe acute malnutrition (SAM) is taken as a general danger sign, and children with SAM and with non severe diseases should be treated with 6 month regimen.

Shorter treatment options for adolescents from 12 years of age: Another implementation consideration is that adolescents aged 12 years and above with TB can benefit from the 4-month regimen that consists of isoniazid, rifapentine, moxifloxacin and pyrazinamide (HPMZ), which is now conditionally recommended by WHO. (conditional recommendation panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects).

Monitoring for potential relapse is a priority for shorter regimens especially when they are introduced into programmatic settings. Therefore, follow-up of children and young adolescents for up to 12 months after completion of the 4-month regimen is important.

Shorter treatment regimens for TB meningitis in children and adolescents: The guidelines also discuss switch to an alternative regimen for TB meningitis in children (clinically diagnosed/bacteriologically confirmed, with no risk for drug resistance). The ethionamide regimen has been widely used in South Africa for many years and exploits the excellent CNS penetration of ethionamide.

In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HRE) (Conditional recommendation, very low certainty of the evidence).

The regimen includes isoniazid, rifampicin, pyrazinamide and ethionamide and is dosed as follows:

- Isoniazid: 20 mg per kg, maximum 400 mg daily
- Rifampicin: 20 mg per kg, maximum 600 mg daily
- Pyrazinamide: 40 mg per kg, maximum 2000 mg daily
- Ethionamide: 20 mg per kg, maximum 750 mg daily

While the ethionamide-based regimen appears promising and merits further evaluation by operational research in the Indian setting, it cannot be adopted at this time due to lack of high-quality data and background INH resistance in India

Monitoring of children in ATT

- First follow up visit is recommended at 2 weeks to recheck doses and assess tolerance
- Thereafter, the child is reviewed every month to
    - monitor adherence
    - response to therapy : symptom improvement, weight gain, adherence, adverse events
- X-ray is done only at completion of treatment
- Remember : defervescence and reduction in cough takes 2-4 weeks
    - weight gain starts by 4 weeks but 25% will not show any weight gain
    - peripheral lymph nodes sometimes may not regress completely
    - tuberculomas may not resolve completely radiologically.

Approach to non responders to treatment

- Verify whether they are true non responders. Symptom improvement should be the purview rather than radiological resolution
- Verify dosing and adherence
- Is it TB? Reverify the diagnosis
- May be due to comorbid conditions like HIV or other intercurrent infections
- Consider drug resistance
- Paradoxical reactions - diagnosis of exclusion

Management of drug induced liver injury (DILI)

DILI is diagnosed in the following circumstances

- Elevation of AST and ALT > 5 times upper limit of normal (ULN)
- Elevation of enzymes more than 3 times ULN and symptomatic child - nausea, vomiting, fatigue, abdominal pain
- Elevation of serum bilirubin > 1.5mg/dl or clinical jaundice

In case of DILI, ATT should be stopped. In case of sick child (e.g. TBM) - start on levofloxacin, streptomycin (amikacin) and ethambutol. The period during which the child is on alternative drugs should not be counted while calculating the final duration of treatment.

If the child is not sick, withhold all ATT for 7 days. Repeat liver enzymes at the end of a week.

- If AST and ALT < 2 times ULN restart rifampicin in full dose
- Check enzymes after 3 days, if < 2 times ULN, add isoniazid
- Check enzymes after 3 days, if < 2 times ULN, restart pyrazinamide
- If the hepatotoxicity is severe, AST > 10 times normal, it may be hazardous to restart PYZ; hence, permanently discontinue Z and complete 9 months of HRE

Managing interruptions in treatment: Treatment options in a child with interruptions to therapy is given in Fig.1.

Management of drug resistant TB

Drug resistant TB: With the availability of bedaquiline and delamanid we are moving towards shorter and all oral drug regimen, even for multidrug resistant TB. Shorter duration means 9 to 10 months of therapy and longer means 18 - 20 months of treatment.

INH monoresistance: In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. The same FDC as in NTEP can be used to complete treatment with added levofloxacin RMP resistance/ MDRTB.

A shorter all-oral bedaquiline-containing regimen of 9-12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/ RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty in the evidence). The shorter regimen is to be used for non severe pulmonary and extra pulmonary TB. The removal of the age restriction for the use of bedaquiline means that children of all ages with confirmed MDR/RR-TB and without fluoroquinolone resistance may be offered the shorter, all-oral regimen with bedaquiline, if they meet the eligibility criteria.

Under NTEP, bedaquiline can be given to children more than 5 years of age and weighing atleast 15 Kg. WHO has removed the age barrier for bedaquiline use; can be used in children of any age.

Shorter regimen

The eligibility criteria are:

- No extensive TB disease
- No severe EPTB (any forms other than TB lymphadenopathy)
- No resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance). The shorter regimen should not be used in the presence of mutations in both the inhA promoter and katG on first-line LPA in the child, as this suggests that both isoniazid at high dose and thioamides are not effective.
- No exposure to previous treatment with second-line medicines in the regimen for more than one month (unless susceptibility to these medicines is confirmed).

This regimen includes 6 months of bedaquiline, along with 4- 5 months of levofloxacin (Lvx), clofazimine (Cfz), pyrazinamide (Z), ethambutol (E), high dose INH (Hh) and

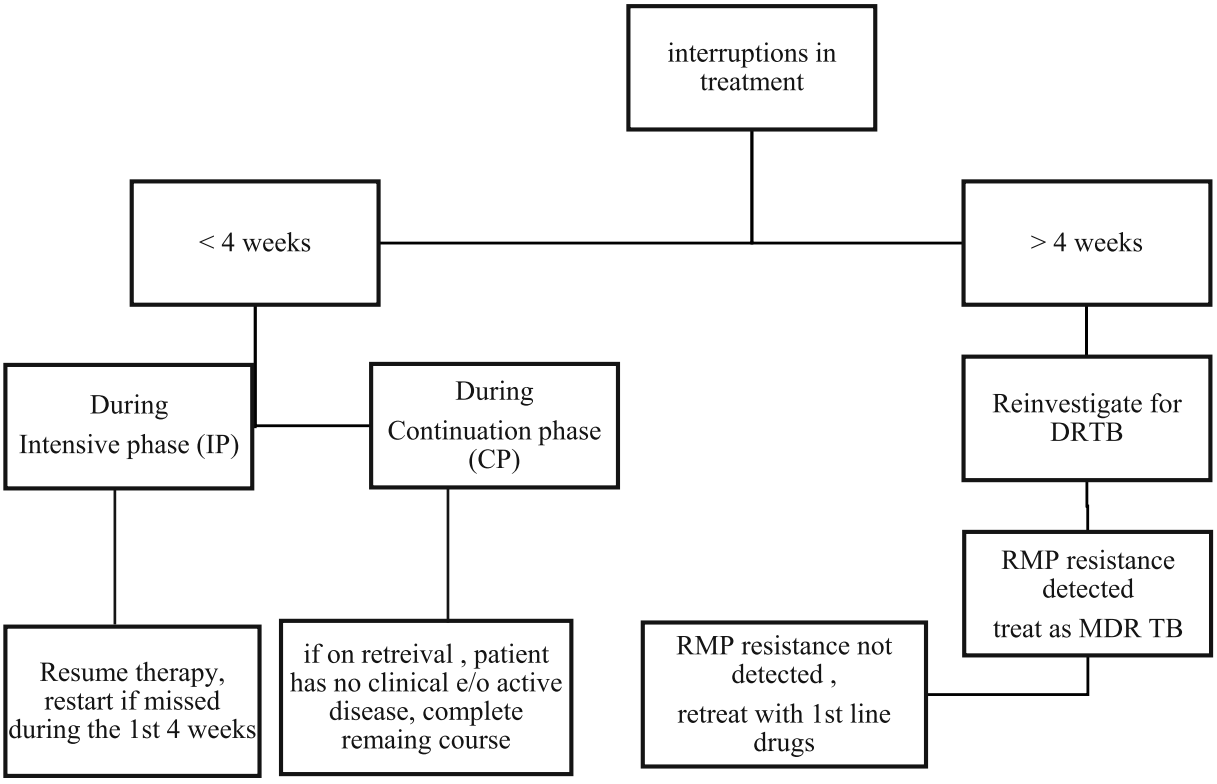

Fig.1. Management of interruption to treatment

ethionamide (Eto) followed by 5 months of levofloxacin, clofazimine, pyrazinamide and ethambutol. [(6) Bdq, (4-5) Lvx, Cfz, Z,E, Hh, Eto followed by (5) Lvx, Cfz, Z,E].

Bedaquiline is not approved for use in children less than 5 years in India, and hence the regimen is modified as 4-6 months of high dose moxifloxacin, kanamycin/ amikacin. ethionamide, clofazimine, pyrazinamide, high dose isoniazid and ethambutol followed by 5 months of high dose moxifloxacin, clofazimine, pyrazinamide and ethambutol.

Longer regimens for multidrug- or rifampicin-resistant tuberculosis (MDR- or RR-TB).

In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment started with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped.

If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. (Conditional recommendation, very low certainty in the estimates of effect)

Group A: Fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.

Group B: Clofazimine and cycloserine or terizidone are conditionally recommended as agents of second choice.

Group C: Includes all other medicines that can be used when a regimen cannot be composed with Group A and B agents. The medicines in Group C are ranked by the relative balance of benefit to harm, usually expected of each.

The WHO recommended longer regimen is 18-20 months of bedaquiline, levofloxacin, linezolid, clofazimine and cycloserine.

(18- 20) Lvx, Bdq (6 months or longer), Lzd, Cfz, Cs

For < 5 years in NTEP, the regimen is modified using SLI agents and Group C drugs employing a longer regimen as bedaquiline is not approved in this age group

Points to Remember

- ***Nucleic acid amplification tests CBNAAT and Truenat have improved case diagnosis of tuberculosis.***
- ***Radiology, inspite of modest specificity still remains an important part of the armamentarium.***
- ***Point of care test like urine LAM have been approved in children with HIV.***
- ***Shorter treatment regimens have been proposed by WHO in non severe TB, adolescents and TB meningitis.***

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CLIPPINGS

Potential for Maternally Administered Vaccine for Infant Group B Streptococcus

In an ongoing phase 2, placebo-controlled trial involving pregnant women, safety and immunogenicity of a single dose of various GBS6 formulations were assessed. Maternally transferred anti-CPS antibodies were assessed. In a parallel seroepidemiologic study conducted in the same population, serotype-specific anti-CPS IgG concentrations associated with a reduced risk of invasive disease among newborns through 89 days of age were assessed to define protective thresholds.

Naturally acquired anti-CPS IgG concentrations were associated with a reduced risk of disease among infants in the seroepidemiologic study. IgG thresholds that were determined to be associated with 75 to 95% reductions in the risk of disease were 0.184 to 0.827 μg per milliliter. No GBS6-associated safety signals were observed among the mothers or infants. The incidence of adverse events and of serious adverse events were similar across the trial groups for both mothers and infants; more local reactions were observed in the groups that received GBS6 containing aluminum phosphate. Among the infants, the most common serious adverse events were minor congenital anomalies (umbilical hernia and congenital dermal melanocytosis). GBS6 induced maternal antibody responses to all serotypes, with maternal-to-infant antibody ratios of approximately 0.4 to 1.3, depending on the dose. The percentage of infants with anti-CPS IgG concentrations above 0.184 μg per milliliter varied according to serotype and formulation, with 57 to 97% of the infants having a seroresponse to the most immunogenic formulation.

GBS6 elicited anti-CPS antibodies against group B streptococcus in pregnant women that were transferred to infants at levels associated with a reduced risk of invasive group B streptococcal disease.

Madhi SA, Anderson AS, Absalon J, Radley D, Simon R, Jongihlati B, et al. Potential for Maternally Administered Vaccine for Infant Group B Streptococcus. N Engl J Med. 2023 Jul 20; 389(3):215-227. doi: 10.1056/NEJMoa2116045. PMID: 37467497.

PULMONOLOGY

PROTRACTED BACTERIAL BRONCHITIS

**** Sarath Balaji B***

Abstract: *Protracted bacterial bronchitis is not an uncommon cause to consider in a child with chronic (>4weeks) wet cough without constitutional symptoms and specific cough pointers. It is increasingly being recognised across the globe after introduction of diagnostic clinical criteria. It is a forerunner of bronchiectasis and needs to be treated with appropriate antibiotics for adequate (2-4 weeks) duration. But in countries like India, common causes such as tuberculosis and foreign body should be ruled out before considering the possibility of PBB.*

Keywords: *Protracted bacterial bronchitis, Chronic cough.*

Cough, despite being a protective reflex and a defence mechanism[1] is the most common reason for pediatric consultations and can influence the quality of life (QOL) of both children and their parents by reducing sleep quality, creating emotional distress and limiting participation in normal activities.[2] Chronic cough is defined as cough lasting for more than 4 weeks duration.[3,4] As cough caused by upper respiratory tract infection (URTI) usually resolves in 1-3 weeks, cough persisting beyond that could indicate underlying ailments and should be evaluated for other etiologies.[4]

Protracted bacterial bronchitis (PBB) is one of the most common causes of chronic wet cough in children in western world. PBB is often under-diagnosed due to a lack of awareness, but is increasingly being recognized, if clinical criteria are fulfilled without the need for bronchoscopy or microbiological evidence. This condition is often misdiagnosed as asthma, primary ciliary dyskinesia, tuberculosis, cystic fibrosis and primary immunodeficiencies resulting in inappropriate investigations and unnecessary drugs.[5] PBB should be identified early and managed with appropriate antibiotics in adequate doses and duration. Inappropriately or inadequately treated PBB can often progress to bronchiectasis in some children.[6] Literature search on PBB in India turned out to be futile. PBB should often be a diagnosis of exclusion in our country where common causes of chronic cough such as neglected foreign body, tuberculosis etc. should be ruled out.

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Definitions

Bacterial infections of lower respiratory tract may manifest as either typical bacterial pneumonia or PBB.[7] In simple terms, PBB is defined as an isolated persistent wet cough lasting more than 4 weeks in the absence of other alternative disorders, that show resolution with a prolonged course (2-4weeks) of antibiotics.[4]

There are clinical (PBB - clinical) and microbiological (PBB-micro) case definitions for PBB.[4,6] PBB-micro criteria includes i) presence of chronic wet cough (>4 weeks), ii) lower airway infection (recognized respiratory bacterial pathogens growing in sputum or bronchoalveolar lavage (BAL) at density of a single bacterial species $\geq 10^4$ colony-forming units/mL and iii) resolution of cough following a 2-week course of an appropriate oral antibiotic. As it is impractical and cumbersome to perform bronchoscopy for all children presenting with chronic cough and also difficult to procure good quality sputum specimens from older children ,criteria were modified to PBB-clinical criteria, which requires absence of signs and symptoms of other causes of chronic wet cough[4]. PBB-extended is where symptom resolution is seen with 4 weeks of antibiotics instead of 2 weeks. Recurrent PBB is 3 or more episodes of PBB in a year (Box 1).

Specific cough pointers[8] that suggest other underlying causes of wet cough are mentioned in Table I.

Pathophysiology

The pathophysiology of PBB is not completely understood.[9] One of the hypotheses is impaired mucociliary clearance caused by recurrent viral infections and gastro-oesophageal reflux(GER) predisposed by structural abnormalities, particularly airway malacias.[5,10,11] This leads

Box 1. Diagnostic criteria for protracted bacterial bronchitis (PBB)

Original diagnostic criteria (PBB-micro)

Chronic wet cough > 4 weeks

Documented lower airway infection (single bacterial species $\geq 10^4$) in sputum or in BAL

Resolution of cough after a 2 weeks course of appropriate antibiotic

Modified diagnostic criteria (PBB-clinical)

Chronic wet cough >4 weeks

No symptoms or signs of other causes of wet or productive cough

Resolution of cough after 2 weeks course of appropriate antibiotic

PBB Extended

All the criteria of PBB- clinical/PBB- micro

Resolution of cough after 4 weeks course of appropriate antibiotic

PBB Recurrent >3 episodes of PBB in one year

to chronic bacterial infection and the formation of bacterial biofilm in the airway.[10,11] Initial viral infection often disrupts surface morphology and ciliary function which leads to chronic inflammation with the formation of bacterial biofilms leading to PBB.[10-13] Airway malacias like tracheobronchomalacia, causes airway collapse and mucous impaction, preventing clearance of secretions[14]. GER and aspirations cause disruption of respiratory epithelium and colonization of organisms like *H.Influenza* resulting in protracted infection.[13]

Studies also suggest that PBB is associated with marked inflammatory mediator response due to activation of innate immune system. High levels of various inflammatory mediators such as interleukin-8 (IL-8) and matrix metallopeptidase MMP-9 along with increased NK cells (CD 56 and CD 16) are found in PBB compared to control subjects.[15]

Microbiology

As the distribution of organisms in PBB is heterogeneous, better bacterial yield is found when BAL is taken from multiple lobes rather than a single lobe (right middle lobe).[16] It is not unusual to find more than one organism in BAL culture. The most common organisms found in PBB are non-typeable *H. influenza, Streptococcus pneumonia, Moraxella catarrhalis* and *Staphylococcus aureus*.[5,17,8]

In most of the western studies, the most common organism isolated was *H. influenza*, while in the Chinese population, the most common organism isolated was *Streptococcus pneumonia*.[17] Many viruses are also isolated in the BAL fluid, but there is no way to prove them to be causative of PBB.[18]

Table I. Clinical clues for children with chronic cough

Findings	Possible diagnosis
Spontaneously resolving cough, good health	Post infectious cough
Wheezing, dry nocturnal cough, atopy, positive family history for asthma or allergy	Asthma
Protracted airway infections, wet cough, positive sputum or BAL culture	PBB, bronchiectasis
Recurrent lower respiratory tract infections, growth failure, chronic sinusitis, hemoptysis, steatorrhea	Cystic fibrosis
Recurrent severe or atypical infection	Immunodeficiency (Primary/secondary)
Vomiting, sialorrhea, neurodevelopmental disorders	Gastroesophageal reflux disease
Stridor, metallic, biphasic cough	Airway anomalies (Tracheomalacia-bronchomalacia)
Situs inversus, recurrent sinusitis and/or otitis, recurrent lower airway infections	Primary ciliary dyskinesia

Clinical features

PBB is usually seen in preschool children, although it is also found in adolescents. It usually presents with an initial event like lower respiratory tract infection (LRTI) or pneumonia. In a study done in UK, about 42% had LRTI and 40% had pneumonia as the preceding event.[12] Children suffering from PBB usually don't have any systemic symptoms and generally look and do well except for the presence of cough.[19,20]

Viral infections can cause exacerbations due to the release of planktonic bacteria from biofilm, similar to cystic fibrosis. After resolution of the infection, they usually return to baseline status[21]. PBB is often misdiagnosed as asthma. Features that differentiate PBB from asthma[7] are mentioned in the Table II. In older children, spirometry can also be used to diagnose asthma. It is to be noted that PBB can coexist with asthma.[7] In a study done in UK, 43 % of the children with persistent wheeze on treatment for asthma were found to have bacterial bronchitis.[22]

Diagnosis

The diagnosis can be made based on the clinical criteria. Obtaining a history from the parent or caregivers regarding symptoms is vital for the diagnosis. Information regarding the nature, duration and therapy so far, along with the duration of antibiotics if used, should be obtained.[23]

As we currently lack a straightforward non-invasive test that allows for a strong diagnosis, over and under diagnosis will be common, as is still the case for asthma.[10] CXR may be normal or can have minor abnormalities.[24] If hyperinflation is seen in X-ray, it should raise the suspicion of asthma or co-existing asthma.

Bronchoscopy and BAL analysis remains the mainstay for definitive diagnosis but should be interpreted with caution. This may be considered if there is relapse after three courses of extended oral antibiotics or if parents insist on microbiological confirmation of diagnosis.[24]

Natural course

Untreated PBB triggers a vicious cycle of infection and inflammation, resulting in the damage of the conductive airways, leading eventually to bronchiectasis.[23] Efforts to break this cycle will help full recovery of the epithelium, which include antibiotics for infection and physiotherapy for clearance of secretions.[24]

A cohort study done in Australia identified recurrence (>3 episodes /year) of PBB and the presence of *H. influenza* infection of the lower airways as major risk factors for bronchiectasis and also found that *H. influenza* infection increased the chance of bronchiectasis by more than seven times when compared to no infection.[6]

During the five year follow-up in the same cohort they found that about 56% of cases developed bronchiectasis by the second year of follow-up. Interestingly, it also found that 27% of PBB cohort found to have asthma at final review, with predictive factors in multivariate analysis including allergy specific IgE and bronchomalacia.[25]

In a retrospective analysis done on 81 children in UK, for three years, 40% of those with chronic wet cough but no signs of bronchiectasis at presentation had clear evidence of bronchiectasis on repeat bronchography.[12]

Management

Antibiotics remain the mainstay of treatment for PBB. When PBB is suspected in a case, efforts should be made to limit the antibiotics and refer to a specialist for further evaluation and management. It is not advised to start antibiotics in primary care in such cases.[9, 26]

Table II. Differentiating features between protracted bacterial bronchitis and asthma

Protracted bacterial bronchitis	Asthma
Persistent wet cough	Dry cough
Cough typically worsens with change of posture	Often nocturnal cough; Shortness of breath not related to cough
Rattle sound	Wheeze sound
Clinical improvement after antibiotics	Clinical improvement after bronchodilator, corticosteroids

The initial course of treatment is intended to address morbidity while also contributing to the diagnostic process, with a clear and unambiguous cessation of coughing seen as confirmatory evidence of the diagnosis.[10]

The most commonly used antibiotic is oral amoxicillin-clavulanate, which is active against beta-lactamase-producing strains of *H. influenza, M. catarrhalis* and *S.aureus,* though alternatives such as oral second- or third-generation cephalosporins, trimethoprim-sulfamethoxazole or a macrolide may be used if an IgE-mediated reaction to penicillin has occurred.[5]

There is no evidence regarding the optimal duration of antibiotics.[20] Different studies mention different duration ranging from 4 weeks to 8 weeks.[20,27] A double-blinded randomized controlled trial in 50 children with protracted bacterial bronchitis observed that antibiotic therapy with co-amoxiclav for 2 weeks resulted in cough resolution in 48% of children compared to 16% of children who received a placebo.[28]

According to one recent study, patients who received 6 weeks of antibiotics were less likely to develop recurrent PBB than those who received it only for 2 weeks[29] and another study indicated that if there is no response after 4 weeks of antibiotics, there is a high risk of developing bronchiectasis.[30] If there is no significant response after 2 weeks of antibiotics, it can be extended to 4 weeks.[31]

Treatment failure

Failure to initial treatment can be due to poor adherence, incorrect diagnosis, unknown host or bacterial factors.[10] These children need further investigations and evaluation to look for progression of the disease.[25]

Points to Remember

- ***PBB is increasingly being recognised globally as a common cause of chronic wet cough in healthy under five children.***
- ***PBB should be suspected in all healthy children who develop persistent wet cough of more than 4 weeks duration with normal physical examination and imaging.***
- ***This condition responds promptly to a course of amoxycillin-clavulanic acid given for 2-4 weeks .***
- ***Other conditions like foreign body airway and tuberculosis should be ruled out.***

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CLIPPINGS

Adenovirus infection is a risk factor for recurrent intussusception in pediatric patients

Human adenoviruses are the most common pathogens to be isolated from cases of pediatric intussusception. Medical records of pediatric patients < 18 years of age with febrile episodes, treated for intussusceptions over a 6 year period were reviewed -27 with and 29 without adenovirus infections (the latter serving as control group). The adenovirus group exhibited a significantly longer febrile duration than the control grou. The recurrence rates were 48.1% and 13.8% in the two groups (p = 0.008). The researchers concluded that adenovirus-related intussusception is associated with a longer febrile period and a higher rate of intussusception recurrence. They recommend that patients suspected of adenovirus-related intussusception should be observed for longer than others prior to discharge.

Tseng WY, Chao HC, Chen CC, Lai MW, Chang YJ. Adenovirus infection is a risk factor for recurrent intussusception in pediatric patients. Pediatr Neonatol. 2023 Jul;64(4):428-434. doi: 10.1016/j.pedneo.2022.03.024. Epub 2023 Jan 2. PMID: 36641360.

PULMONOLOGY

BRONCHIECTASIS - NON CYSTIC FIBROSIS

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Abstract: *'Non-cystic fibrosis bronchiectasis' is an end stage lung disease characterized by dilatation and thickening of airways secondary to diverse etiologies causing chronic inflammation and recurrent infections. It is a common chronic respiratory morbidity in children. The etiologies are diverse and depend on the geographic region and availability of diagnostic work up of underlying illness. The most common cause is idiopathic followed by post-infectious. The diagnosis should be suspected in children presenting with chronic wet cough of >4 weeks duration. Clinical presentation depends on the severity of illness and underlying cause and Computed Tomograph of chest is the diagnostic modality of choice. Management is mainly medical with surgery reserved for localized disease not responding to medical management.*

Keywords: *Suppurative lung disease, Primary ciliary dyskinesia, Chronic cough, Wet cough, Protracted bacterial bronchitis.*

'Bronchiectasis' is end stage lung disease characterized by dilatation and thickening of airways secondary to diverse etiologies causing chronic inflammation and recurrent infection.[1] 'Chronic suppurative lung disease'(CSLD) is often used in the same context, with slightly different meanings.[2] Bronchiectasis is a pathological diagnosis confirmed by a computed tomography (CT). CSLD is a clinical diagnosis secondary to endobronchial suppuration, without CT evidence of bronchiectasis. Both bronchiectasis and CSLD are the end result of protracted bacterial bronchitis (PBB), and PPB progresses to bronchiectasis through stages of CSLD. PBB is characterized by isolated persistent wet cough lasting for >2 weeks that resolves with 2-4 weeks course of oral antibiotics.[3] Bronchiectasis on the other hand is characterized by recurrent (>3) or persistent episodes of chronic productive cough (>4 weeks duration) associated with coarse crackles and clubbing with or without hypoxemia.[1] Two broad types of bronchiectasis are often described in clinical medicine - cystic fibrosis (CF) related and non-CF related. Non-CF bronchiectasis includes a wide variety of diseases, some of which are treatable.

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Epidemiology

The precise etiology of non-CF bronchiectasis is not known. This is because of the heterogeneity in definitions, limited access to diagnostic technology in some areas and lack of epidemiologic data from developing countries. What is clear is that low-income populations have a higher incidence of bronchiectasis, generally of infectious origin, with early severe manifestations in some populations.[4,5] CF is a major cause of bronchiectasis in developed countries, whereas in developing countries non-CF conditions are the major causes. After a decline in the early part of the 20th century, the prevalence of bronchiectasis has again started increasing over the last decade. This is because of wide availability of CT scan, the gold standard imaging modality of bronchiectasis in place of symptoms and chest radiographs for diagnosis of bronchiectasis.[4,5]

Though the overall prevalence in India is not known, studies have predicted the prevalence from pneumonia studies. The prevalence of bronchiectasis may vary from 27,22,814 to 3,38,40,694 per year due to pneumonia alone.[5] It gives a figure of 212 to 2646 children developing bronchiectasis per one million children under-five years of age. These numbers may not be actuals, but indicates the huge burden of non-CF bronchiectasis. A survey in New Zealand estimated an overall incidence of 3.7 per 100,000 in an year among children under 15 years of age.[6] Prevalence in Central Australian indigenous population, was estimated to be 1470/100,000.[7]

Etiology

A large number of diseases or precipitating factors other than CF can lead to bronchiectasis in due course of

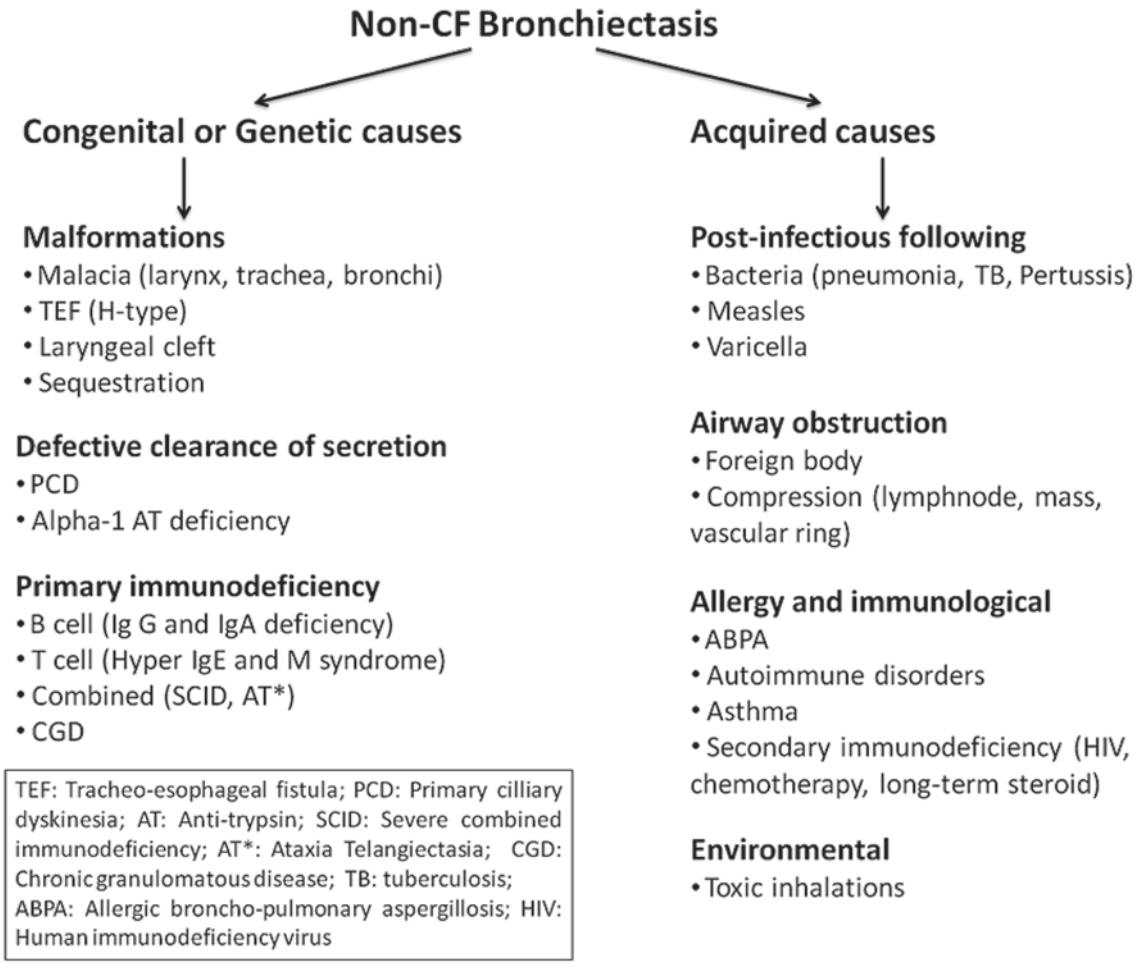

Fig.1. Etiology of non-CF bronchiectasis

time and are enumerated in Fig.1.[4,5] However, the list is not exhaustive. A large number of patients are labeled to have 'idiopathic' bronchiectasis when the initial evaluation for underlying causes is not successful in identifying one. It may represent the limited availability of medical facilities at that time and might also be because incomplete manifestation of the disease. Over a period of time, specific causes have been identified in a lot of these idiopathic cases. In one large study of nearly 1000 patients, the etiologies were as follows: Idiopathic (34%), infectious (19%), primary immunodeficiency (17%), aspiration or foreign body inhalation (10%), primary ciliary dyskinesia (PCD) (7%), congenital malformations (4%), secondary immunodeficiency (3%), asthma (2%), bronchiolitis obliterans (1%), skeletal causes (1%) and others (1%).[4] In the largest Indian study in children, following causes were identified: Idiopathic (36.2%), post-infectious (23.8%), primary ciliary dyskinesia (15%), allergic broncho-pulmonary aspergillosis (7.5%), congenital malformations (3.7%), aspiration syndromes (2.4%), primary immunodeficiency (6.2%), foreign body (1.2%), Steven Johnson's syndrome (1.2%), HIV infection (1.2%), and asthma (1.2%).[5] Among the infectious causes, tuberculosis was the commonest.

Pathophysiology

Whatever be the disease, the common cause of bronchiectasis is repeated or persistent airway injury, mucus stasis, infections and predominantly neutrophilic inflammation. The detailed process has been outlined in Fig.2.[8] Infection leads to airway mucosal infiltration by neutrophils and T lymphocytes causing increased concentrations of inflammatory mediators such as IL-8, neutrophil elastase, TNF-α and prostanoids.[5] A complex interaction among these mediators results in permanent dilatation and remodeling of airways, which is the end-stage lung disease or bronchiectasis. The initiating event may differ in patients, ranging from a inborn error of immunity, to an accidentally aspirated foreign body in a previously healthy child. It has been suggested that under-

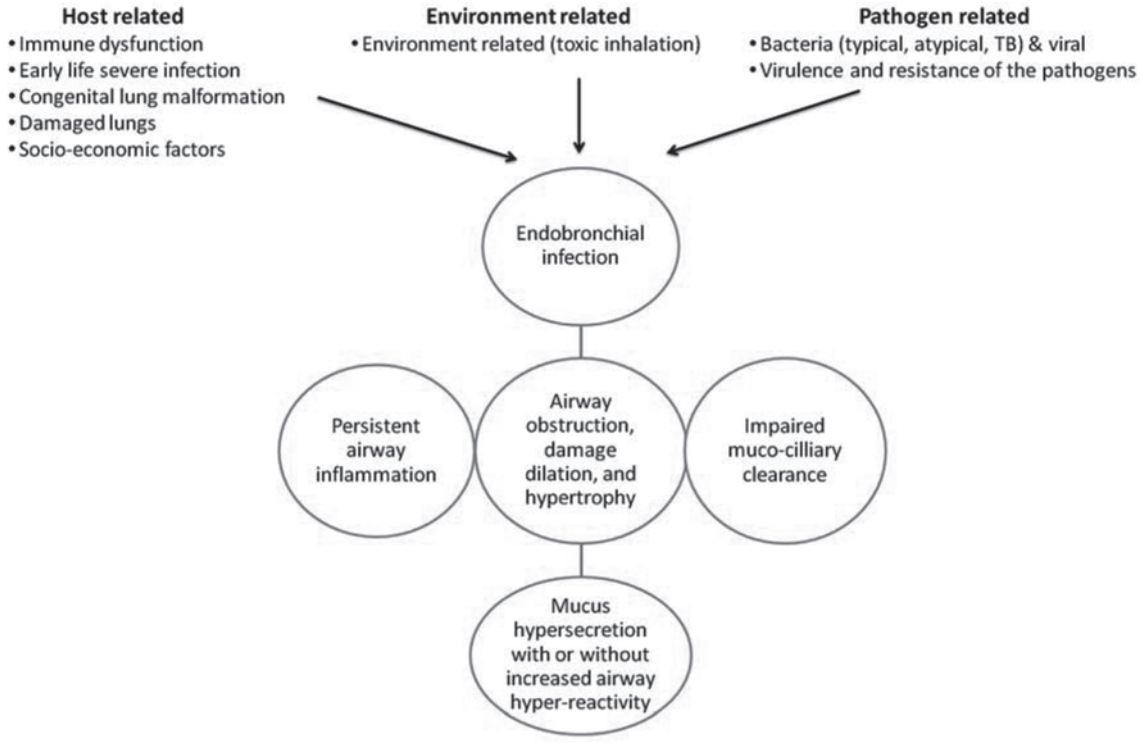

Fig.2. Suggested patho-physiology of non-CF bronchiectasis

recognition and inappropriate treatment of PBB may lead to bronchiectasis in both developing and developed countries.[5] Overall, based on the gross appearance of airways, bronchiectasis is classified as cylindrical, varicose and cystic, in increasing order of severity.

Clinical features

The median age of diagnosis in developed countries is 4 to 5 years. A study from India found the mean age to be around 9 years (range, 2 to 15 years) with nearly 2/3rd of children being under five years of age with male preponderance.[9] The 'sine qua non' of bronchiectasis is persistent or recurrent productive or wet cough. Reliability of caretakers in reporting wet cough might be poor, therefore, it is best to hear the cough for oneself and decide. Cough and expectoration of mucopurulent or purulent sputum might be most marked in the early morning, as the child wakes up. Other symptoms are exertional dyspnea, tachypnea, poor weight gain and restriction of activity. On examination, failure to thrive, clubbing, hyperinflation in early disease or signs of volume loss in advanced stage are present. Examination should be carefully done to look for findings of associated conditions, and developmental assessment. Auscultation may reveal coarse crackles over the most affected regions or may be normal. Reduced oxygen saturations and abnormal cardiac sounds associated with pulmonary hypertension are very late signs in bronchiectasis. Triad of Kartagener syndrome is only seen in 50% of children with PCD.

In a study from India, the clinical presentations in decreasing order of frequency are as follows - cough, breathlessness, expectoration, fever, wheezing, repeated pneumonia, chest pain, sneezing, repeated nasal discharge, pain abdomen, hemoptysis, recurrent vomiting, failure to thrive, ear discharge (active or in the history) and salt craving.[9]

A patient may present with an acute exacerbation, which is commonly associated with increase in cough, increase in amount of sputum and consistency, dyspnea and new findings on auscultation. Fever and hemoptysis may sometimes be present. A recent European Respiratory Society (ERS) guideline recommends that an exacerbation should be considered when the symptoms have increased for at least 3 days and that dyspnea and/or hypoxia should be considered as severe exacerbation, irrespective of duration.[10]

Diagnosis

Diagnosis of bronchiectasis should be suspected in children presenting with any of the following clinical symptoms: Persistent wet cough lasting for >4 weeks, asthma not responding to appropriate treatment, persistence or recurrent pneumonia, pertussoid cough lasting for

>6 months, persistent crepitations in the chest without obvious explanation, recurrent respiratory problems with associated esophagitis and upper respiratory illnesses and unexplained hemoptysis.[11]

Chest imaging is the cornerstone of diagnosis of bronchiectasis. Chest X-rays (CXR) are not sensitive enough and early lung changes may be missed. CXR abnormalities that suggest bronchiectasis include - prominent broncho-vascular markings, dilated bronchus, loss of lung volume and peri-bronchial thickening. Bronchography used previously is not used now-a-days. Multidetector CT (MDCT) scan with HRCT reconstruction is the current imaging modality of choice.[5,10,11] Contrast study may be required if tuberculosis, mass lesion or lymphnodes are suspected to be the underlying pathology. The characteristic CT finding is a dilated bronchus, with an elevated bronchoarterial ratio (BAR). BAR is the ratio of the inner diameter of the airway to the outer diameter of the adjacent artery and the recent recommendation is to use a pediatric specific cut off of 0.8.[10] Other associated changes on CT include failure of airways to taper toward the periphery, bronchial wall thickening, mucus impaction, air-fluid levels inside airway lumen and sometimes, frank cystic changes. Central bronchiectasis suggest ABPA (allergic broncho-pulmonary aspergillosis), or bronchiectasis secondary to recurrent aspirations.[5]

Once a diagnosis of bronchiectasis is made, further investigations are oriented to find out the etiology and should be prioritized based on the clinical picture. The panel of tests as recommended by ERS include sweat chloride estimation (to exclude CF), lung function test (spirometry), complete blood count, tests for immune function (immunoglobulin profile - IgG, IgA, IgM and IgE, flow-cytometry for CGD) and tests to rule out TB and HIV.[10] Further, specialized tests like bronchoscopy and bronchoalveolar lavage (BAL) might be needed based on the yield from the initial tests. Fiber optic bronchoscopy helps in identification of airway abnormalities and obtaining samples from the airways. It can identify airway abnormalities like laryngotracheomalacia very well.[12] PCD needs to be ruled out by demonstration of ciliary motility or structure (under electron microscope), nasal nitric oxide (NO) measurement and genetic studies (clinical exome sequencing) may be required. ABPA diagnosis requires a set of clinical and laboratory criteria.[13]

Bacterial culture of lower airway secretions is warranted at diagnosis, during exacerbations and sometimes, for routine surveillance. A spontaneously expectorated or induced sputum (following 3% to 7% saline nebulization) sample usually suffices. Otherwise, a BAL might help in organism isolation. Oropharyngeal and nasopharyngeal specimens are sometimes used as surrogate, but might lack specificity.

It is important to monitor children with bronchiectasis to assess progression of the illness and effect of the treatment.[5] In older children, spirometry may be repeated every 3 to 6 months. In younger children, symptom relief and weight gain may be used as surrogate markers of disease control.[5] Sputum examination during follow-up visits may give clear idea about colonization of the airways. It may also help in deciding about antibiotic regimen for pulmonary exacerbations. CXR and CT chest are not required routinely. These may be obtained in pulmonary exacerbations that are not responding to the treatment.

Management

Mainstay of treatment in children with bronchiectasis is medical, with surgery being reserved for rare indications. Medical treatment includes nutritional support, keeping airways clear and antibiotics treatment of exacerbation.

General measures

These include adequate protein and calories intake, good hydration, vaccination against respiratory pathogens (pneumococcal, influenza, measles, *Haemophilus influenza*, and pertussis) and avoidance of exposure to smoke (biofuel, tobacco) or environmental pollution.[5]

Specific therapy

It is possible in a handful of conditions like airway foreign body, ABPA and active infections (e.g. TB). Children with aspiration syndromes may benefit from medical (treatment of reflux) or surgical treatment (in case no response to medical treatment). Those with hypogammaglobulinemia may benefit from monthly intravenous gammaglobulin supplementation (0.5 g/kg). In case of evidence of reactive airway disease (e.g. presence of wheezing), inhaled steroids (ICS) and bronchodilators can be used. Treatment if started early in the course of disease, the airway changes can be reversed, especially in younger children.

Supportive therapy

(a) Airway clearance therapy: It is the mainstay of non-pharmacological treatment of bronchiectasis. To keep secretions thin, child should be encouraged to drink plenty of fluids and avoid dehydration. Daily chest

physiotherapy for draining impacted secretions is an essential part of treatment and needs to be emphasized to the family early. Traditional chest physiotherapy has four components: postural drainage, percussion, vibration of the chest wall and coughing. Various techniques of physiotherapy including active cycle of breathing techniques (ACBT), forced expiration techniques (FET), autogenic drainage, postural drainage, oscillating positive expiratory pressure (OPEP) and high frequency chest wall oscillation (HFCWO) may be used by taking into consideration the age of the patient, compliance and available resources.[5] Current ERS recommendations are not to use mucoactive agents as a routine in non-CF bronchiectasis. Hypertonic saline (3% to 7%) nebulization 2 to 3 times as a mucoactive agent may be considered in selected patients.[10]Inhaled mannitol has similar effect as hypertonic saline, but availability may be an issue. Pre-treatment with a bronchodilator might be essential to avoid bronchospasm. Chest physiotherapy usually follows the mucoactive agent inhalation. Recombinant human DNase may worsen lung function and should be avoided.

(b) Treatment of infections: Both viral and bacterial infections may cause exacerbations and need to be treated aggressively. Efforts should be made for eradication after the first isolation of *Pseudomonas aeruginosa*. Inhaled antibiotics (Tobramycin) may be added to systemic ones for this purpose. Intermittent exacerbations are also treated with systemic antibiotics for 14 days, guided by culture of sputum or BAL and sensitivity patterns. Severe exacerbations often require admission and intravenous antibiotics. Long term macrolides are now a part of recommendation in patients with recurrent exacerbations.[10]

Surgical treatment

The indications of surgery are limited and include localized disease that is uncontrolled with medical treatment or localized bleed, which may be an indication for resection of a lobe or whole lung.[9] Lobectomy should be viewed only as a last resort and has few indications like poor control of symptoms and growth failure despite optimal medical management and uncontrolled hemoptysis despite bronchial artery embolization. Surgery is usually not a valid option in extensive or diffuse disease.

Follow-up

Long term regular follow-up is usually essential for patients with monitoring of growth, lung function and airway microbiology.[5] Poor prognostic factors include asthma, bilateral lung disease, saccular bronchiectasis, frequent exacerbations and *Pseudomonas* colonization.

Prognosis

With better understanding of pathophysiology and diagnostic workup, prognosis of bronchiectasis has improved. In a study from India, 11% patients died of pulmonary infections. Morbidities in children who survived included poor growth in 76.3%, pulmonary hemorrhage in 16.2%, chronic hypoxemia in 10% and pulmonary hypertension in 3.8%. Surgical intervention was needed in 17.5% children.[9]

Conclusions

Bronchiectasis is a common chronic respiratory morbidity in children. The etiologies are diverse; depend on the geographic region and availability of diagnostic work up of underlying illness. Common causes of non-CF bronchiectasis in Indian children are post-infectious, PCD and ABPA. The diagnosis should be suspected in children presenting with chronic wet cough of >4 weeks duration. Clinical presentation depends on the severity of illness and underlying cause and CT chest is the diagnostic modality of choice. Management is mainly medical with surgery reserved for localized disease not responding to medical management.

Points to Remember

- ***Non-CF bronchiectasis occurs secondary to diverse etiologies except cystic fibrosis.***
- ***Common causes of non-CF bronchiectasis in Indian children are post-infectious, primary cilliary dyskinesia, and allergic bronchopulmonary aspergillosis.***
- ***The diagnosis should be suspected in children presenting with chronic wet cough of >4 weeks duration.***
- ***Clinical presentation depends on the severity of illness and underlying cause; CT chest is the diagnostic modality of choice.***
- ***Management is mainly medical with surgery reserved for localized disease not responding to medical management.***

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CLIPPINGS

Childhood and Adolescent television viewing and metabolic syndrome in Mid adulthood

Excessive sedentary behaviors, such as television viewing or other screen time, may have adverse metabolic effects. The authors hypothesized that television viewing time in childhood would be associated with the risk of metabolic syndrome at 45 years of age.

They studied a population-based birth cohort born in Dunedin, New Zealand in 1972 and 1973. Parent- and self-reported weekday television viewing times were recorded at ages 5, 7, 9, 11, 13, 15, and 32 years. The primary outcome was metabolic syndrome at age 45 years, defined as 3 or more of: high glycosylatedhemoglobin; high waist circumference; high blood triglyceride; low high-density lipoprotein cholesterol; and high blood pressure. Reported television viewing time and metabolic syndrome data were available for 870 (87%) of 997 surviving participants.

Mean television viewing time between ages 5 and 15 years was associated with metabolic syndrome at 45 years of age. This association persisted after adjusting for sex, socioeconomic status, and BMI at age 5 and after further adjustment for adult television viewing. Childhood television viewing was also associated with lower cardiorespiratory fitness and higher BMI at 45 years of age.

The authors conclude that t**ime** spent watching television during childhood and adolescence is associated with the risk of metabolic syndrome in mid-adulthood. Interventions to reduce screen time for children and young people may have long-lasting benefits for health.

MacDonell N, Hancox RJ. Childhood and Adolescent Television Viewing and Metabolic Syndrome in Mid-Adulthood. Pediatrics. 2023 Jul 24:e2022060768. doi: 10.1542/peds.2022-060768. Epub ahead of print. PMID: 37483126.

PULMONOLOGY

CYSTIC FIBROSIS

**** Priyanka Medhi***
***** Sneha Varkki***

Abstract: *Cystic Fibrosis (CF), an autosomal recessive condition is being increasingly recognised in India. Early diagnosis followed by prompt initiation of treatment is important to minimize malnutrition and to preserve lung functions. With the availability of highly effective modulator therapy, the prognosis of the disease has improved remarkably. Global disparities in access to care need to be addressed.*

Keywords: *Cystic Fibrosis (CF), Cystic fibrosis transmembrane receptor (CFTR) gene, Pancreatic sufficient (PS), Pancreatic insufficient (PI), Highly effective modulator therapy (HEMT).*

Cystic fibrosis, no longer considered an exclusive Caucasian disease, is being diagnosed frequently in India.[1] This autosomal recessive, monogenic condition due to mutation in the CFTR gene has a diverse phenotype. From a life limiting condition encountered only in paediatric practice, it has now changed to a chronic morbidity with near normal life expectancy.

Epidemiology

Cystic fibrosis affects approximately 89,000 people worldwide.[2] Prevalence of cystic fibrosis in the US is 7.97 per 100,000[3] and similar figures are reported from Europe too. Among Caucasians, the incidence of CF varies from 1 in 2500 to 3500. No systematic studies have ever been done in India to understand the true prevalence of the condition.

Pathophysiology

Pathophysiological changes in cystic fibrosis are primarily due to loss of Cystic Fibrosis Transmembrane Regulator (CFTR) protein function. CFTR protein is an epithelial chloride channel, encoded by CFTR gene. It has a crucial role in maintaining hydration of luminal surface of many ducts in the human body.

Absent or deficient CFTR protein leads to disturbance in optimal hydration of airway surface liquid layer. Dehydrated mucus layer paralyses the mucociliary clearance system. Ensuing obstruction of airways due to thick mucus, predisposition to infection and inflammation sets the stage for relentless destruction of the normal airway anatomy, development of bronchiectasis and eventual respiratory failure.

Dysfunctional or absent CFTR protein in lining cells of pancreatic duct interferes with normal chloride and bicarbonate ion transport across the cell. This leads to decreased secretion of a relatively acidic fluid into the duct, precipitation of proteins, injury and inflammation of the duct and eventual pancreatic atrophy and pancreatic insufficiency.

Increased viscosity of intestinal fluid can lead to constipation and sometimes distal intestinal obstruction syndrome (DIOS). Inspissated bowel contents can cause meconium ileus in approximately 10% of patients with CF in the neonatal period.

CFTR gene and classes of variants

CFTR gene resides in the long arm of 7th human chromosome. More than 2000 variants in the gene have been described and 700 are classified as pathogenic.[4] Based on functional consequence of a mutant gene and its impact on synthesis of CFTR protein within the cell, these variants are grouped into six classes (Table I).

Genotype - Phenotype correlation

Generally, variants of class 1 to 3 result in severe phenotype, often associated with high sweat-chloride values, severe lung disease, and pancreatic insufficiency while class 4 and 5 variants are associated with milder phenotype and may be associated with pancreatic sufficiency in the affected individual. Pancreatic insufficiency is predictable by the genotype, but other clinical features correlate poorly with the genotype.

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Table I. Classes of CFTR variants, their site of dysfunction and effect of CFTR protein on cell surface

Classes	Site of CFTR dysfunction	Status of CFTR protein on cell surface	Examples of common variants
1	Transcription phase in the early part of CFTR protein synthesis	No CFTR protein present	G542X
2	Interferes with processing of the CFTR protein, resulting in misfolded form	No CFTR protein present	phe508del
3	Affect the regulation of CFTR channel	Chloride transport doesn't occur across the cell, though protein is present	G551D
4	Decrease the chloride conduction property of the CFTR protein	Less amount of functional protein	R117H
5	Reduction in synthesis or maturation	Reduced amount of protein	3,849+10kbC→T
6	Result in unstable protein production	Fewer functional channels available for chloride transport	Q1412X

Clinical features

Clinical features and rate of progression are very variable in patients affected by CF. In the majority, recurrent or chronic pneumonias eventually lead to bronchiectasis. Complications like allergic bronchopulmonary aspergillosis, pneumothorax, hemoptysis and pulmonary hypertension can develop. Upper respiratory symptoms like recurrent sinusitis and nasal polyposis are also seen. Most common cause of death is respiratory failure. Children with pancreatic insufficiency present with oily, bulky and foul smelling stools, any time after birth. They may also develop symptoms of fat soluble vitamin deficiency. Young infants can present with a triad of oedema, hypoalbuminemia and anemia as a consequence of fat malabsorption. Those with pancreatic sufficiency, may initially remain well-nourished but can develop recurrent pancreatitis. CF related diabetes (CFRD) usually occurs in the 2nd decade of life. Gastrointestinal manifestations include meconium ileus at birth, rectal prolapse in early childhood and distal intestinal obstruction syndrome (DIOS). CF also affects the liver and the biliary tree and can lead to portal hypertension as well as cirrhosis. Younger children can have hypochloremic hypokalaemic alkalosis from excessive chloride loss through sweat during summers. Delayed puberty is a known endocrine complication. Males with CF can have congenital bilateral absence of vas deference (CBAVD) leading to infertility whereas females can have subfertility.

Diagnosis (Table II)

Sweat testing

Sweat test described by Gibson and Cooke in 1959 is the gold standard test for CF.[5] Pilocarpine iontophoresis is used to stimulate localised sweating and the sweat sample collected in a standardized manner is analysed to estimate chloride content. Sweat chloride value of ≥60 mmol/L suggests that CF is likely, value between 30-59 mmol/L suggests an equivocal possibility and value less than 29 mmol/L suggests that CF is unlikely.[6]

CFTR genetic testing

Demonstration of presence of two CF causing variants (biallelic) is diagnostic of CF. When using a panel of common CFTR variants for screening, rare variants which are not included in the panel will not be identified. Hence, a negative result will not exclude the condition. CFTR gene sequencing and checking for deletion and duplication is needed in such cases. Measurement of nasal potential difference, another diagnostic test is a research tool as of now.

Benefits of early diagnosis

Early initiation of treatment minimizes malnutrition and is associated with better BMI and better lung functions.[7] It also avoids misdiagnosis and exposure of the child to other unnecessary investigations and medications, apart

Table II. Diagnostic criteria for Cystic fibrosis (Cystic fibrosis foundation consensus guidelines)[6]

Both the following criteria must be met to diagnose CF	
	Evidence of CFTR dysfunction(any one of the following):
Clinical symptoms consistent with CF in at least one organ system, or positive newborn screen or having a sibling with CF	Elevated sweat chloride ≥60 mmol/L Presence of two disease causing mutations in the CFTR gene, one from each parental allele Abnormal chloride transport (nasal potential difference)

from offering survival benefit. Family members can benefit from genetic counselling and option of prenatal diagnosis.

New born screening (NBS)

Dried blood spot sample obtained by heel prick is used for measurement of immunoreactive trypsinogen (IRT), a pancreatic enzyme. Babies affected by CF have high IRT levels, due to pancreatic injury which has onset in utero. Most countries have developed an algorithm which involves a 2 or 3 tier testing to improve the sensitivity and specificity of the screening program. Some strategies are IRT/ IRT algorithm, IRT/ DNA algorithm and IRT/ DNA/ IRT algorithm.[8]

Screen positive infants are referred for sweat chloride testing for confirmation of diagnosis. Treatment is initiated after confirmation generally. However, infants who have already manifested early symptoms like steatorrhoea and poor weight gain, can be started on pancreatic enzyme supplements empirically.

Some countries use estimation of pancreatitis associated protein (PAP) level, another pancreatic enzyme in NBS algorithm to improve the specificity of the system.[9]

Other investigations recommended when a child is suspected/confirmed to have CF are

1. Tests for pancreatic insufficiency

- Measurement of faecal elastase - Level >200mcg/gm of stool confirms pancreatic insufficiency. This is an ELISA test specific for human enzyme and hence pancreatic enzyme supplements do not affect the result of this test.
- 72 hour stool collection and estimation of stool fat can confirm pancreatic insufficiency.

2. Assessment of fat soluble vitamin deficiency (A, D, E, K).

3. Sputum culture sensitivity - Coughed up sputum, induced sputum or a deep throat swab after chest physiotherapy are acceptable ways for specimen collection.

4. Screening for tuberculosis or atypical mycobacteria infection.

5. Radiological imaging - Chest X-rays and low dose HRCT are used to demonstrate bronchiectasis.

6. Pulmonary function tests - Monitoring forced expiratory volume in 1 second (FEV1) by spirometry helps to track decline in lung functions over time. Reduction in forced expiratory flow (FEF) 25-75% reflects earliest small airway disease in children with CF.

7. Annual screening of all children with CF - In addition to routine radiology and sputum test, one should include estimation fat soluble vitamin levels, serum IgE levels to monitor for ABPA and oral glucose tolerance test (>10 years) to screen for CF related diabetes.

8. Metabolic alkalosis, hyponatremia, hypochloremia and hypokalemia are encountered during illnesses and dehydration. These values may be normal when patients are well.

9. Liver function tests and ultrasound screening of liver.

10. Where sweat testing facility is not available, aquagenic wrinkling is a simple bedside test used to identify children who have high probability of the condition.

Aquagenic wrinkling test - Wrinkling of fingers and hands when immersed in water for 3 minutes has a high sensitivity(81%), but low specificity (56%) for identifying children with CF who need referral for diagnostic confirmation.[10]

Additional useful newer tests

Lung clearance index - lung clearance index (LCI) measured by multiple breath washout is a sensitive measure of ventilation inhomogeneity; reflects abnormalities of the smaller airways which are considered the site of early lung injury in CF.[11]

Treatment

Treatment of CF has been largely supportive and symptomatic.

Pulmonary treatment

With a goal to clear secretions from airways, many airway clearance therapy (ACT) techniques are employed. These include postural drainage, vibration and percussion, positive pressure devices ± oscillation, various breathing techniques and physical exercises. There is divergence of opinion on the best methods and specific evidence is lacking on superiority of any particular modality. Supervision by a trained physiotherapist and adherence to a regime that is acceptable/suitable for the patient is important.

Nebulised hypertonic saline (HTS) (3 to 7%) is a hyperosmolar agent which helps to rehydrate the dehydrated mucus layer thus enhancing mucociliary clearance. It has been proven to be helpful in decreasing frequency of infective exacerbations.[12] Dose used is 4 ml of 3-7% HTS twice a day.

Recombinant human DNAse is the inhaled form of enzyme that cleaves extracellular DNA of neutrophils and bacteria accumulated in CF airways. This is used in conjunction with ACT and is usually administered anywhere between 30 min to 8 hours before a chest therapy.[12] Recommended dose is 2.5 mg per day. Another hyperosmolar agent mannitol when used as inhaled dry powder preparation can improve sputum viscosity. Dose recommended is 400 mg twice a day.[13] Both DNAse and mannitol are not yet available in India.

The recommended protocol for airway clearance therapy (ACT) involves bronchodilator administration first followed by hypertonic saline nebulization. This in turn is followed by chest tapping, vibration or use of devices for airway clearance. Following this, the child is taught to effectively cough out any airway secretions. Any prescribed inhaled medications (e.g. nebulised antibiotics, inhaled steroids etc) are used after the above steps.

Antibiotics

Antibiotics are used in CF for 3 main indications - infective exacerbations, eradication of pathogens like pseudomonas aeruginosa and for chronic maintenance therapy (inhaled antibiotics) to suppress bacterial load.

Indicators of pulmonary exacerbation include decreased exercise tolerance, increased cough and sputum, loss of appetite or weight and increase in the intensity of adventitious sounds on examination of the lung.[14]

Antibiotic choice for an infective exacerbation is made based on the on the available sputum culture results; conventionally 2 sensitive antibiotics are used for a duration of 2 weeks.

Eradication of initial Pseudomonas aeruginosa infection

Many strategies are reported

1. Inhaled tobramycin 300 mg twice a day for 28 days (most widely used regime)
2. Inhaled gentamicin (intravenous preparation 80 mg for those <12 years and 160mg for >12 years) twice a day combined with oral ciprofloxacin for 3 months (this regime has been used in resource poor country i.e. Africa).[13]

Anti-inflammatory treatment

Azithromycin - Chronic therapy is used in patients colonised with Pseudomonas aeruginosa

Dose for <40 kg body weight is 250 mg and ≥ 40 kg body weight is 500 mg as a single dose three days a week.

Ibuprofen can be used in patients aged 6 - 18 years, to limit annual decline in lung function (FEV1).[12] However this drug is not routinely used.

Use of inhaled steroids is restricted to those who have asthma.

Vaccination

Routine vaccination is mandatory as many of the vaccine preventable diseases (measles, chicken pox etc) can cause rapid deterioration of pulmonary status in children with CF.

Pancreatic enzyme replacement therapy

Pancreatic enzyme replacement therapy (PERT) refers to the administration of pancreatic enzymes (porcine or

Table III. Methods of PERT dosing

Methods	Doses	
Meal method (Commonly followed)	Infants < 12 months of age	2000 - 5000 lipase unit per feed or 120 ml of formula
	12 months to 4 years	Initial dose is 1000 units per kg /meal
	Older children and adolescents	Starting dose is 500 lipase units per kg per meal
Fat gram method	500 to 4000 lipase units per gram of fat ingested	

bovine origin) along with all fat containing foods in individuals with pancreatic insufficiency (Table III).

Indications of PERT include presence of features of frank fat malabsorption, evidence of pancreatic insufficiency as proven by tests, and when a patient has 2 CFTR mutations known to be associated with PI.

Young infants under evaluation for CF, may be initiated on PERT, as soon as a diagnosis of CF is considered highly likely, even while awaiting results of the tests. This is a life saving measure as any delay can result in fatal outcome.

Dosage of PERT can be decided by meal method or fat gram method.

Adequacy of PERT dose is indicated by passage of one to two non greasy, non foul smelling stools per day and adequate gain in body weight.

Administration of PERT

Enzymes are dispensed as enteric coated granules within each capsule. Strength of the enzyme is expressed as International Units of lipase content. Commonly available strengths in India are 10000 IU and 25000 IU.

When a lower dose is prescribed for an infant, the capsule needs to be opened and the contents divided into small portions approximately containing required dose (e.g. $1/5^{th}$ of a 10000 IU capsule to give 2000 IU).

It is preferably administered mixed with a small amount of acidic food so that the activation is delayed till it reaches the alkaline medium of the duodenum. Fruit jam, yoghurt, apple sauce etc. are usually used for this purpose.

Vitamin supplementations

Supplementation of fat soluble vitamins is required. The dosage guide is given in Table IV.

Salt supplementation

Addition of extra salt is very important in infants to ensure growth and prevent salt loss symptoms. Children who play outside or exercise need extra salt intake. This is especially important on hot days.

Suggested doses for infants -

$1/8^{th}$ of teaspoon of table salt till 6 months of age

$1/4^{th}$ of teaspoon after 6 months of age

This amount should be measured and evenly divided and added to feeds throughout the day.

Precision therapy for CF

CFTR Modulator treatment

Last couple of decades have seen unprecedented progress in CF care with the advent of CFTR modulators. Modulators are highly effective small molecules which through their intracellular action, help to improve CFTR function at the cell surface.

There are 2 types of modulators.

Potentiators enhance the opening of the CFTR channels which are already existing on the cell surface to allow transport of chloride and bicarbonate ions.

Correctors increase the CFTR channel quantity. This is done by helping the protein fold correctly, enabling transport to the surface of the cell.

Four molecules have been approved for clinical use. Ivacaftor (potentiator), lumacaftor, tezacaftor (both first generation correctors) and elexacaftor (second generation corrector).

Available therapies are

- Ivacaftor as monotherapy for patients aged >1 month with ≥ 1 copy of 97 variants including G551D, 3849 +10kbC→T etc.

Table IV. Doses for VITAMIN A, D, E, K supplementation in CF[15]

Fat soluble vitamins	Age category	Daily doses
Vitamin A (Recommendations based on retinol form)	Infants	1500 IU
	Toddlers	5000 IU
	4 to 8 years	5000-10,000 IU
	> 8 years	10,000 IU
Vitamin D (Cholecalciferol is the preferred form for supplementation)	Infants	400-500 IU
	1 to 10 years	800-1000 IU
	> 10 years	800-2000 IU
Vitamin E	Infants	40-50 IU
	toddlers	80-150 IU
	4-8 years	100-200 IU
	> 8 years	200-400 IU
Vitamin K	All age groups	0.3-0.5 mg

- Combination of lumacaftor and ivacaftor approved for patients >1 year of age with 2 copies of del508phe.
- Combination of elexacaftor-tezacaftor-ivacaftor approved for children above 2 years with at least 1 copy of del 508phe and other variants.

Theratyping: A technique used to check for invitro response of a certain mutation to the modulators. If there is a response, a patient with that mutation is given a trial of the modulator combination even though elaborate clinical trials have not been done to prove that the drug is useful.

Side effects commonly encountered during treatment with CFTR modulators include liver function derangement (monitoring needed every 4 months), cataract, drug interactions and gastrointestinal symptoms

While ivacaftor and triple drug combination treatment are considered highly effective modulator treatment proven to improve lung functions, BMI, quality of life indices and decrease the sweat chloride values, issues related to the cost (roughly USD 300000 per year per person) and nonavailability, make these drugs inaccessible for most children in the low and middle income countries.

Treatment modalities other than modulators in the therapeutic pipeline[16] and their proposed mechanism of action.

- Stabilizers: Rescuing the protein stability at the plasma membrane
- Read-through agents and NMD Inhibitors: Rescuing the protein synthesis
- Amplifiers: Increasing the abundance of protein substrate
- Antisense oligonucleotides: Correcting the aberrant splicing
- Gene therapy

Prognosis of CF

There has been a steady increase in life expectancy of patients with CF over the years.

Now, adults comprise 58.3% of the total US cystic fibrosis population. In 2021, the median age of survival in the US was approximately 53.1 years (95% CI, 51.6-54.7 years) for people born from 2017[3] through 2021.

High infant mortality and severe morbidity are associated with late diagnosis of CF in Indian subcontinent. Life expectancy in the majority is upto the second decade only. However, with increasing awareness and concerted efforts of all stake holders, this is sure to change in the next decade.

Points to Remember

- ***Cystic fibrosis (CF) an autosomal recessive condition exists in India, determination of its precise magnitude is urgently needed considering its implications on childhood mortality.***
- ***Sweat chloride estimation is the gold standard test for diagnosis of CF. Elevated sweat chloride level >60mmol/L or demonstration of the presence of two disease causing variants in the CFTR gene confirms the diagnosis.***
- ***Early initiation of treatment with pancreatic enzyme replacement therapy, good nutrition and airway clearance therapies minimizes malnutrition, improves quality of life and is associated with better lung functions.***
- ***In this era when highly effective modulator therapy (HEMT) has changed the trajectory of disease progression, global disparities in access to care need to be urgently addressed.***

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PULMONOLOGY

PULMONARY MANIFESTATIONS IN PRIMARY IMMUNODEFICIENCY

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Abstract: *Primary immunodeficiency diseases are a group of inherited disorders characterized by susceptibility to infections, allergies, autoimmunity and malignancies. These disorders are better known as inborn errors of immunity. While inborn errors of immunity can affect every organ system, the respiratory system is the most commonly afflicted. Sinopulmonary infections cause significant morbidity and mortality, however, the spectrum of sinopulmonary involvement also includes immune dysregulation, bronchiectasis, interstitial lung disease and malignancies. In this article, we discuss the pulmonary manifestations of inborn errors of immunity and provide a diagnostic approach and simplified algorithms to ensure a timely diagnosis in these patients.*

Keywords: *Inborn errors of immunity, Pneumonia, Immune dysregulation.*

Primary immunodeficiencies (PIDs) are a group of genetically heterogenous diseases that predispose the affected individuals to recurrent infections, allergy, autoimmunity and malignancy.[1] The term inborn errors of immunity' (IEI) was introduced by the International Union of Immunological Societies (IUIS) expert committee in 2017 to highlight the wide spectrum of manifestations noted in these diseases. As per the recent IUIS 2022 update, 485 IEI have been described to date and this list keeps evolving with better understanding and advancements in molecular genetics. It is estimated that 1% of the world's population is affected by an IEI; however, 70-90% of these cases remain undiagnosed.[1,2] IUIS 2022 update has classified IEI into 10 broad groups based on the underlying fundamental immune defect.[3] Combined immune deficiencies with severe T-cell deficiency are likely to present at a younger age and have poor outcomes unless treated with a hematopoietic stem cell transplant (HSCT). Humoral immune deficiencies with B cell defects often present beyond six months of age, as placentally transferred maternal IgG levels diminish in the body.[4]

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Pulmonary manifestations in IEI

While IEIs can affect any organ system in the body, the respiratory system is the most commonly affected in patients with IEI.[4] Upper respiratory tract infections (otitis media, sinusitis) and lower respiratory tract infections (bronchitis, pneumonia) are often the presenting manifestations in IEI. Undue delay in diagnosis results in irreversible lung damage and bronchiectasis in a subset of these patients. Interstitial lung disease is another significant complication and needs special mention in the context of IEI. In this article, we shall discuss infectious and non-infectious manifestations of IEI and present a few real-life case scenarios highlighting the diagnostic approach. Pediatricians and physicians must be aware of these diseases to ensure a timely diagnosis and appropriate

Table I. Pulmonary manifestations of IEI

1. Infections
a. Bacterial
b. Fungal
c. Viral
2. Immune dysregulation
a) Granuloma
b) Pulmonary fibrosis
c) Inflammation
d) Bronchiectasis
e) Obliterative Bronchiolitis
f) Interstitial lung disease
g) Pulmonary fibrosis
3. Malignancy

therapy. The complete spectrum of pulmonary manifestations in IEI has been summarised in Table I.

1. Infections

Sinopulmonary infections are a dominant manifestation of humoral defects and contribute significantly to morbidity and mortality. Classically described as severe, persistent, unusual and recurrent (SPUR), respiratory infections in IEI differ from non-IEI patients.[4] The underlying immune defect determines the profile of infections.

a. Primary antibody deficiency (PAD) / Humoral immune deficiency

Antibody deficiency predisposes patients to recurrent infections with encapsulated organisms, including *Streptococcus pneumoniae, Haemophilus influenzae and Staphylococcus aureus*.[4] All the diseases in the group present with pneumonia, sinusitis, otitis media and upper respiratory illness. As these infections readily respond to routinely used antimicrobials, the diagnosis is often delayed by months to years. X- linked agammaglobulinemia(XLA), common variable immunodeficiency (CVID) and hyper IgM (HIgM) syndrome are the common humoral immune deficiencies.[4]

i) X- linked agammaglobulinemia (XLA)

XLA is a humoral defect where patients do not have B-cells and as a result, fail to produce antibodies. XLA was the first officially reported IEI, described by Colonel Bruton in 1952 and has a variable pulmonary presentation.[5] Besides the encapsulated organisms, *Mycoplasma pneumoniae* and *Bordetella pertussis* have also been reported in XLA patients.[4,6]

ii) Common variable immunodeficiency (CVID)

CVID is characterized by defective antibody production and is the most common symptomatic IEI known to manifest in adults.[7,8] These patients are predisposed to develop secondary complications including cavitation and pneumatocele formation.[8] Haemophilus and streptococcal infections cause acute exacerbation, while pseudomonas and staphylococcal infections cause progressive lung damage.[9] Opportunistic infections like mycobacterial infections, mycoplasma and ureaplasma have also been reported in CVID.[4,10] Cytomegalovirus (CMV), varicella-zoster virus (VZV) and herpes simplex virus (HSV) have been reported to cause severe pulmonary infections in CVID patients.[4,11]

iii) HIgM syndrome

This is a group of disorders characterised by defective class-switch recombination and as a result, these patients only produce IgM antibodies. Patients with HIgM syndrome have the predisposition to develop *Pneumocystis jirovecii* pneumonia (PJP).[8] Candida, cryptococcus and histoplasma have been isolated in these patients. Rare organisms like *Talaromyces marneffei* and viral infections caused by CMV and adenovirus have also been reported in HIgM syndrome patients.[4,12]

b. Defects of cellular immune response

Combined immune deficiency disorders involve cellular and adaptive immunity, predisposing the patients to a broad range of pathogens. Severe combined immunodeficiency (SCID) is a type of combined defect that presents in early infancy and has a poor outcome.

i) SCID

SCID is an inherited disorder with functional or quantitative defects in T lymphocytes with variable involvement of B and NK cells or large granular lymphocytes (LGL). This is a severe form of immune deficiency that predisposes young infants to several opportunistic infections and is universally fatal, unless the patient is subjected to an HSCT. A large multi-centric study of SCID patients from India has reported pneumonia in 82% of SCID patients.[13] The common viral infections in SCID include parainfluenza type 3, CMV, adenovirus and respiratory syncytial virus (RSV). Mortality due to persistent RSV bronchiolitis has also been reported in SCID patients.[4] SCID is the most common IEI associated with PJP.[14]

ii) Combined immune deficiency (CID)

This group of disorders encompasses combined defects with a milder presentation compared to SCID. Signal transducer and activator of transcription 3 (STAT3) deficiency and dedicator of cytokinesis 8 (DOCK8) are two prototype diseases described as autosomal dominant and autosomal recessive hyper IgE-syndrome (HIES) respectively. Patients with STAT3 deficiency can develop large pneumatoceles due to poor collagen remodelling. Aspergillus and Scedosporium species have also been isolated in STAT3 deficient patients.[4]

c. Phagocytic disorders

Phagocytes(neutrophils and monocytes) are the primary drivers of the innate immune response. Chronic granulomatous disease (CGD), congenital neutropenia and leukocyte adhesion defect (LAD) are the common disorders included in the group.

i. Chronic granulomatous disease (CGD)

CGD is the prototype macrophage defect with defective NADPH oxidase necessary for effectively killing bacterial and fungal pathogens. Pulmonary infections constitute 80% of the disease burden, with the most common manifestation being pneumonia, followed by lung abscess formation.[15] The common pathogens are catalase positive organisms, including *Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia, Klebsiella pneumoniae*, Nocardia and pseudomonas species. *Mycobacterium tuberculosis*, BCG and Salmonella also affect CGD patients in endemic countries.Organisms like *Legionella pneumoniae*, Actinomyces species and *Neosartorya udagawae* are pathognomonic in CGD.[4] Aspergillus is the most common fungal infection in CGD and is a leading cause of mortality in these patients. Aspergillosis may not be picked up on plain radiographs and require computed tomography (CT). CT signs include ground-glass opacities suggestive of pulmonary haemorrhage and a classic "air crescent sign", indicating the evolving cavity formation. Other organisms like candida are also frequent.[4] Pulmonary botryomycosis is a rare infection reported in CGD.[16] Isolation of organisms is always challenging in CGD patients and the success rate is only around 52% despite invasive procedures like needle biopsy or bronchial lavage.[15]

ii. Congenital neutropenia

Congenital neutropenia is a group of disorders associated with low neutrophil counts (<1500 cells/mm^3) predisposing patients to recurrent infections. It may be intermittent or permanent, mild (500 - 1500 cells/mm^3) or severe(<500 cells/mm^3) and affect organ systems such as the central nervous system, heart, pancreas and skin. The infection risk increases profoundly if the neutrophil counts are less than 200 cells/mm^3.[17] Severe congenital neutropenia is associated with frequent staphylococcal infections. Aspergillosis is also known in severe congenital neutropenia.[4]

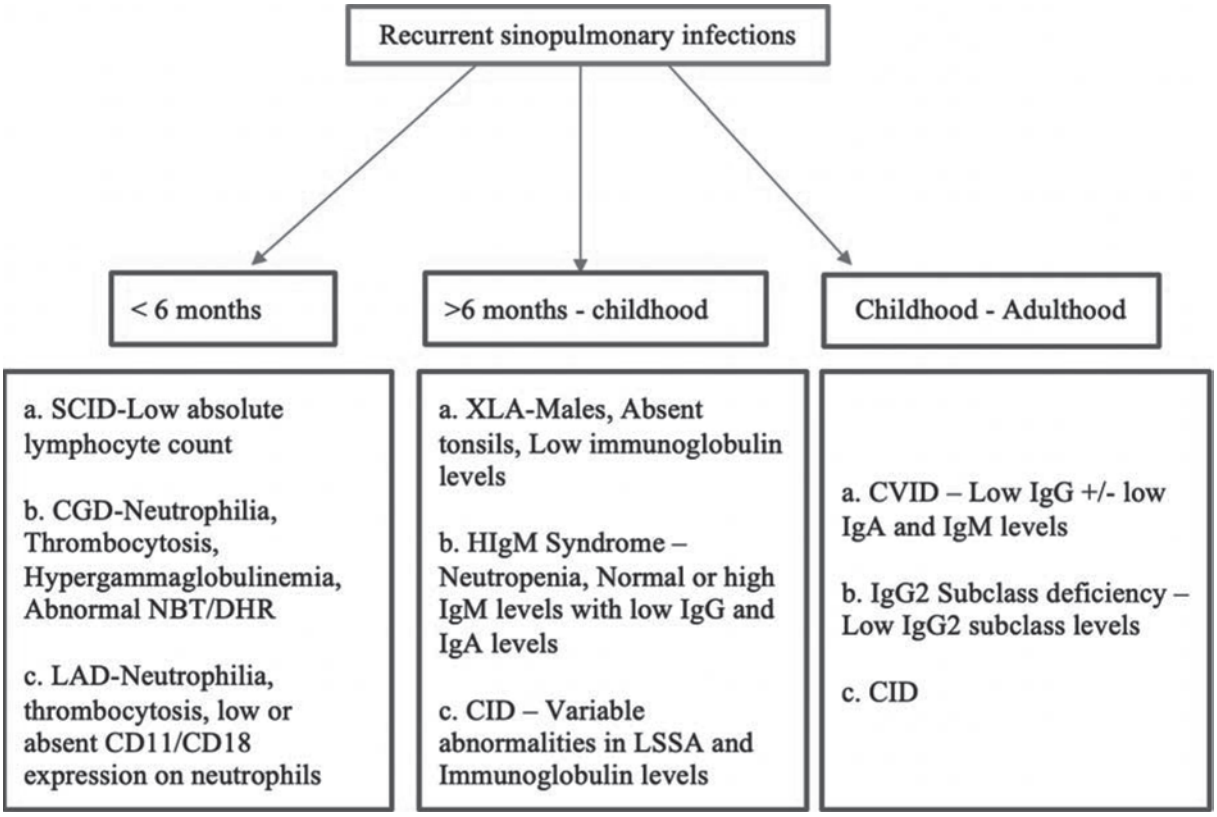

Fig.1. Common immune deficiencies known to present with recurrent sinopulmonary infections.

(SCID - Severe Combined Immune Deficiency, CGD - Chronic granulomatous disease, LAD - Leucocyte adhesion defect, XLA - X linked agammaglobulinemia, HIgM - Hyper-IgM, CID - Combined Immune Deficiency, LSSA- Lymphocyte Subset Analysis, CVID - Common Variable Immune Deficiency) , NBT/DHR - Nitroblue tetrazolium test/ Dihydrorhodamine (DHR) test

iii. Leukocyte adhesion defect (LAD)

LAD is an autosomal recessive leukocyte functional defect where the neutrophils fail to emigrate towards sites of inflammation from the bloodstream, which leads to reduced inflammatory response despite significant neutrophilia. The infection profile is similar to patients with neutropenia.[4] Delayed cord fall, omphalitis and non-healing cutaneous ulcers are peculiar features of this disease.

d. Complement deficiencies

Complement system deficiencies are rare and present with life-threatening pneumonia. Early complement system involvement (C1-C4) is associated with pyogenic infections, while terminal complement defects present with neisserial infections. C3 deficiency is associated with recurrent streptococcal pneumonia.[18]

e. Other immune deficiencies

Certain IEIs predispose to peculiar infections. Epstein Barr virus (EBV) is reported in numerous IEIs, including patients with activated phosphoinositide 3 kinase delta syndrome (APDS) and X-Linked lymphoproliferative disease.[19]

Various immune deficiencies known to present with sinopulmonary infections based on the typical age of presentation have been highlighted in Fig.1.

2. Immune dysregulation

a. Granulomas

Granulomas have been widely reported in CVID and CGD patients. Pulmonary granulomas in CGD are non-caseating and composed of multinuclear giant cells. They involve the main bronchus and cause obstructive symptoms. They are often sterile, suggesting the underlying inflammation can be independent of infections. Nocardia, aspergillus and *Burkholderia cepacia* infections have been implicated in granuloma formation.[20-22] Granulomas have also been reported in CVID. They have been described under the broad spectrum of granulomatous-lymphocytic interstitial lung disease (GLILD). The exact pathogenesis remains unclear. There have been associations with infections, including human herpes virus type 8, EBV and CMV.[4]

b. Lymphoproliferation

Abnormal proliferation of lymphocytes in lymphoid organs causes lymphadenopathy, adeno tonsillar hypertrophy and hepatosplenomegaly.Lymphoproliferation is well known in CVID and CVID-like illnesses {lipopolysaccharide responsive and beige-like anchor protein (LRBA), Cytotoxic T lymphocyte antigen 4 (CTLA-4), activated phosphokinase delta syndrome (APDS)} APDS patients have mucosal lymphoid hyperplasia present throughout the airway and may develop into B-cell lymphomas.[19]

c. Primary alveolar proteinosis

Primary alveolar proteinosis (PAP) is characterized by the accumulation of pulmonary surfactant, leading to respiratory insufficiency and recurrent infections. It may be an autoimmune condition due to anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies or congenital due to colony stimulating factor 2 receptor subunit alpha (CSF2RA) mutations and ADA deficiency. It has been reported in HIgM with PCP.[23] Guanine Adenine Thymine Adenine binding protein 2 (GATA2) deficiency is another condition where alveolar macrophages fail to clear the proteins and lipids, leading to the deposition of this lipoproteinaceous material in the alveoli. PAP has been documented in up to 43% of patients with ADA-deficient SCID.[24]

d. Allergy

Patients with primary humoral defects have allergic complaints such as allergic rhinitis and asthma. Patients with CVID have a chronic productive cough indicative of chronic bronchitis and sinusitis. Severe eczema has been noted in patients with Wiskott Aldrich syndrome, DOCK8 deficiency, STAT3 deficiency etc.[4]

e. Angioedema

Hereditary angioedema belongs to the complement pathway disorders associated with reduced or dysfunctional C1 inhibitor. Laryngeal involvement can be life-threatening in these patients.[25] Patients often present with recurrent non-pruritic swelling involving various parts of the body and recurrent pain abdomen. Low serum C4 levels can be a simple screening test.

f. Bronchiectasis

Recurrent pyogenic bacterial infections in IEI patients cause air trapping, bronchial hypertrophy, abnormal dilatation and terminally secondary bronchiectasis.[11] Bronchiectasis marks the onset of irreversible or late end-stage lung disease in these patients. The exact pathogenesis of bronchiectasis remains poorly understood.

However, there are certain plausible explanations. Patients with humoral defects have poor mucociliary functions. The pathogenic organisms create a biofilm that drives local inflammation. Once triggered, chronic local and systemic inflammation can continue without active infection. Phagocyte recruitment in the local tissue and subsequent pro-inflammatory cytokine release causes direct airway damage as bronchial wall fibrosis and atelectasis. Despite the increased number of airway macrophages, these patients have an impaired ability to clear apoptotic neutrophils and organisms. Non-typable *H. influenza* has been particularly implicated in the pathogenesis of bronchiectasis in these patients.[26]

Bronchiectasis predominantly involves the middle and lower lobes more than the upper lobe. It more frequently affects the proximal bronchi and is cylindrical in type. It is more common in adults than children with humoral deficiency.[4] While 94% of CVID patients have variable lung involvement by computed tomography(CT), 23% have evident bronchiectasis.[26] Fourteen per cent of HIgM syndrome patients develop bronchiectasis. Half of them have abnormal pulmonary function tests with a restrictive pattern which may help to pick up the patients early during the evolution of the disease.[16] Patients with STAT3 deficiency also have a higher risk of developing bronchiectasis and pneumatoceles.[4]

g. Obliterative bronchiolitis (OB)

Chronic airway insult from recurrent infections induces progressive bronchial narrowing and inflammation, leading to obliterative bronchiolitis. It is challenging to differentiate OB from bronchiectasis, and subtle changes like decreased diffusion capacity of the lungs for carbon monoxide (DLCO), obstructive patterns disproportionate to the degree of bronchiectasis and oxygen desaturation on exertion suggest evolving OB changes.[8]

h. Interstitial lung disease

Interstitial lung disease is a late complication in IEI. In CVID, a specific entity called granulomatous-lymphocytic interstitial lung disease or GLILD is responsible for high morbidity and mortality in these patients. GLILD is a broad-spectrum group which includes follicular bronchiolitis, nodular lymphoid hyperplasia, reactive lymphoid infiltrates, lymphocytic interstitial pneumonia, granulomatous lung disease and organizing pneumonia. The pathogenesis is secondary to a combination of lymphoid hyperplasia and granuloma formation. It is a distinct clinical entity from bronchiectasis as GLILD is due to immune dysregulation, unlike bronchiectasis, where bronchial cicatrization occurs. Pulmonary nodules have been reported in 20-40% of patients with CVID, while interstitial lung disese (ILD) has been reported in 10%.[4]

3. Malignancy

The overall risk for malignancy in IEI is 1 to 25%. It is higher in patients with CVID and Wiskott-Aldrich syndrome(WAS). Most tumours are associated with EBV (30-60%) infection. CVID patients develop pulmonary lymphomas, especially Non-Hodgkin's lymphoma.[27] Solid tumours are rare and sparsely reported as case reports of pulmonary adenocarcinoma and leiomyoma. Secondary metastasis, for example, gastric carcinoma, is more common in the lungs.[4,28] Rarely, thymomas have been reported in 1-6% of patients with primary humoral immunodeficiencies and this syndromic association is known as Good's syndrome.[28]

Diagnosis

The diagnosis of IEI is based on a thorough history and examination. Jeffrey Modell Foundation's 10 warning signs of primary immune deficiency is an easy guide for screening IEI patients.[29] Specific tests include measuring the serum immunoglobulin levels, lymphocyte subset assay and nitro blue tetrazolium (NBT) / dihydrorhodamine 123(DHR) assay.[30]

i. Immunoglobulins

B cells produce immunoglobulins or antibodies to defend the body against infections, especially encapsulated bacteria. Once activated, B cells secrete four types of antibodies, including IgG, IgM, IgA and IgE. There are four IgG subclasses (IgG1, IgG2, IgG3 and IgG4) and two IgA subclasses (IgA1 and IgA2). During the first few months of life, children are protected by maternal antibodies, as a result, antibody defects begin to manifest in the second half of infancy. It is, therefore, prudent to interpret the immunoglobulin levels using age-specific normative data.

ii. Lymphocyte subset assay(LSSA)

T, B and NK cells can be enumerated using flow cytometry. Low T cells in an infant with recurrent infections is suggestive of SCID. Children with XLA have low B cells. Lymphocyte subsets can be affected in a wide variety of immune deficiencies and this assay is an important screening tool while evaluating patients with suspected immune defects.

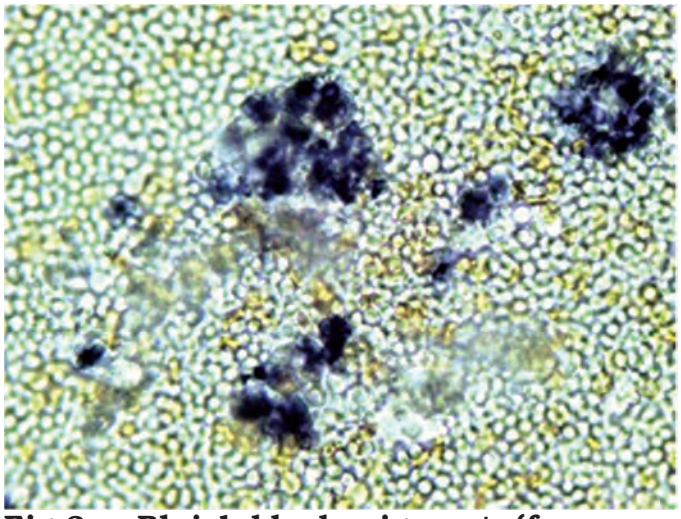

Fig.2a. Bluish-black pigment (formazan granules) formation in slide indicates normal oxidative burst. This pigment formation will not be seen in a patient with CGD.

iii. Nitro blue tetrazolium (NBT) and Dihydrorhodamine (DHR) tests

NBT test is a slide test useful for screening CGD. CGD patients have a defective oxidative burst identified by the inability to reduce yellow NBT dye to bluish-black pigment (Formazan granules) (Fig.2a). However, there is a high observer bias involved in interpretation; hence dihydrorhodamine 123 (DHR) assay is the method of choice. Healthy phagocytes reduce DHR to fluorescent compounds, and this change in fluorescence of DHR-loaded granulocytes after phorbol-myristate acetate (PMA) stimulation is measured by flow cytometry (Fig. 2b). This test can detect CGD patients and carriers.

iv. Genetic testing

Molecular testing is the definitive diagnostic modality. As majority of immune deficiencies are single gene disorders, Sanger sequencing of the gene involved can be carried out. However, exome sequencing is the most commonly used test in clinical practice, as it enables testing for a large number of genes in a cost-effective manner. Moreover, immune deficiencies with a similar clinical and immunological phenotype can be caused by defects in a variety of genes and hence, exome sequencing seems a rational choice in this setting.

Following are a few cases of IEI where pulmonary involvement was a predominant manifestation.

Case 1

Master A, a seven-year-old boy, presented with recurrent pneumonia from three years of age. Three of his maternal uncles had expired in childhood due to severe infections. On examination, tonsils were absent and lymph nodes were not palpable.

Investigations:CBC: Hemoglobin (Hb)-11 gm/dL, Total white cell counts (TC)-11,000/mm^3 (N_{66} L_{30}), Platelet counts (PC)-3,43,000/mm^3. CRP 30 mg/L

HIV rapid test: Negative, Chest X-ray: Bilateral consolidation, IgG:<270 mg/dL (608-1572), IgA <40 mg/dL (33-236), IgM <25 mg/dL (43-207) LSSA - CD3 80% (1552 cells/cu mm), CD19 0%, CD56 18% (359 cells/cu mm). Whole exome sequencing-pathogenic mutation in *BTK* gene.

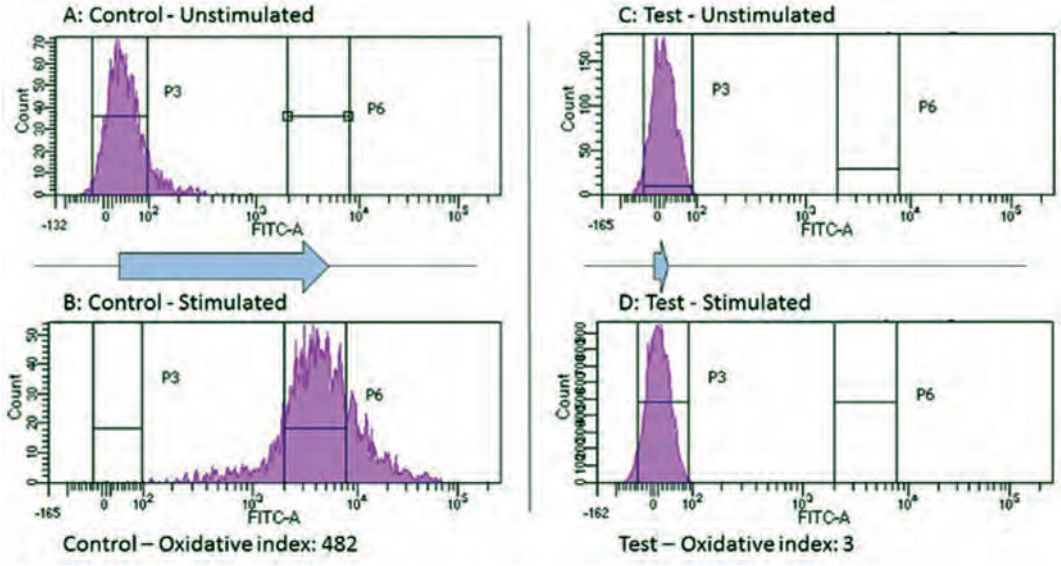

Fig.2b. DHR assay in a patient with CGD in comparison to a healthy control.

Diagnosis: X-linked agammaglobulinemia (XLA)

He was started on IVIg replacement, following which there were no further episodes of pneumonia.

Message: Patients with XLA present with recurrent sinopulmonary infections. Absent tonsils and non-palpable lymph nodes in a boy presenting with recurrent infections - one must think of XLA.

Case 2

Mrs A, a 35-year-old lady, presented with recurrent pneumonia for five years. She was on home oxygen therapy for more than two years. She was diagnosed with bronchiectasis and was under the care of pulmonology services.

Investigations: Complete blood count (CBC): Hb-10 mg/dL, Total count (TC)-10,000/mm^3 (N60 L35), Platelet count (PC)-2,43,000/mm^3.

Sputum examination - Negative for AFB. HIV rapid test: Negative. HRCT Chest: Bronchiectasis.

She was referred to the Immunology services and the following tests were carried out - IgG:90 mg/dL (639 - 1349), IgA <25 mg/dL(70 - 312), IgM 24 mg/dL (56 - 352)

Detailed lymphocyte subset assay showed low un-switched and switched memory B cells, Diphtheria antibody titres (post vaccination) - undetectable

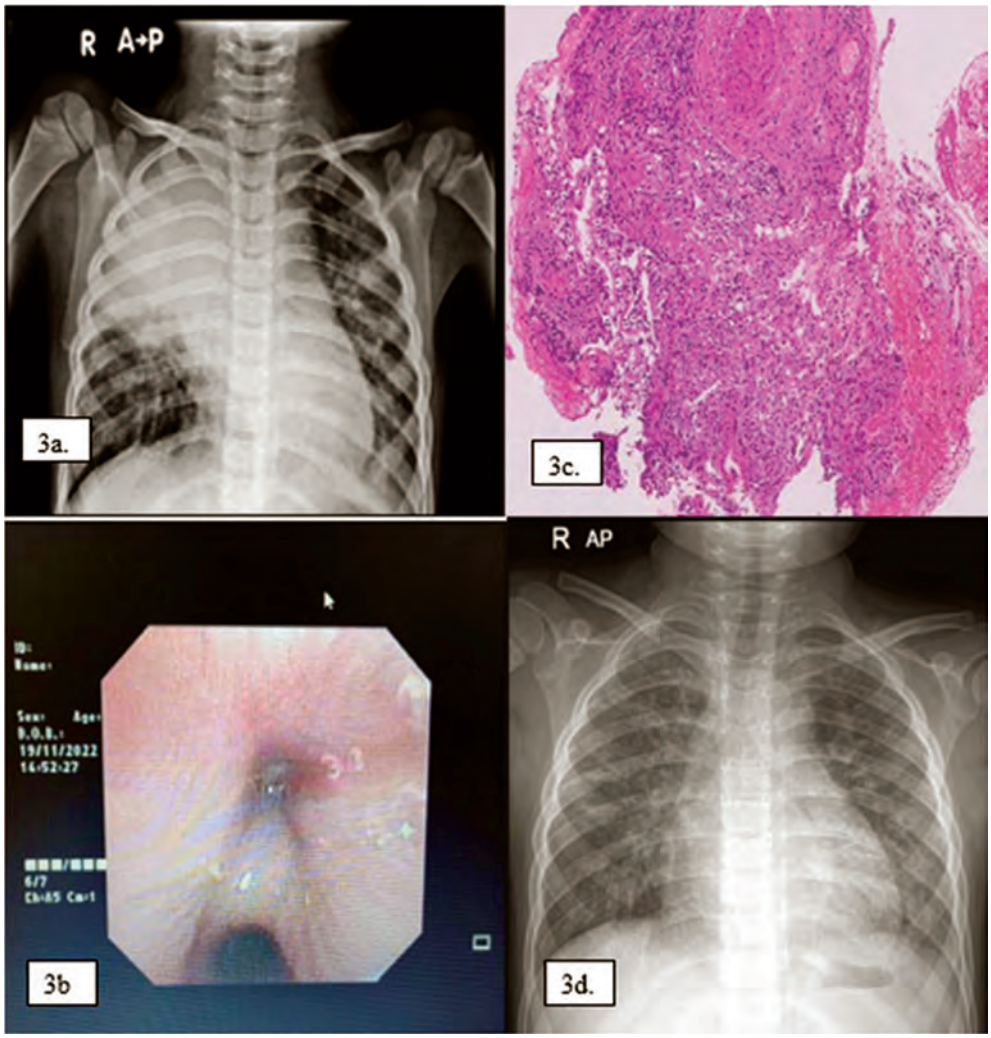

Fig.3a. Chest radiograph showed consolidation of right upper lobe. 3b. Bronchoscopy showed extrinsic compression of right upper bronchus with significant narrowing and mucopurulent secretions in right upper bronchus and left lower bronchus. 3c. Histopathological examination (bronchial tissue) - Focal expanded interstitium with mixed inflammation 3d. Chest radiograph on 3 month follow-up showed complete resolution of patch.

Whole exome sequencing - negative.

Diagnosis: Common Variable Immune Deficiency

She was started on immunoglobulin replacement therapy.

Message: CVID can manifest with recurrent pulmonary infections in adulthood. Immunoglobulins must be tested in all patients with bronchiectasis, with no clear underlying diagnosis.

Case 3

Master A, a three-year-old boy, presented with non-resolving pneumonia for three months. He was born to a third-degree, consanguineously married couple and had two episodes of pneumonia in the first year of life.

Investigations: CBC: Hb-8.8 gm/dL, TC-60,000/mm^3 DC-N70, L30, PC-7,43,000/mm^3.

CRP 120 mg/L, sputum examination - negative for AFB, HIV rapid test - negative, chest Xray - consolidation involving the right lung (Fig.3a).

Bronchoalveolar lavage (BAL) was positive for galactomannan, and he was diagnosed with aspergillus pneumonia. He was treated with oral voriconazole for three months, following which his pneumonia resolved.

Immunological evaluation-IgG: 2520 mg/dL (345-1,236), IgA: 120 mg/dL (14-159), IgM: 324 mg/dL (43 - 207)

NBT and DHR tests were performed and showed reduced oxidative burst.

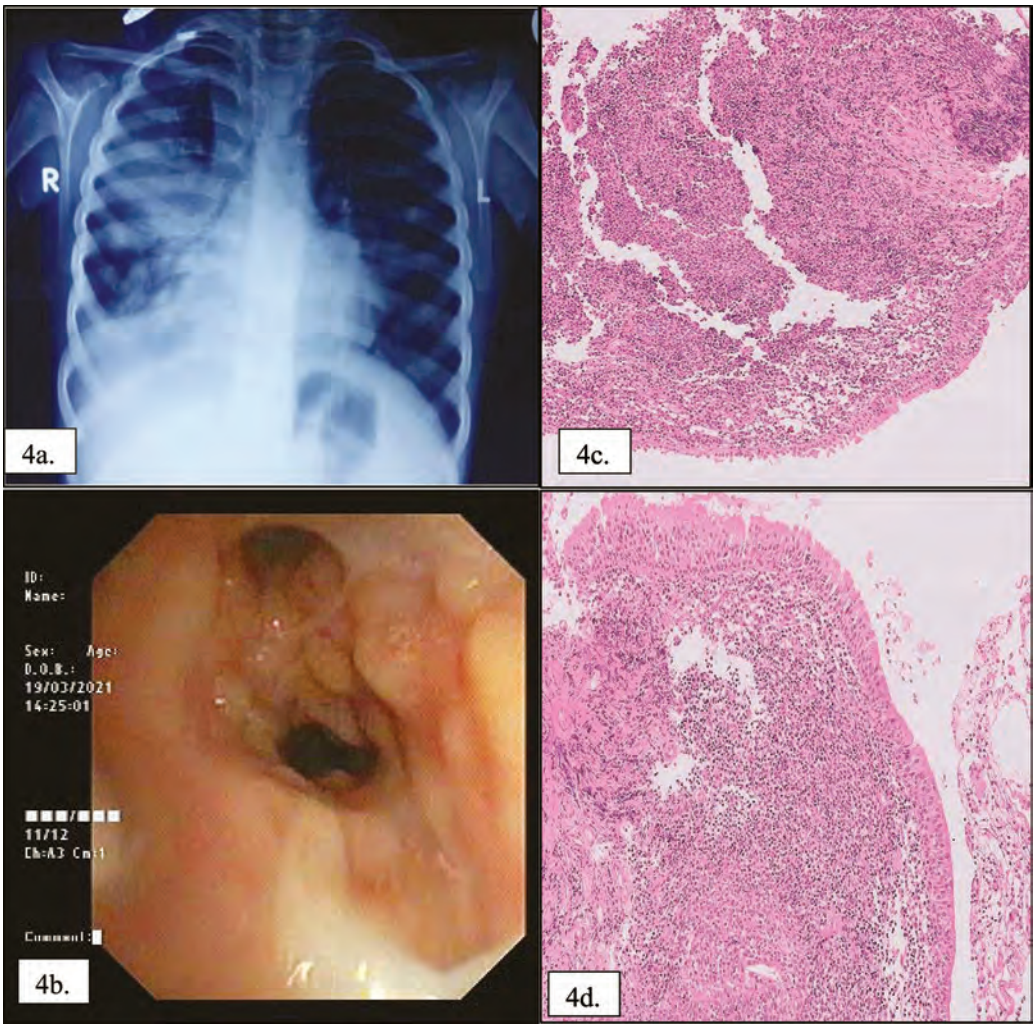

Fig.4a. Chest radiograph showed right upper love consolidation. 4b. Bronchoscopy showed significant nodularity noted over the posterior membranous wall throughout the tracheobronchial tree. 4c. Histopathological examination (specimen – bronchial tissue) high power field showed lymphoid aggregates in the subepithelial stroma. 4d. Lymphocytic exocytosis in the mucosal lining with stromal plasma cells entrapping mucosal glands.

Genetic studies: homozygous pathogenic mutation in neutrophil cytosolic factor 1(*NCF1*) gene.

Diagnosis: CGD (due to *NCF1* gene defect)) with non-resolving pneumonia

Message: Patients with aspergillus pneumonia must be screened for CGD.

Case 4

Master K, a seven-year-old boy, presented with recurrent cough with expectoration for the past four years. On examination, he had bilateral cervical lymphadenopathy and hepatosplenomegaly.

Investigations: CBC: Hb-10 mg/dL, TC -10,000/mm^3 (N70 L30), PC -2,43,000/mm^3.

HIV rapid test: Negative, Chest X-ray - consolidation involving the right lung (Fig.4a).

The bronchoscopy showed significant nodularity over the posterior membranous wall throughout the tracheobronchial tree (Fig.4b). The histopathological examination was consistent with follicular bronchiolitis. IgG: 1830 mg/dL (608-1572), IgA: 138 mg/dL (33-236), IgM: 233 mg/dL (43 - 207), IgE 41 IU/L

LSSA: CD3 67% (1927), CD19 3.6% (104), CD56 28.9% (829), CD4 17.8%(512), CD8 .40% (1160), CD4/8 0.44

Genetic studies: Heterozygous mutation [c.1573G>A (p.Glu525Lys)] in *Exon 10* of PIK3CD

Diagnosis: Activated phosphokinase delta syndrome (APDS)

Message: Follicular bronchiolitis is a form of mucosal lymphoproliferation and has been reported in patients with APDS.

Conclusion

Respiratory involvement is the most common systemic involvement in patients with IEI. Both infectious and non-infectious complications are well-reported. Patients presenting with recurrent pneumonia, recurrent sinusitis, non-resolving pneumonia and complicated pneumonia (empyema, lung abscess) must be screened for an underlying IEI. Interstitial lung disease at a young age and unexplained bronchiectasis warrants evaluation for an underlying IEI. Immunoglobulins must be tested in patients with recurrent sinopulmonary infections.

Points to Remember

- ***Respiratory system is the most commonly affected system in patients with primary immunodeficiencies (PIDs), also known as Inborn Errors of Immunity (IEI).***
- ***Humoral defects (antibody deficiencies) are the most common group of IEI known to present with recurrent sinopulmonary infections.***
- ***IEIs can also manifest with immune dysregulation, bronchiectasis, interstitial lung disease and malignancies.***
- ***Certain organisms may point towards the underlying diagnosis - Aspergillus pneumonia in chronic granulomatous disease, Pneumocystis jirovecii pneumonia in severe combined immune deficiency (SCID) and hyper IgM syndrome (HIgM).***

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PULMONOLOGY

INVESTIGATIONS IN OBSTRUCTIVE SLEEP APNEA

**** Neha Mohan Rao***
***** Ilin Kinimi***

Abstract: *Quality sleep is essential for normal growth and development of a child. Obstructive sleep apnea in children is an under-recognized entity, which if present, significantly affects a child's quality of life. Early recognition of the condition and formal evaluation with a polysomnography, the gold standard for diagnosis of OSA, enhances the child's daytime functionality. Other supportive investigations that help identify the cause of upper airway obstruction are useful. Clinical correlation of the data obtained from tests is essential. Untreated obstructive sleep apnea can have adverse long term metabolic, cardiovascular and neurobehavioral effects.*

Keywords: *Pediatric obstructive sleep apnea, Polysomnography.*

Pediatric obstructive sleep apnea (OSA) has a prevalence of about 1.2% to 5.7% world-over, depending on the age group and definitions used.[1] However, this number is the tip of the iceberg and OSA is a highly under recognized entity in the pediatric population. Timely diagnosis of pediatric OSA is important in order to prevent long-term complications such as behavioral problems, adverse neuro cognitive, metabolic, cardio vascular effects and impairment of growth. Pediatric OSA is a difficult entity to diagnose based on clinical presentation alone. Polysomnography, which is the gold standard investigation for OSA in children, helps in confirmation of diagnosis and grading the severity. Multidisciplinary input is required for the diagnosis and treatment of pediatric OSA, with the involvement of pediatricians, ENT surgeons, speech therapists, cardiologists and geneticists. Early diagnosis and intervention help improve the quality of life of these children.

All children seen in the pediatric outpatient services should be evaluated with a sleep history as a part of their routine evaluation. The most common presenting symptoms of OSA in children include snoring, mouth breathing, daytime sleepiness, poor school performance, behavioral disturbances, hyperactivity, inattentiveness, difficulty paying attention or difficulty concentrating and nocturnal enuresis. Children with OSA also have frequent night time awakenings and occasionally parents also observe cessation of breathing followed by audible gasps while their children are asleep. Parents also report abnormal postures during sleep including extension of the neck, which is a posture assumed in order to attempt to keep the upper airway open. High-risk population groups for OSA include children with craniofacial syndromes such as Pierre Robin sequence, Trisomy 21, neuromuscular disorders and obesity. Co-morbidities like allergic rhinitis and asthma have an association with OSA.

Clinical signs include examination of the nose for hypertrophy of turbinate and nasal polyps and examination of the oral cavity for the presence and grading of enlarged tonsils. Enlarged adenoids can lead to fluid in both middle ear cavities and hence otoscopy and assessment of hearing become important. In addition to looking for adenoid facies or midfacial hypoplasia, it is important to auscultate the heart to look for signs of pulmonary hypertension, which is a consequence of severe untreated OSA. Untreated OSA can also lead to systemic hypertension and hence measurement of blood pressure is essential. Facial dysmorphism and craniofacial anatomy must be evaluated and growth including body mass index (BMI) should be formally plotted on an appropriate growth chart.

Good quality sleep is essential for children to grow, and impaired sleep can lead to school absenteeism, poor daytime functioning, mood disorders, impaired growth and development, poor cardiovascular health and metabolic syndrome. Not all children with snoring need evaluation for OSA, since 3-15% of all children may have primary snoring. Although some children with OSA present with classical symptoms and signs, it is often a condition that

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presents with no specific symptoms. History and clinical examination have been reported to have positive predictive value for diagnosis of OSA of 65% and 46% respectively.[2] Hence it becomes important to have a high degree of clinical suspicion, especially in children with underlying syndromes and have a low threshold to perform relevant investigations to confirm the diagnosis of OSA.

Pediatric sleep questionnaires are useful tools for screening children with suspected OSA. The Obstructive Sleep Apnoea-18 (OSA-18), the Pediatric Sleep Questionnaire (PSQ) and the Children's Sleep Habits Questionnaire (CSHQ) are a few available questionnaires and these exhibit varying degrees of performance. In a systematic review conducted by Incerti Parenti, et al[3], Sleep related breathing disorders-PSQ (SRBD-PSQ) proved to be the most sensitive questionnaire with the most robust characteristics. Questionnaires have a good sensitivity for detecting symptoms of mild OSA in children.[4] Additionally, certain questionnaires, for instance the PSQ could be considered in combination with another modality such as pulse oximetry as an early detection tool for diagnosis of OSA in children. The Pediatric Sleep Questionnaire developed by Chervin, et al is the most commonly used questionnaire, with its short version of 22 questions available in several languages.[5]

Investigations

Investigations to confirm diagnosis of pediatric OSA can be classified into three groups

1) **Investigations for confirmation of diagnosis:** Polysomnography(PSG) is the gold standard for diagnosis of pediatric OSA. It is also known as level 1 sleep study. Other tests such as overnight oximetry and cardiorespiratory sleep study (CRSS) are useful in situations where PSG is unavailable.
2) **Investigations for upper airway evaluation:** This includes X-ray nasopharynx, nasal endoscopy, computerized tomography (CT) and magnetic resonance imaging (MRI) of the upper airway. Newer modalities such as drug induced sleep endoscopy (DISE) may be used in certain special situations.
3) **Newer modalities:** This include Watch-PAT(Watch Peripheral Arterial Tonometry) and biomarkers for OSA

1) Investigations for confirmation of diagnosis

a) Overnight pulse oximetry

Overnight pulse oximetry measures a change in oxygen saturation as a surrogate marker for an obstructive event (Fig.1). The test is simple and easily available; however, it does not measure airflow. It is important to use the right type of oximeter with recommended averaging time of 2-3 seconds. While overnight oximetry has a high specificity of about 98%, it has a sensitivity of only 43%. On comparing overnight oximetry with PSG, oximetry showed sensitivity of 60% and specificity of 67% in detection of moderate OSA.[6-8]

However, there are a few practical issues. The averaging time of the pulse oximeter should be less than 3 seconds to obtain accurate data. Movement artifacts with the pediatric oximeter probe are common. Oximetry provides limited information as children with severe OSA may have disturbed sleep and an arousal with minimal dip in saturation. Therefore, overall oximetry alone is inadequate for diagnosis but is useful for screening patients and triaging. Advantages are that the test is of low cost, can be done at home and has good positive predictive value (97%).

The McGill oximetry scoring system, which is the most common scoring system used for oximetry was developed by Nixon, et al.[9] It is based on the number of drops in arterial oxygen percent saturation (SaO2) and the number of clusters of desaturation events, with scores ranging from 1 to 4. A score of 1 indicates a either normal or inconclusive for OSA, a score of 2 designates mild OSA, 3 indicates moderate OSA and 4 is severe OSA.

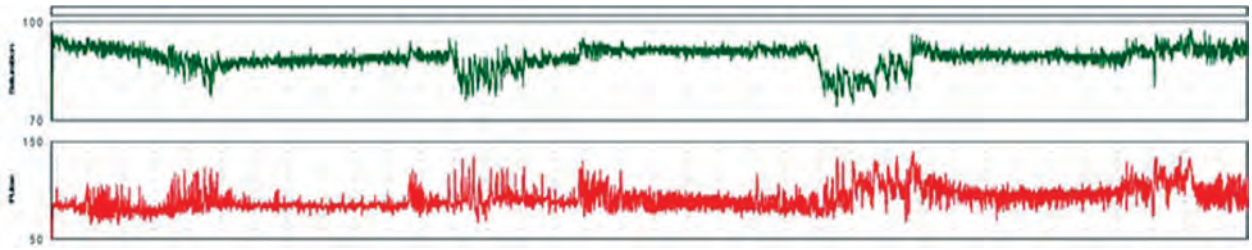

Fig.1. Overnight oximetry with oxygen saturation in green and heart rate in red

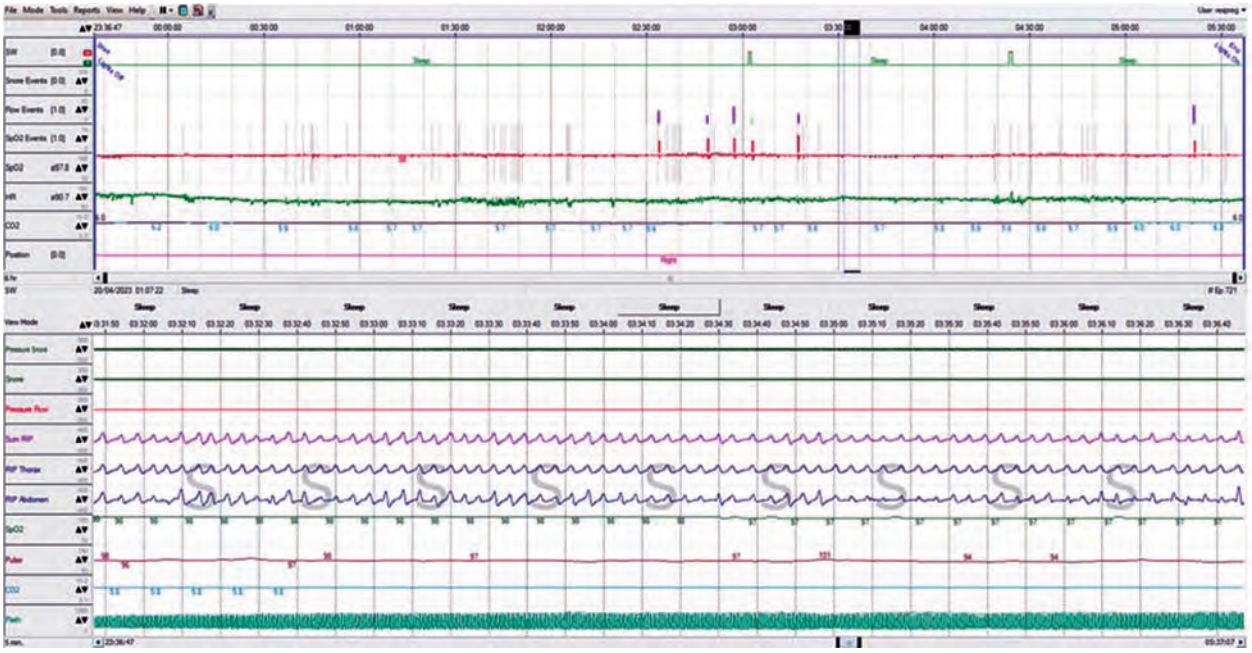

Fig.2. Cardiorespiratory sleep study with channels

Wu, et al.[4], in their meta-analysis, showed that pulse oximetry had a high specificity for screening children without mild OSA. They determined that the combined use of the PSQ with pulse oximetry can detect OSA in children, but is only to be used if PSG is not available.

b) Cardiorespiratory sleep study

A cardiorespiratory sleep study(CRSS) incorporates limited channels for assessment of sleep, and can be performed either in hospital or at home (Fig.2). Equipment consists of a video camera, chest and abdomen bands for respiratory effort using plethysmography, airflow measurement via thermistors or nasal cannula, measurement of heart rate, oxygen saturation and transcutaneous carbon dioxide.

The advantages of a CRSS is that it provides adequate data for detection of apnea, helps in differentiating central and obstructive apneas and helps quantifying the degree of hypoxia. It can also be done at home. The disadvantages are that since it does not have an electroencephalograph (EEG), it cannot pickup seizures or arousals and the absence of EEG and electromyograph (EMG) make sleep staging difficult. Hence it is not an ideal test.

c) Polysomnography

A level 1 polysomnography is the internationally recognized gold standard test for diagnosis of OSA. The test should be supervised by personnel and performed in a dedicated pediatric sleep lab. The test is performed preferably at night, since night time sleep includes REM sleep, usually in the second half of the night. REM sleep is when muscle tone drops and OSA becomes prominent. An ideal polysomnography contains at least six hours of good quality sleep recording. Polysomnography may also be used for titration of ventilator settings following treatment of OSA.

PSG records the duration and quality of sleep, documents episodes of apnea and hypopnea, arousals and measures oxygenation. It includes the following channels- electroencephalography (EEG), electromyography(EMG), electrooculography (EOG), oxygen saturation (SpO_2), heart rate, electrocardiography (ECG), measurement of respiratory effort by abdomen and thoracic bands (plethysmography), measurement of airflow via nasal cannula or thermistor, video camera, microphone and end tidal carbon dioxide (ETCO2). From the parameters recorded, a respiratory disturbance index (RDI), apnea hypopnea index (AHI) and degree of hypoventilation are derived (Table I).

Definitions of apnea and hypopnea

As per the American Academy of Sleep Medicine (AASM)[10] manual for scoring of sleep and related events, obstructive events have a reduction in airflow, as measured by the nasal cannula or thermistor, but with sustained respiratory efforts, as measured by respiratory and

Table I. Levels of pediatric sleep studies and channels used

Level of study	Name	Channels used
Level 1	Polysomnography	Electroencephalography (EEG) Electromyography (EMG), Electrooculography (EOG), Oxygen saturation (SpO_2), Heart rate, Electrocardiography (ECG), Abdomen and thoracic bands (plethysmography), Measurement of airflow via nasal cannula or thermistor, Video camera, Microphone End tidal carbon dioxide ($ETCO_2$)
Level 2	Cardio-respiratory sleep study	Video camera, Chest and abdomen bands for respiratory effort using Plethysmography, Airflow measurement via thermistors or nasal cannula, Measurement of heart rate, oxygen saturation, transcutaneous carbon dioxide
Level 3	Overnight pulse oximetry	Oxygen saturation Heart rate

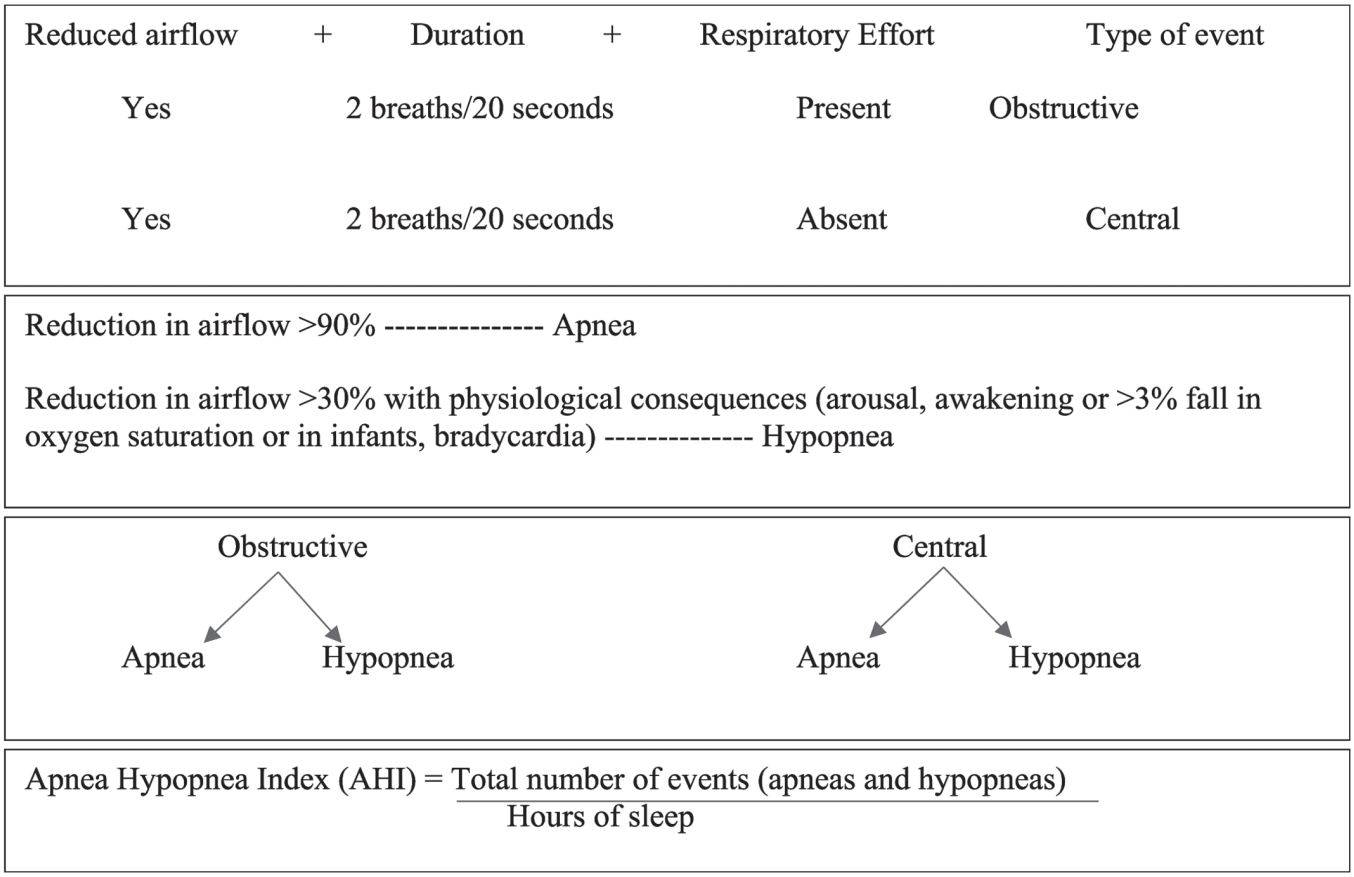

Fig.3. Apnea hypopnea index (AHI)

Table II. Severity of OSA based on AHI

Severity of OSA	AHI
Mild OSA	1-4
Moderate OSA	5-9
Severe OSA	≥ 10

Box.1 Challenges faced while performing pediatric PSG

- Limited availability
- High costs
- Personnel dependent
- Time consuming
- Need for specialized equipment
- Long waiting lists
- Night to night variability
- New sleeping environment for child- inaccurate representation of events at night

abdominal bands, indicating an obstruction at the level of the upper airway. A central event, on the other hand, has a reduction or cessation of airflow, with the absence of respiratory efforts.

An apnea is usually defined as a >90% reduction in airflow while a hypopnea is given by >30% reduction in airflow. Both obstructive apneas and hypopneas should last for a duration of at least 2 breaths or 20 seconds).

An obstructive apnea in children is scored if a respiratory event is associated with an absence (or >90% reduction) of airflow that lasts for 2 or more missed breaths and is associated with maintained (or increased) inspiratory effort.

Anobstructive hypopnea is described as having a >30% reduction in airflow signal and also lasts for 2 or more missed breaths with preservation of respiratory effort. An obstructive hypopnea needs to be associated with aphysiological consequence, namely an arousal, an awakening or a >3% fall in oxygen saturations (SpO_2) in order to be scored.

A central apnea is an event associated with absent inspiratory effort and an absence (or >90% reduction) of airflow lasting for > 20 seconds duration or lasting for >2 missed breaths and associated with a physiological consequence (arousal, awakening, a >3% fall in SpO_2 or in infants, bradycardia).

A central hypopnea is scored when a 30% reduction in airflow associated with concurrent reduction in inspiratory effort lasting >2 missed breaths occurs in association with a physiological consequence.

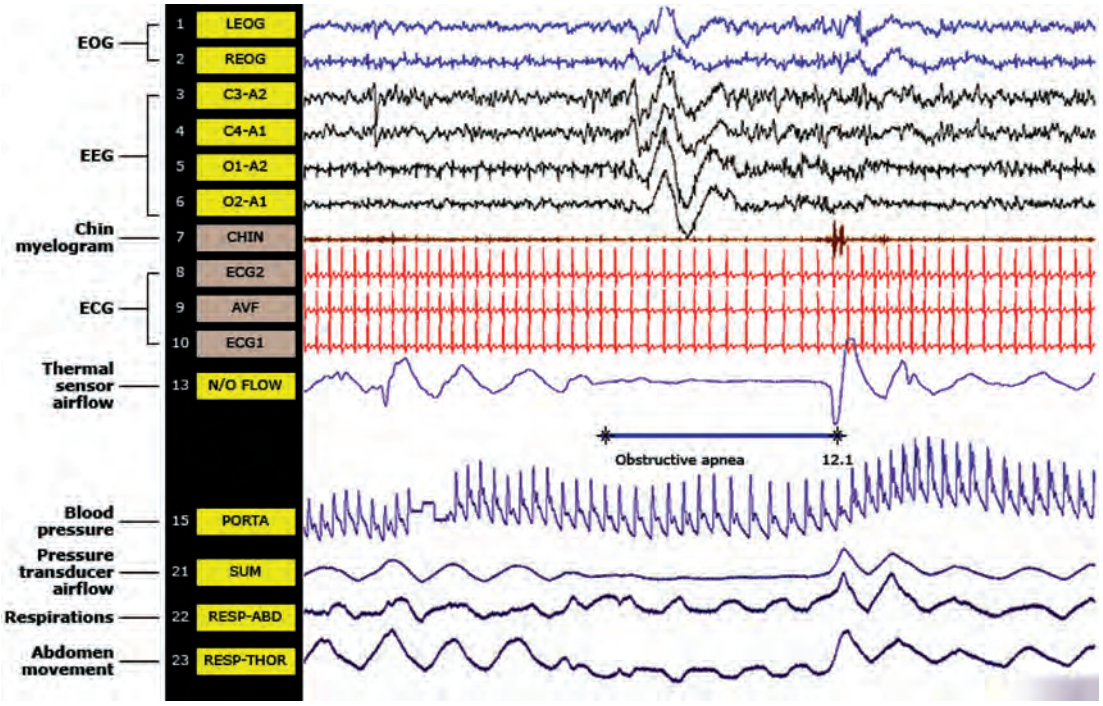

Fig.4. Polysomnography with channels

The Apnea-Hypopnea index (AHI) is the number of obstructive and mixed apneas and hypopneas per hour of total sleep time. The AHI is used to identify the presence of OSA and determine the severity of OSA. Based on the AHI, the severity of pediatric OSA can be determined (Fig.3. & Fig.4).

Three degrees of OSA severity are identified according to the AHI (Table II).

There are several challenges to performing a PSG, as listed in Box 1.

c) i. Single channel recordings

Few of the PSG parameters have been studied in isolation and evaluated based upon their potential as a single channel recording for pediatric OSA.[11] These include overnight ECG measuring heart rate variability, overnight oximetry (discussed above), detection of body position using actigraphy and assessment of respiratory events using nasal cannula. All have limited ability to detect OSA on their own, but when used in combination with other testing, have shown promise. Further studies are needed.

Similarly, Thomas RJ, et al recently developed and tested a scoring system for sleep videos taken at home by caregivers during episodes of abnormal breathing. The authors found that low scores ruled out moderate-severe OSA, while higher scores showed a sensitivity and negative predictive value of 100%, for moderate to severe OSA. They concluded that this newly validated clinical scoring system is valuable in triaging children with sleep related breathing disorders.[12]

c) ii. Home based PSG

Post the COVID 19 pandemic era, home based sleep apnea testing has become a popular method of testing. Some of the advantages of home-based testing include lower cost, better resource utilization and increased comfort. In a systematic review and meta-analysis performed in 2021[13] home testing showed good sensitivity and specificity, indicating that it may be used as a screening method for OSA provided it is used appropriately. Patient selection for home-based studies is crucial. Withers at al compared level 1 hospital-based PSG with level 2 home-based PSG in children aged 5 to 16 years and found excellent correlation, with better sleep efficiency in the home-based study.[14] Similar results were obtained by Ioan, et al[15], who suggested that unattended home PSG can be used for screening of OSA in otherwise healthy children when installed correctly.

2. Investigations for evaluation of upper airway

Adeno-tonsillar hypertrophy is the commonest reason for anatomic obstruction of the upper airway in children. This usually occurs between the ages of 3 years and 8 years and the size of the adeno-tonsillar tissue in relation to the upper airway is largest then. However, it is known that the size of the adeno tonsillar tissue alone does not correlate with the severity of OSA. Instead, the size of the adeno tonsillar tissue relative to the size of the upper airway is what is relevant.

a) Lateral X-ray nasopharynx is a readily available, inexpensive, fast tool with minimal radiation exposure. However, its role is limited as it has poor tissue visualization and is a 2-dimensional imaging technique.[16] In addition, interpretation of the radiograph is dependent on the position of the neck of the child and is subject to inter observer variability.

b) CT scans allow for 3-dimensional visualization of the upper airway and are fast and quite easily available, however sedation for smaller children, high radiation exposure continue to remain problematic.

c) MRI scans allow for 3-dimensional visualization with lesser radiation exposure when compared to CT scans. However, they come with disadvantages such as requirement of sedation, longer scan times, cost implications and unavailability. Cine-MRIs are useful in patients with residual OSA after adenotonsillectomy to identify the site of obstruction. Recent studies done have shown the utility of cine-MRI in patients with persistent OSA after adenotonsillectomy and failed initiation of positive airway pressure therapy by helping identify the site of residual obstruction.[17]

d) Nasal endoscopy with flexible scope allows for evaluation of the patency of nasal cavities in addition to assessment of enlarged adenoids. It helps assessing dynamic airway obstruction, in addition to precisely identifying the level of obstruction. It is a simple, easily available, reliable, quick test but requires a reasonable level of cooperation from the child and can therefore be challenging to perform in younger children.

e) Drug induced sleep endoscopy(DISE) in performed in selected children, usually in the presence of residual OSA after adenotonsillectomy. The drugs commonly used are propofol, midazolam and dexmedetomidine. This involves the placement of an endoscope on different levels of the upper airway via the nose and direct visualization of the site of obstruction. In a study by

Gazzaz, et al[18] to examine if DISE alters surgical management in patients with OSA, it was found that 35% had changes made to their surgical plan secondary to findings on DISE. It is plausible that by using DISE patient's surgical treatment plan may be individualized and DISE may be used to prevent unsuccessful surgeries. The major disadvantage of DISE is that since the patient is sedated, the visualized upper airway dynamics may not truly be representative of those during natural sleep. In addition, it is expensive and not easily available. Additionally, introduction of an instrument into the airway affects resistance and pressures in the airway and has potential to alter the site of obstruction.[19]

3. Newer modalities.

a) **Watch-PAT** (Watch Peripheral Arterial Tonometry): May be performed when PSG is unavailable. It is a portable wrist worn device that uses actigraphy to differentiate between sleep and wake stages.[20] It has a signal probe that measures the arterial volume change in the fingertip. It is believed that episodes of apnea and hypopnea induce awakenings and cause activation of the sympathetic nervous system, leading to vasoconstriction which is detected by the probe. The device is simple and can measure certain parameters but data on pediatric OSA are limited. Pediatric specific probes have not been developed yet and accessibility continues to remain a problem.

b) **Biomarkers for OSA**: Since untreated OSA has a significant impact on long term health, certain biomarkers have been evaluated as adjuncts for diagnosis of OSA. Pre-operative cardiac evaluation has been considered, since untreated long standing OSA can lead to altered left ventricular function and right heart failure from pulmonary hypertension.[21] OSA is believed to lead to systemic inflammation and the role of measuring CRP, both to predict development of cardiovascular disease and for identification of residual OSA has been studied.[22,23] However, its use is limited due to several other confounding factors that can lead to elevation of CRP.

Salivary and urinary biomarkers have been tested for diagnosis and prediction of severity of OSA in children, however further data are needed to better evaluate these.[24,25]

Challenges in evaluation of pediatric OSA

History and examination alone are insufficient for establishment of diagnosis of pediatric OSA. Inaccessibility to PSG is the biggest challenge. Other issues are the cost implications of the test and availability of qualified sleep technicians who can monitor the overnight test. Lack of awareness amongst both patients and doctors about pediatric OSA contributes to the problem. Long wait times for PSG due to limited resources and lack of trained personnel to interpret the test are other barriers.

Points to Remember

- ***A good sleep history is part of pediatric history taking in the outpatient department.***
- ***Children with craniofacial syndromes such as Pierre Robin sequence, Trisomy 21, neuromuscular disorders and obesity are at high risk for developing OSA.***
- ***Polysomnography or level 1 sleep study is the gold standard investigation for the diagnosis of pediatric OSA.***
- ***Untreated OSA can have adverse neurobehavioral, cognitive, metabolic and cardiovascular effects.***
- ***Salivary and urinary biomarkers have been evaluated for diagnosis but still further data are needed for better evaluation.***
- ***Multidisciplinary approach is the key to optima*l management of *OSA*.**

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CLIPPINGS

Human milk oligosaccharides as prebiotics

Human milk oligosaccharides (HMOs) are unique, bioactive carbohydrates identified to be one of the most significant components of breast milk with structural complexity and promote development of the neonatal intestinal immune and nervous systems. This article describes the history, complex structure and different functions of HMOs highlighting the importance of maternal diet for HMO biosynthesis.

Okburan G, Kiziler S. Human milk oligosaccharides as prebiotics. Pediatr Neonatol. 2023 May; 64(3): 231-238. doi: 10.1016/j.pedneo.2022.09.017. Epub 2023 Jan 2. PMID: 36642576.

PULMONOLOGY

OXYGEN THERAPY

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Abstract: *Oxygen therapy is inherent part of pediatric critical care, with supplemental oxygen offered to nearly every acutely ill child. However, there are potential risks related to the administration of oxygen and therefore only the lowest amount of oxygen should be given for the shortest period of time to maintain required oxygen saturation. Observational data suggest harm from too generous use of supplemental oxygen in children.Oxygen therapy is useful in treating hypoxemia but is often thought of as harmless. Risk, cost and benefits of oxygen therapy should be considered in the same way as other drugs. This review highlights the benefits ,various oxygen delivery devices with indications and potential risk of oxygen administration.*

Keywords: *Oxygen delivery, Oxygen therapy, Oxygen review, Gas therapy.*

Oxygen is usually the first drug used in the care of a very sick child and though considered harmless, has its own risk if used inappropriately.[1] Oxygenation is defined as the mechanism of diffusion of oxygen from alveolar lining into the pulmonary vasculature. Oxygen delivery is the amount of oxygen and its rate of transfer from the lungs to the tissues.Oxygen consumption is the rate of utilisation of oxygen by the tissues and its rate of extraction from the blood.[2] Oxygen released to the peripheral tissues from the lungs, depends on the content of oxygen in blood and ventricular output. Mathematically, this is expressed as: $DO_2=CaO_2\times Q_T$, where DO_2 is oxygen delivery, CaO_2 is blood O_2 content, and Q_T is cardiac output.[3]

Hypoxemia is defined as PaO_2 (partial pressure of oxygen in arterial blood) of less than 80 mm Hg. Since a PaO_2 of 60 and 80 corresponds respectively with a non-invasive oxygen saturation (SpO_2) of 90% and 95%, respectively (Fig.1), in the patient with a normal pH, PCO_2, temperature and diphosphoglycerate, oximetry is often used to help identify hypoxemia non-invasively. Hypoxia is reduced oxygenation at the tissues due to impaired delivery of oxygen to the tissues or defective utilization of oxygen by the tissues. Clinically hypoxia is accepted as oxygen saturation of arterial blood less than 90%, on breathing air at sea level which corresponds to partial pressure of oxygen PaO_2 less than 60mm Hg. Hypoxemia and hypoxia need not coexist. There may not be hypoxia in spite of hypoxemia due to compensatory measures such as increased hemoglobin level and cardiac output. The goal of oxygen delivery is to achieve adequate oxygenation through the provision of supplemental oxygen in a safe and effective way which is tolerated by infants and children. Adequate oxygenation in the simplest terms is the balance between oxygen delivery to the tissues and their rate of oxygen consumption which in turn allows the cells to produce energy normally. If adequate oxygen delivery is not provided, anaerobic metabolism and cell death occurs.[4]

Oxygen is necessary for adequate metabolism of carbohydrates and the production of adenosine triphosphates. Thus, hypoxia may produce complications, such as vasodilation, pulmonary vasoconstriction, lactic acidosis and metabolic acidosis.

Physiological homeostasis requires that oxygen delivery meet the demands of tissue oxygen consumption. Oxygen delivery is the product of cardiac output and blood oxygen content, which depends on hemoglobin concentration and hemoglobin-oxygen saturation (SaO_2). Hypoxia can be caused by inadequate transfer of oxygen across the lungs (hypoxemic hypoxia), decreased arterial oxygen content (anemic hypoxia), inadequate blood flow (ischemic hypoxia) or abnormal cellular oxygen utilization (cytotoxic hypoxia).[5]

The goals of providing oxygen therapy are to:

- Relieve hypoxemia and maintain adequate oxygenation of tissues and vital organs, as assessed by SpO_2 /SaO2 monitoring and clinical signs.

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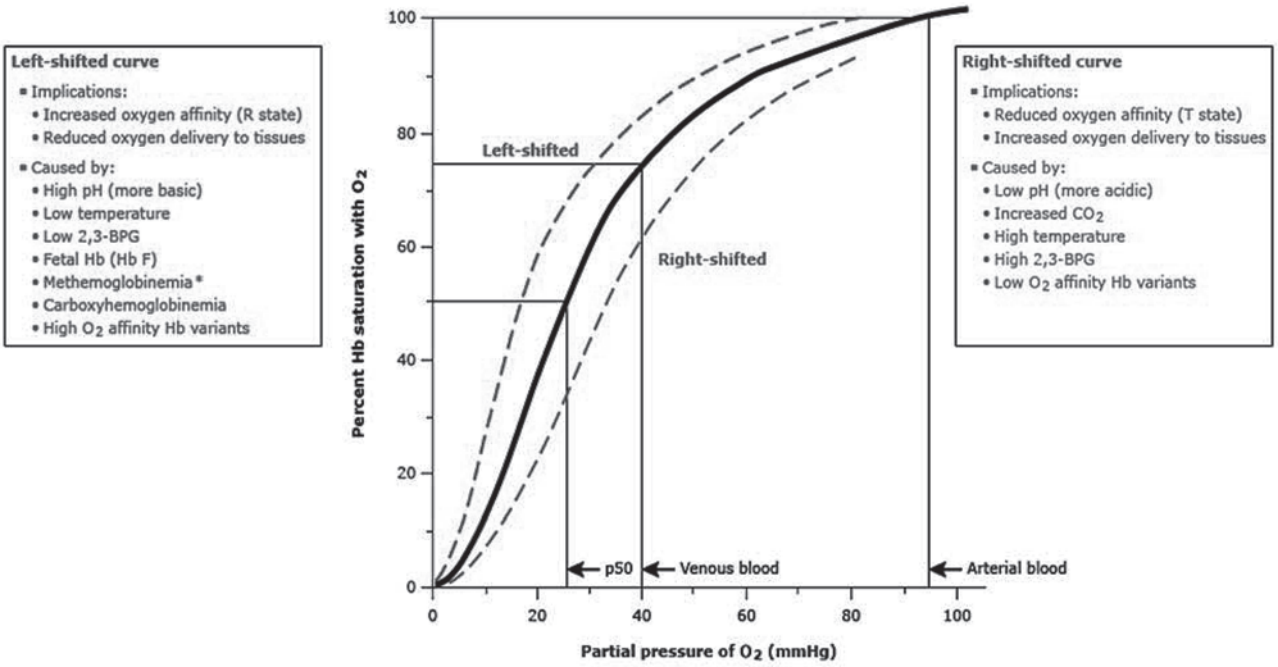

Fig.1. Oxygen dissociation curve

- Give oxygen therapy in a way which prevents excessive CO2 accumulation - i.e. selection of the appropriate flow rate and delivery device.
- Reduce the work of breathing.
- Ensure adequate clearance of secretions and limit the adverse events of hypothermia and insensible water loss by use of optimal humidification (dependent on mode of oxygen delivery).
- Maintain efficient and economical use of oxygen.

Oxygen therapy should be commenced in the treatment of an acute or emergency if,

- Hypoxemia or hypoxia is suspected, and the child is in respiratory distress as manifested by
  - dyspnea, tachypnea, bradypnea, apnea
  - pallor, cyanosis
  - lethargy or restlessness
  - use of accessory muscles: nasal flaring, intercostal or sternal recession, tracheal tug
- SpO_2 is less than 92% (PaO_2 less than 80mmHg in patients without cyanotic heart disease
- SpO_2 is less than 70% (PaO_2 less than 37mmHg) in patients with cyanotic heart disease who have had cardiac surgery
- SpO_2 is less than 60% (PaO_2 less than 32mmHg) in patients with cyanotic heart disease who are waiting for cardiac surgery.[6]

Monitoring of oxygen therapy

The most important monitoring is the clinical condition of the child along with other parameters such as pulse oximetry, blood gas analysis and continuous monitoring of vital parameters. The most commonly used monitoring strategy is to use pulse oximetry to monitor SpO_2. Blood gas analysis to assess PaO_2, is not used very frequently and usually used in critically ill children requiring high oxygen supplementation and generally the use is restricted to intensive care units. Monitoring usually focuses on the following

a. respiratory rate (to identify tachypnea, bradypnea or apnea)
b. work of breathing (nasal flaring, retractions)
c. breath sounds (abnormal or diminished)
d. mental status (irritability, anxiety, altered mental status)
e. oxygen saturation or blood gas analysis
f. heart rate (tachycardia and bradycardia or any arrhythmias)
g. blood pressure
h. skin colour (pallor or cyanosis)

The frequency with which we monitor these parameters will depend of the criticality of the illness and amount of supplemental oxygen required.

Oxygen toxicity

High concentrations of oxygen given to a child over a prolonged period of time can be detrimental to the body. High FiO_2 damages the capillary endothelium leading on to the interstitial edema. This in turn leads to decrease in the compliance of the lungs which worsens, the work of breathing and hypoxemia by virtue of the low ventilation perfusion ratio.Inappropriate oxygen use in patients at risk of type 2 respiratory failure (when the respiratory system cannot adequately remove carbon dioxide from the body, due to respiratory pump failure) can result in life-threatening hypercapnia, respiratory acidosis, organ dysfunction, coma and death.[7]

Administration of oxygen with FiO_2 in excess of 50 %, decreases the nitrogen content in the inspired air. Nitrogen is a non-absorbable gas and helps to keep alveoli patent, hence high oxygen administration decreases nitrogen levels, reducing the total pressure of gases, leading to collapse and atelectasis of alveoli known as de-nitrogenation atelectasis. This risk of absorption atelectasis maximises in children breathing at low tidal volumes.[8]

Oxidative stress

Oxidative stress has been defined as generation of or increase in pro-oxidant forces in the body. These include oxygen radicals or reactive oxygen species (ROS). Increase in these elements leads to cytotoxicity, oxidative injury, necrosis, or apoptosis. The body has many antioxidant systems to nullify this oxidative stress such as superoxide dismutase, catalase and glutathione, but these get blunted with usage of FiO_2 in excess of 50%.

Oxygenation targets

Normoxia, which is the target for therapy, is usually defined as the SpO_2 of 94% or higher. However,the World Health Organization recommends permissive hypoxemia of an oxygen saturation of 90% for children with lower respiratory tract infections such as bronchiolitis. Maintaining SpO_2 above 90% corresponds to the safe section of the oxygen-hemoglobin dissociation curve and in the absence of co-morbid derangements in oxygen will ensure adequate cerebral oxygenation and avoid hypoxia or hyperoxia.[9]

Permissive hypoxemia

Permissive hypoxaemia describes a concept in which a lower level of arterial oxygenation (PaO_2) than usual is accepted to avoid the detrimental effects of high fractional inspired oxygen and invasive mechanical ventilation. This is achieved by maintaining a level of oxygen delivery that is adequate to avoid tissue hypoxia while minimizing the detrimental effects. A potential strategy for the management of such patients involves goal-oriented manipulation of cardiac output and if necessary, hemoglobin concentration, to compensate for hypoxemia and maintain a normal (but not supranormal) value of oxygen delivery.[10]

Principles of oxygen therapy

a. Dyspnea can occur for many reasons other than cardiorespiratory disease, including metabolic acidosis, anxiety, pain and treatment with oxygen is not indicated in these cases.

b. Transient, self-correcting desaturations that have no other physiological correlates (e.g. tachycardia, cyanosis) may not routinely require oxygen therapy in most cases.

c. Monitoring of the patient, at the least with pulse oximetry is desirable whenever the child is on oxygen therapy. Frequency of monitoring will depend upon the underlying disease condition and amount of oxygen administered. Limitation of pulse oximetry should also be taken into account in conditions such as carbon mono-oxide poisoning.

d. All patients with severe hypoxemia (including arrest and peri-arrest situations), acute breathlessness, severe sepsis and any other critical illness should be given high- concentration supplemental oxygen in the initial stages of the resuscitation process. Once the patient is stable, formal assessment of the need for oxygen should be made, guided by pulse oximetry plus arterial blood gas (ABG) analyses, if required.

e. Arterial blood gas analysis is not mandatory for monitoring a child on oxygen therapy, although there are few indications:[11]

   i. child with desaturation (SpO_2 < 92%)

   ii. child with hemodynamic compromise or on life support systems

   iii. child with associated hypercapnia

   iv. severe compromised circulation where pulse oximetry is not reliable.

   v. dyspneic patients who are at risk of metabolic acidosis

f. Oxygen is a drug and the indication, amount to be administered (avoiding both hypoxemia and hyperoxemia), duration and target of oxygen saturation depending upon the underlying disease condition should be clearly determined and documented.

g. Apart from administration of oxygen, management also comprises of optimizing hemodynamics, cardiac output and any specific therapy against the process which prevents the off-loading of oxygen at tissue level (like poisoning etc).

Oxygen delivery

The administration of oxygen to children requires the selection of an oxygen delivery system that suits the child's age, size, needs, clinical condition and therapeutic goals. Oxygen delivery systems should also be chosen keeping in mind the acceptability of the device. Younger children, who do not require too high oxygen fraction, may not tolerate the tight fitting mask or the devices which covers the entire face.[12]

Oxygen delivery systems are categorized as low-flow (variable performance) systems or high-flow (fixed performance) systems.

Low flow delivery devices: These delivery systems provide oxygen flow (flow less than 10 L /min) less than child's inspiratory flow rate with variable FiO_2 concentration (22% to 60%). They are more useful in children who are stable, but require low FiO_2.

High flow delivery devices: High flow systems are specific devices that deliver the patient's entire ventilatory demand, meeting, or exceeding the patients peak inspiratory flow rate (PIFR), thereby providing an accurate FiO_2.

These delivery systems provide oxygen flow (flow more than 10 L,/min) higher than child's inspiratory flow rate with FiO2 concentration >60%.

A. Blow by oxygen: It is the simplest, least cumbersome form of oxygen devices; it is also barely reliable for delivering a specific amount of FiO_2. It usually is delivered via a large bore oxygen tubing with a simple face mask kept at a distance from face. It delivers FiO_2 of 0.3-0.4 at 10L/min.

B. Oxygen hood : It is a plastic enclosure that surrounds the head of a neonate or a child to which continuous flow of humidified oxygen is supplied via air blender. Fixed concentration of 22-80% is supplied at 7-10L/minute. Minimum gas flow ensures the exhaled $C0_2$ is flushed out and not rebreathed. It can deliver an FiO_2 of less than 0.5 and can be used for patients requiring FiO_2 of <0.5.

C. Low-flow nasal cannula: Low-flow nasal cannula remains one of the most common and widely used oxygen delivery devices. It delivers a fractional concentration of oxygen to the patient through two soft prongs that snuggly fit into child's anterior nares. It allows continued oxygen therapy during feeding/ eating and re-breathing of CO_2 is not a potential complication. For infants and toddlers who may poorly tolerate a mask, nasal prongs may be a good alternative. The child inspires room air in addition to the supplemental oxygen, and a variable concentration of oxygen is delivered. A nasal cannula can deliver 22% to 60% oxygen with appropriate oxygen flow rates of 0.5 to 2 L/minute. Simple nasal prongs are available in different sizes. To ensure the patient is able to entrain room air around the nasal prongs and a complete seal is not created, the prong size should be approximately half the diameter of the nares.For nasal prong oxygen without humidification, a maximum flow of

2 L/minute in infants/children < 2 years of age

4 L/minute for children > 2 years of age.

1 L/minute for neonates, is recommended.

With the above flow rates, humidification is not usually required.

D. Oxygen mask: A **simple face mask** is a low-flow oxygen device. It can deliver 35% to 60% oxygen with an appropriate flow rate of 6 to 10 L/minute. A minimum of 6 L/minute of oxygen flow is needed to prevent rebreathing of exhaled carbon dioxide.

E. Partial rebreathing mask with a reservoir bag: It is a face mask that delivers moderate to high concentrations of oxygen. The reservoir bag has to remain inflated, or else exhaled air collects in it, which results in the child rebreathing large amounts of exhaled carbon dioxide. Side port openings on the mask vent exhaled air on expiration and allow room air to enter on inspiration. The delivered oxygen percentage varies, depending on the rate and depth of the child's breathing.

F. Venturi mask is a cone-shaped device with entrainment ports of various sizes at its base. The entrainment ports adjust to deliver various oxygen concentrations. The advantage of venturi mask is that it delivers a more precise concentration of oxygen to the child, such as 0.24, 0.28, 0.31, 0.35, 0.4 or 0.6 depending on the mask chosen.

G. **Non-rebreathing mask with reservoir**: It is a high-flow oxygen delivery device used for children requiring a higher concentration of oxygen. A non-rebreathing mask (NRM) can deliver a concentration of up to 95% oxygen with an oxygen flow rate of 10 to 15 L/minute.

H. **High-flow nasal cannula (HFNC):** It is a form of oxygen therapy used to treat hypoxemic respiratory failure. This type of oxygen delivery device is composed of traditional nasal cannula style prongs that rest in the patient's anterior nares and allows heated, humidified oxygen to be delivered at flows of 2-8 L/min for neonates and 4-10 L/min for children, whereas an air-oxygen blender allows FiO_2 to be directly manipulated. As higher flows are reached, set oxygen flows exceed demand, thus preventing the entrainment of room air, while it flushes the dead space and results in the delivery of higher, more precise fractional inspired oxygen concentrations. Improvements in oxygenation associated with HFNC may also be related to the creation of PEEP (Positive end expiratory pressure) for a given flow.[13]

I. **Continuous positive airway pressure (CPAP)**: This consists of delivery of mild air pressure which keeps the airways open. CPAP delivers PEEP. It delivers variable amount of oxygen to the airway of spontaneously breathing patient to maintain lung volume during expiration. CPAP decreases atelectasis and also reduces respiratory fatigue along with improvement of oxygenation.

J. **Mechanical ventilation:** It is used to treat moderate to severe hypoxia . This can take up the entire work of breathing and the PEEP, PIP (Peak inspiratory pressure), tidal volume, respiratory rate, inspiratory or expiratory time can be adjusted to restore normoxia.

Humidification

Oxygen which is usually delivered through the oxygen manifold is usually cold and dry, which has a drying effect on mucous membranes, resulting in airway damage.

This can cause the secretions to become thick and difficult to clear or cause airway obstruction.

Oxygen therapy with usually high flow systems require humidification. The type of humidification device selected will depend on the oxygen delivery system in use, and the patient's requirements. The humidifier should always be placed at a level below the patient's head.[1]

Weaning oxygen

Unless clinically contraindicated, an attempt to wean oxygen therapy should be made as early as possible. The requisites for weaning off oxygen therapy are:

a. child should appear clinically well.

b. vital signs should be with normal limits

c. minimal or no respiratory distress

d. feeding adequate amounts orally.

e. normal level of consciousness

Oxygen therapy in the mainstay of treatment for any sick child and is often the first intervention to be started in emergency room and have saved many a lives. However, oxygen is a drug, hence, initiation, dosage, mode of administration, titration of dosage and end point to stop should be closely monitored to prevent inadequate or excessive use. Usage of oxygen without appropriate indication can prolong hospitalization and increase the cost of care. Oxygen administration should be coupled with the intervention to optimize oxygen content and cardiac output for ensuring effective management of hypoxemia and hypoxia. The other important aspect of oxygen therapy is the device selection depending on the age and the acceptability of the child and also the amount of oxygen to be administered.

Points to Remember

- ***Oxygen administration should be considered in the same way as other drugs and titrated to a measured end point to avoid excessive or inadequate dosing.***
- ***Both hypoxemia and hyperoxemia are harmful, oxygen treatment should be commenced or increased to avoid hypoxemia and should be reduced or ceased to avoid hyperoxemia.***
- ***For children receiving oxygen therapy, SpO_2 targets will vary according to the age of the child, clinical condition and trajectory of illness.***
- ***Oxygen treatment is usually not necessary unless the SpO_2 is less than 92%.***
- ***Device selection is vitally important in pediatric population as the size of the patients is highly variable, and their acceptance of a device is an additional consideration.***

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CLIPPINGS

Effectiveness of handwashing with soap for preventing acute respiratory infections in low-income and middle-income countries: a systematic review and meta-analysis

This study aimed to estimate the effect of interventions promoting handwashing with soap on ARI in low-income and middle-income countries (LMICs). In this systematic review and meta-analysis for studies of handwashing with soap interventions in LMICs from inception to May 25, 2021. Inclusion criteria were randomised and non-randomised controlled studies of interventions conducted in domestic, school, or childcare settings. Exclusion criteria were studies promoting hand hygiene methods other than handwashing with soap as well as interventions in health-care facilities or the workplace.

The primary outcome was acute respiratory infection (ARI) morbidity arising from any pathogen for participants of any age. Secondary outcomes were lower respiratory infection, upper respiratory infection, influenza confirmed by diagnostic test, COVID-19 confirmed by diagnostic test, and all-cause mortality.

26 studies with 161659 participants met inclusion criteria. Interventions promoting handwashing with soap reduced any ARI compared with no handwashing intervention (RR 0·83). Interventions also reduced lower respiratory infections (RR 0·78) and upper respiratory infections (0·74) but not test-confirmed influenza or all-cause mortality. They concluded that interventions promoting handwashing with soap can reduce ARI in LMICs, and could help to prevent the large burden of respiratory disease.

Ross I, Bick S, Ayieko P, Dreibelbis R, Wolf J, Freeman MC et al. Effectiveness of handwashing with soap for preventing acute respiratory infections in low-income and middle-income countries: a systematic review and meta-analysis. Lancet, 2023; 401(10389): 1681-1690.

PULMONOLOGY

ALLERGEN IMMUNOTHERAPY

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Abstract : *Allergen immunotherapy is a disease-modifying therapy, used in the treatment of many allergic conditions where gradually increasing doses of specific allergen extracts are administered to achieve clinical tolerance to the allergens which produce symptoms in patients. The major indications for allergen immunotherapy are allergic rhinitis, asthma, insect venom hypersensitivity and allergic conjunctivitis.There are different types of immunotherapy based on the route of administration and duration of therapy. It is highly imperative to use high quality standardised allergen extracts in adequate doses where possible.*

Keywords : *Allergen immunotherapy, Subcutaneous immunotherapy, Sublingual immunotherapy.*

The prevalence of allergic diseases is increasing rapidly all over the world in epidemic proportions.[1] Allergen avoidance and pharmacotherapy forms the mainstay of therapy. Though majority of the available drugs provide very good symptomatic relief, allergen immunotherapy is the only truly disease modifying treatment for allergic diseases which provides long term benefits.

Definition

It is a disease-modifying therapy, used in the treatment of conditions like allergic rhinitis and allergic asthma. Specific immunotherapy (SIT) is the administration of gradually increasing doses of allergen extracts to achieve clinical tolerance to the allergens which produce symptoms in patients with type I hypersensitivity.[2] This reduces the patient's adverse clinical response to subsequent natural exposure to those allergens. It also prevents new sensitization and prevents progression of the allergic disease.

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Mechanism of allergen immunotherapy[3,4]

Allergic diseases represent a unique response of our innate and adaptive immune systems to the environmental antigens. Allergy is mediated by dysregulated Th2 type of inflammation in contrast to infectious diseases which triggers Th1 type of inflammation. Aim of the immunotherapy is to restore tolerance to the allergen by reducing the tendency to induce allergen specific IgE production. The mechanism of immunotherapy is complex and not fully understood. It is mainly through induction of regulatory T-Cells which secrete Interleukin 10 (IL-10) and transforming growth factor beta (TGF- β). IL-10 blocks the production of allergen specific IgE from B cells and also simultaneously produce IgG 4 antibodies. Increase in IL-10 causes decrease in eosinophils, basophils and mast cells. Specific IgG4 prevents production of IL-4, IL-5 and IL-13. There will be a significant decrease in allergen specific IgE/IgG4 ratio. To simplify, allergen immunotherapy "trains" the immune system to produce the "desirable" IgG response in place of "undesirable" IgE response. (Th1 instead of Th2)

Indications of allergen immunotherapy (AIT)

1. **Allergic rhinitis**: The efficacy of immunotherapy in both seasonal and perennial allergic rhinitis is well established. AIT is recommended in moderate to severe cases of allergic rhinitis.[5]
2. **Bronchial asthma**: Immunotherapy has proven to be of benefit in asthma caused by house dust mites, and grass pollens. The global initiative for asthma (GINA) is now recommending allergen immunotherapy with house dust mites for age group 12 years and above for those patients sensitized to house dust mite allergen.[6]
3. **Venom hypersensitivity**: Effectiveness of immunotherapy for venom hypersensitivity is well established. Anaphylaxis to hymenoptera venom can be fatal. Hymenopterans, are winged insects, which include bees, fire ants, wasps and hornets. Anaphylaxis to hymenoptera venom is underreported in India
4. **Allergic conjunctivitis**: Cochrane systematic review has found some efficacy of immunotherapy in subjects with allergic rhino conjunctivitis with sublingual immunotherapy

5. **Atopic dermatitis**: Only anecdotal accounts of clinical improvement with the immunotherapy for atopic dermatitis is available.

Contraindications[2]

- Uncontrolled asthma (FEV_1 < 70%) in spite of adequate medical therapy
- Serious immunological diseases
- Patients receiving beta blockers (are at increased risk of systemic reactions)
- Malignant neoplasm
- Age< 3 years
- AIDS, serious immunodeficiency conditions

Types[7]

There are various types of immunotherapy, depending on the route of administration, which are given in Box 1.

Subcutaneous immunotherapy (SCIT)

SCIT is the most researched form of immunotherapy and its efficacy and safety are well documented by several scientific studies. There is no absolute lower age limit for SCIT. But considering the difficulty in recognizing a systemic reaction in young children, it is started usually above 5 years of age. The injection should only be taken at a medical facility with personnel trained in emergency treatment and the child is kept under observation for 30 minutes after each injection.

Sublingual immunotherapy (SLIT)

SLIT is administered as drops of high dose allergen solution or in the form of tablet which is kept sublingually and then swallowed later. It may be started as the full maintenance dose, without up-dosing phase and is continued daily for a period of 3-5 years. SLIT has the advantage of ease of administration, home based therapy and averting painful injections. Though SLIT is not as efficacious as SCIT, safety wise it is much superior.

Box 1. Types of immunotherapy

a. Subcutaneous (SCIT)
b. Sublingual (SLIT)
c. Epicutaneous (EPIT)
d. Oral (OIT)
e. Intranasal
f. Intra lymphatic

Phases of immunotherapy

Subcutaneous immunotherapy is given in two phases:

1. Up-dosing phase (Build-up phase)
2. Maintenance phase

Up-dosing phase: It consists of twice or once weekly injection for 3-4 months. To start with, lowest dose of highest dilution (1 in 100,000) is administered which is increased slowly till patient reaches tolerable dilution. (1 in 10)

Maintenance phase: It is given for a period of 3-5 years. Minimum 12 months of allergen specific immunotherapy is required before considering failure. If there is no response after one year, immunotherapy can be discontinued

Depending on the duration of therapy there are different types of subcutaneous immunotherapy:

a. **Conventional immunotherapy**: This involves administration of increasing dosages for 12 weeks followed by maintenance therapy for 2 to 5 years. Doses are given biweekly or weekly. Rate of systemic reaction is less and can be done on OP basis
b. **Cluster immunotherapy**:Here the build-up phase is shortened (about 6-8 weeks). It is comparable to conventional therapy at the same time reduces the time to start maintenance by almost half.
c. **Rush immunotherapy**: This type of therapy is done, when there is a need to complete the build up phase quickly which takes only 3- 4 days. But the rate of systemic side effects is much higher and this can be done only as an inpatient procedure.
d. **Ultra-rush immunotherapy**: Here the build-up phase takes only about 1-2 days sometimes with significant side effects. It is used if immediate protection is needed to prevent further anaphylactic reaction.

Allergen extracts

Clinically relevant allergens need to be selected from the various allergens included for testing. There are two types of allergen extracts - standardised and non-standardised. Standardised extract is the one where the total allergenic reactivity or the content of major allergen is known. This gives uniform potency to the extract among batches. High quality standardised allergen extract to be used wherever possible.The doses of the allergens are determined based on the concentration of the major allergens which gives good clinical results. The dosages are available in the guidelines presented in the text books. Adequate allergen doses have to be administered.

It is imperative to first determine the clinical effectiveness of the allergen extracts used, and the dilution of the extracts, so that the effective concentrations are maintained. Fungal and some insect extracts contain proteases that can degrade the proteins in other allergen extracts and hence may reduce the allergenic potency. Hence, these extracts cannot be mixed together. Single allergen specific immunotherapy will give better results compared to multi allergen specific immunotherapy even in poly sensitized patients.

"Allergoid" is a term used to describe natural allergen products that have been modified with aldehydes (formaldehyde and glutaraldehyde) to decrease their allergenicity and potentially increase their safety. Allergoids are commercially available in Europe from the 1980s and have demonstrated successful clinical results. Allergoids are not freely available in India as of now.

Side effects and risks

Systemic reactions to immunotherapy usually occur within an hour as scattered hives and rarely, as severe anaphylaxis, whereas local reactions may occur up to 24 hours (delayed local reaction).[8,9] The incidence of severe systemic reactions are approximately 1 in one million injections, whereas the incidences of fatal anaphylaxis are 1 per 2.5 million injections.

Sublingual immunotherapy has more incidences of local reactions than systemic.

Common local reactions for SCIT are wheals, indurations and rarely, granuloma.

Common local reactions for SLIT are oral mucosal reactions (75%), itching of oral mucosa, lips, swelling of oral mucosa, lips and rarely, mouth ulcers.

Life threatening reactions tend to occur early and hence it is mandatory that the patients remain in the clinic for 30 minutes which is equipped to handle emergencies after the therapy.

Equipments and medications required

1. Stethoscope and sphygmomanometer
2. Oxygen mask, self -inflating bag or other airway devices
3. IV fluid set up, syringes and needles
4. Epinephrine 1:1000
5. Short acting H1 antihistamine and corticosteroid for IM/IV administration
6. Glucagon kit for patients receiving beta blockers

Advantages

The advantages of immunotherapy include

1. Prevention of newer sensitisations
2. Prevention of development of asthma in patients with rhinitis only
3. Persistence of clinical improvement after cessation of immunotherapy
4. Long term cost benefits due to lesser utilisation of health care.

Points to Remember

- ***Allergen specific immunotherapy is effective and provides long term disease remission.***
- ***It is the only disease modifying treatment available for diseases like allergic rhinitis and asthma.***
- ***Allergen immunotherapy prevents new sensitization and prevents progression of the allergic disease.***
- ***High quality standardised allergen extract have to be used in adequate doseswhere possible.***
- ***Subcutaneous immunotherapy should only be administered at a medical facility with personnel trained in emergency treatment and kept under observation for 30 minutes after each injection.***
- ***Sublingual immunotherapy is a safe, effective, convenient and promising route especially in pediatric age group.***

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CLIPPINGS

Evaluating efficiency and equity of prevention and control strategies for rheumatic fever and rheumatic heart disease in India: an extended cost-effectiveness analysis

There is a dearth of evidence on the cost-effectiveness of a combination of population-based primary, secondary, and tertiary prevention and control strategies for rheumatic fever and rheumatic heart disease. The present analysis evaluated the cost-effectiveness and distributional effect of primary, secondary, and tertiary interventions and their combinations for the prevention and control of rheumatic fever and rheumatic heart disease in India.

A Markov model was constructed to estimate the lifetime costs and consequences among a hypothetical cohort of 5-year-old healthy children. Both health system costs and out-of-pocket expenditure (OOPE) were included. OOPE and health-related quality-of-life were assessed by interviewing 702 patients enrolled in a population-based rheumatic fever and rheumatic heart disease registry in India. Health consequences were measured in terms of life-years and quality-adjusted life-years (QALY) gained. Furthermore, an extended cost-effectiveness analysis was undertaken to assess the costs and outcomes across different wealth quartiles.

A combination of secondary and tertiary prevention strategies, which had an incremental cost of 23051 (US$30) per QALY gained, was the most cost-effective strategy for the prevention and control of rheumatic fever and rheumatic heart disease in India. The number of rheumatic heart disease cases prevented among the population belonging to the poorest quartile (four cases per 1000) was four times higher than the richest quartile (one per 1000). Similarly, the reduction in OOPE after the intervention was higher among the poorest income group (29·8%) than among the richest income group (27·0%).

The combined secondary and tertiary prevention and control strategy is the most cost-effective option for the management of rheumatic fever and rheumatic heart disease in India, and the lowest income groups are more likely to be benefited. The estimation of non-health gains provides strong evidence for making policy decisions by efficient resource allocation on rheumatic fever and rheumatic heart disease prevention and control in India.

Dixit J, Prinja S, Jyani G, Bahuguna P, Gupta A, Vijayvergia R, et al. Evaluating efficiency and equity of prevention and control strategies for rheumatic fever and rheumatic heart disease in India: an extended cost-effectiveness analysis. Lancet Glob Health. 2023 Mar;11(3):e445-e455. doi: 10.1016/S2214-109X(22)00552-6. PMID: 36796988.

Therapeutic alteration of the microbiota in rheumatic diseases: Hype or potential?

.....studies evaluating probiotics in rheumatoid arthritis, spondyloarthritis or systemic sclerosis; a small number of studies have tested fecal microbial transplantation (FMT) in rheumatic diseases. .....few studies detected meaningful clinical benefit regardless of indication. One of the two randomized studies evaluating FMT showed minimal clinical benefit, while the other demonstrated worsening compared to placebo treatment.

Stoll ML. Therapeutic alteration of the microbiota in rheumatic diseases: Hype or potential? Best Pract Res Clin Rheumatol. 2022 Dec; 36(4):101806. doi: 10.1016/j.berh.2022.101806. Epub 2022 Dec 21. PMID: 36564273.

PULMONOLOGY

WHAT'S NEW IN CONGENITAL DIAPHRAGMATIC HERNIA ?

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Abstract: *Despite great strides in surgical and ventilatory management of congenital diaphragmatic hernia, survival rates and long term outcomes seem to have plateaued out. This article attempts to review the advances in the early detection of and antenatal management of diaphragmatic hernia and the outcomes of postnatal management of these children.*

Keywords: *Congenital diaphramatic hernia.*

Congenital diaphragmatic hernia (CDH) is a structural anomaly of the fetal diaphragm that is characterized by a defect in the diaphragm leading to the herniation of intra-abdominal organs into the thoracic cavity. Its incidence ranges from 1-5 cases per 10,000 births[1,2] and up to 20-30% cases are not antenatally detected. CDH has been found to have a slightly higher male preponderance with the African-American race having a lower risk.[2,3] Even as medical and surgical management of this condition has improved by leaps and bounds, the mortality and morbidity of these infants remain high[4,5] with many requiring long-term follow-up and multidisciplinary care well into their adolescent years. The causes of significant mortality and morbidity is the pulmonary hypoplasia and pulmonary hypertension that is seen as a result of the lower number and decreased volume of alveoli and pulmonary vascular abnormalities in children with diaphragmatic hernia.

There are 3 types of CDH: A posterolateral defect in the diaphragm known as the Bochdalek hernia which is the most common type, accounting for up to 95% of cases, an anteromedial, parasternal defect, known as a Morgagni hernia, accounting for 3-5% of cases and a central tendon defect which is the rarest variant accounting for less than 1% of cases.[6] CDH is most commonly found on the left side (80-85%) with around 10-15% of cases being on the right and very rarely, bilateral.

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Etiopathogenesis

The diaphragm begins to develop around the 4th week of gestation and is usually completed by the 12th week. It is derived from four structures - septum transversum, pleuroperitoneal membrane, dorsal mesentery of esophagus and somites from the body wall. The initial hypothesis for the etiopathogenesis of CDH was that the diaphragmatic defect was secondary to a failure of development or fusion of one or more of these four progenitor structures[7], which leaves a defect for intra-abdominal structures to enter the thorax, interfering with lung development and gas exchange. Another theory is that lung hypoplasia may be the initial event in the pathophysiology. The post hepatic mesenchymal plate (PHMP) is both closely related to the development of the lung and the diaphragm and when there is hypoplasia of the lung, there is an associated disturbance of the PHMB which may lead to a diaphragmatic defect.[8] This has been supported by evidence from rat model electron microscopy.[9]

Most of the data on CDH pathophysiology is derived from murine models[10,11] which illustrate the baseline molecular changes that underscore CDH. During the fetal period, the pulmonary vascular resistance (PVR) is more than the systemic resistance and normally reverses with the baby's first breath after delivery, leading to increased pulmonary blood flow to facilitate gas exchange. In babies with CDH, the lung hypoplasia, associated decreased pulmonary vasculature and increased vascular tone in the lung lead to pulmonary hypertension.[12,13] Endothelin-1 (ET-1) is a polypeptide produced by vascular endothelial cells which binds to pulmonary arterial smooth muscle cells and induces vasoconstriction.[14] In rat models, both the over-expression of ET-1 receptor genes and the exaggerated vasoconstrictor response to ET-1 have been demonstrated[15,16] leading to pulmonary vasoconstriction and increased smooth muscle cell proliferation leading to increased pulmonary pressures.[14,17] Lower levels of nitric oxide (NO) which is a potent vasodilator have also been

demonstrated in murine models.[18] The vascular endothelial growth factor (VEGF) and its receptors induce angiogenesis in the fetal lung by promoting vessel proliferation and hence providing support for alveolar development and airway branching. It has also been demonstrated that VEGF promotes pulmonary surfactant production from glycogen in pneumocytes.[19] Decreased levels of VEGF and its receptorVEGFR has been demonstrated to lead to lower lung volumes in murine models, which leads to the pulmonary hypoplasia and pulmonary hypertension seen in CDH.

The most recent and widely accepted theory proposes a two-hit hypothesis, which incorporates both of the above theories.[20] According to this theory, the first hit is during organogenesis with both lungs being underdeveloped due to molecular mechanisms followed by the second hit where, due to the diaphragmatic defect, the ipsilateral lung is compressed by the herniation of abdominal organs and compromised further. This explains the bilateral nature of the pulmonary pathology in CDH infants with the contralateral lung being affected to varying levels. This interference results in less bronchiole branching and thicker alveolar septa, leading to acinar hypoplasia and impaired gas exchange while the decreased branching of the pulmonary arterioles and increases vascular tone leads to the developed of persistent pulmonary hypertension of the newborn (PPHN).[21,22]

Due to increased pulmonary pressures, there is an increased strain on the right ventricle during fetal life due to the ductus arteriosus which shunts blood into the systemic circulation. After birth, the ductus arteriosus closes, leading to right ventricular strain, hypertrophy and eventual dysfunction and failure. Left ventricle abnormalities have also been reported in CDH infants with lower left ventricular mass and hypoplasia.[23] This leads to increased pulmonary venous pressures and further exacerbates the pulmonary hypertension and right heart failure.[24]

Diagnosis

Prenatal diagnosis of CDH is possible, with a mean detection gestational age of 24 weeks.[25] Prenatal diagnosis is important, as severe cases may require extra-corporeal membrane oxygenation (ECMO) which mandates a planned delivery of babies with CDH, as this treatment modality is available only in select institutions. There are two modalities for diagnosis - ultrasound and fetal MRI. As it is not possible to predict the size of the defect and hence the severity of the disease with prenatal imaging techniques, indirect assessment criteria are used.

The time-tested predicting factor for CDH severity is the foetal lung-head ratio (LHR) which is the ratio of the cross-section of the contralateral lung at the level of the four-chamber cardiac view to the head circumference, with a value of less than 1 considered as 'severe.'[26] However, it is useful only between 22-28 weeks of gestation and is operator dependant, both factors limit its dependability.[27] Many centres have shifted to fetal MRI with is less operator dependant and gives more accurate measurements and is not affected by maternal habitus and fetal position. An independent predictor of the severity of PPHN and need for ECMO and hence, the postnatal survival, is the observed/expected total lung volume (TLV)[28], with a value of less than 30% translating into a mortality risk of 50-75%. Other indicators of severity are MRI-calculated liver herniation (greater than 20% being of higher risk)[29], laterality (right being worse than left) and position of the stomach at the level of the four-chamber cardiac view.

Fetal therapy

Earlier the repair of the diaphragmatic defect, more the chance for the fetal lung to develop normally and hence, fetal endoscopic tracheal occlusion (FETO) was developed.[30-32] A endoscope of 3mm diameter is inserted through the maternal abdomen into the fetal mouth and then into the fetal trachea.[33] Once the carina is seen, a detachable and inflatable balloon with a one-way valve in inflated below the glottis. Occlusion of the trachea prevents the egress of lung fluid into the amniotic cavity, trapping it into the lungs and causing its expansion over time. Before birth, a second procedure is performed where the balloon in ruptured under vision and removed. It is performed under maternal; local anaesthesia with a combination of analgesics and muscle relaxants administered to the fetus intramuscularly just prior to the procedure. A scheduled removal a few weeks before birth is ideal as it allows type 2 pneumocytes to develop appropriately as well as allows the fetus in transition to the ex-utero environment.[34,35] If removal is an emergency due to early labour or for obstetric indications, the baby may need to be delivered with an ex-utero intra-partum treatment (EXIT) which will allow balloon removal while the baby is still attached to the placenta.

Data supporting the use of FETO have been mixed with an initial randomized control trial (RCT) showing no survival benefit in children with liver herniation and a LHR of less than 1.2.[36] It was also seen that mothers undergoing FETO had a higher rate of premature rupture of membranes and delivered premature babies. However, smaller studies have shown a survival benefit. A cohort study involving 210 cases showed a 49.1%and 35.3%

survival in left and right sided CDH respectively in the test arm as compared to 24.1.% and 0% in historical controls.[26] A smaller RCT with 41 severe CDH cases showed a 6-month survival rate of 50% in the FETO group as compared to 4.8% in the postnatal surgery group.[37] FETO has also been demonstrated to reduce the possibility of persistent pulmonary hypertension at 1 year of age among survivors.[38] Establishing the actual benefit of FETO has been difficult due to heterogeneity of the studies published as well as the capabilities of the centres in which the procedure has been performed. In order to get this answer, the TOTAL (Tracheal Occlusion to Accelerate Lung Growth) trial in currently being conducted to determine whether the use of FETO increases survival and decreases oxygen requirements in moderate and severe CDH cases.

However, FETO is not without probable complications such as fetal tracheomegaly and tracheomalacia but the incidence of these complications has not been recorded. Upto 50% of mothers undergoing FETO develop premature rupture of membranes, chorion-aminon separation and preterm delivery due to the need for two amniotic cavity punctures.[26] In cases in which labour is induced peri-procedure, there is a risk of fetal demise due to the balloon being lodged in the trachea, with 56% of cases requiring an intrapartum (EXIT) procedure and 5% mortality,[26] especially as EXIT is not available in all centres at present.

Seeing the complications due to the double amniotic punctures of FETO, scientists from Strasbourg, France have developed the 'Smart-TO' balloon. Around the balloon neck, there is a metallic cylinder and inside a magnetic ball, which together act as a valve. Deflation occurs under the influence of a strong magnetic field, which is present around any clinical MRI machine. This enables non-invasive, externally controlled balloon deflation. When it is time to remove the balloon prior to labour, the mother is subjected to a MRI, which draws the ball out of the cylinder, deflating the balloon, which is then washed out of the lung with the lung fluid into the amniotic cavity.[39]

Even with FETO, survival rates of severe CDH are low and hence, specific therapies targeting pulmonary hypertension are being developed using rabbit models. In rabbits with a surgically created CDH, the test arm underwent tracheal occlusion with injection of human amniotic fluid stem cells.[40] The similar experiment has also been conducted in rodents using nitrofen-induced CDH using intra-amniotic injection of human mesenchymal cells.[41] Histopathological examination of the test arm lungs from both studies show increased alveolar number with larger volume, thinner walls and more compliant pulmonary vasculature.[40,41] Given the success in animal models, these therapies' utility in human models are being studied.

Birth and postnatal management

The timing of delivery of CDH infants has been historically controversial but recent studies have shown better outcomes with greater gestational ages.[42] Therefore, current recommendations suggest that delivery on completion of 39 weeks is optimal, with the mode of delivery depending on obstetric factors.[43] Prenatal diagnosis of CDH is crucial so that the labour room team is prepared for the infant and the birth occurs in a center equipped for management of CDH. All CDH infants need gastric decompression with a naso/orogastric tube with suction. Peripheral and central venous access catheters should be placed for fluid and inotrope administration and blood pressure should be kept within the normal range for gestational age. As they will have respiratory distress, the instinct to apply bag-mask ventilation should be suppressed as it may lead to distension of the herniated bowel. Instead, there should be a low threshold for intubation. Preductal saturation is measured on the right upper limb and ventilation pressures should be low to avoid harm to the underdeveloped lung.

The optimal mode of ventilation of CDH infants is controversial with two main strategies being used gentle ventilation and high frequency oscillatory ventilation (HFOV). What both these techniques have in common is the low pressure at which they operate, reducing the risk of permanent pulmonary damage to already hypoplastic lungs. Gentle ventilation operates on the principle of permissive hypercapnia and hypoxemia, as long as the blood pH and saturation are maintained. The target values are a preductal saturation >85%, postductal saturation ≥70%, pH ≥7.2, lactate levels <5mmol/L and a urinary output of ≥1ml/kg/hr. The peak inspiratory pressures should be titrated to less than 25cm of water and a PEEP of 2-5cm H20. There are many studies comparing gentle ventilation with conventional ventilation and though results are conflicting, there is a definite decrease in mortality and hence, even though there is weak scientific evidence, it is strongly recommended to give an initial trial of gentle ventilation.[44] HFOV has a ventilation rate of around 4 times the normal physiological rate with a small tidal volume, while maintaining a mean airway pressure of less than 17cm H20. Its efficacy may be affected by obstructed airways (eg. thick secretions). Though there is insufficient scientific evidence due to the heterogenicity of trials and study bias, it is recommended to be used as second line strategy[45].

The recent HFO versus conventional **V**entilation in **I**nfants with **C**ongenital diaphragmatic hernia an **I**nternational randomized clinical trial (VICI trial) in Europe has shown that though there is no difference in the rates of mortality and bronchopulmonary dysplasia between the two strategies, though lesser number of ventilatory days and less need for ECMO was seen in the gentle ventilation group.[46]

As pulmonary hypertension is a key factor that translates into increased mortality and morbidity in CDH, lower pulmonary pressures is key to reducing right ventricular strain and better outcomes. Systemic vasodilators decrease pulmonary resistance along with systemic vascular resistance and hence, a vasodilator that acts purely on pulmonary vasculature was thought to be better leading to the first use of inhaled nitric oxide (iNO) in 1992.[24,47] However, data regarding its long-term results and prognosis is lacking. Though a lot of research has gone into the use of iNO in CDH, differences in the basic treatment plan, bias and an inability to differentiate between the advantage of iNO alone as compared to its use along with other therapeutic modalities leave it on shaky scientific ground.[45] Difference in the therapeutic background compared to the present, the presence of a significant bias, or the influence of factors other than iNO. However, as iNO is now routinely used for neonates with PPHN without CDH and the fact that there are no systemic side effects and the easy incorporation of the drug into the ventilation circuit with no added burden to the patient has lead to iNO being incorporated into standard guidelines for the management of CDH. Use of systemic vasodilators however have been firmly established as a cornerstone in management. Milrinone, a phosphodiesterase 3(PDE3) inhibtor, has been shown to cause pulmonary vasodilation along with an improvement in right ventricular function with its inotropic and lusitropic action.[48] It, however, has the side effects of hypotension and cardiac arrythmias. Sildenafil, a PDE5 inhibitor, improves cardiac function, gas exchange, increases the efficacy of iNO and prevents rebound pulmonary hypertension during ablactation of nitric oxide.[49] Intra-amniotic sildenafil administration has been studied in murine and rabbit CDH models and has shown to improve vascular compliance and oxygenation by crossing the placenta to reach the fetus.[50,51] A prospective human trial is underway to prove its efficacy in humans.[52]

ECMO functions by passing the blood from the body through an external oxygenator thus maintaining saturation while allowing rest to the failing heart and lungs. It was first used in a CDH infant in 1977[45] but its role at present is of a rescue therapy.[53] Though there are RCTs and observational studies at hand evaluating the use of ECMO, there is a significant bias in these studies as well as confounding factors such as the progress of other therapeutic modalities. Literature shows that the use of ECMO improves the short-term prognosis of such infants; however, a similar improvement in long-term prognosis was not seen.[45] Complications of treatment include life threatening hemorrhage, cerebral hypoxia and neurological impairment. Due to the improvement of other, less invasive modalities of treatment, use of ECMO in CDH neonates has gradually decreased.[54] For these reasons, the efficacy of ECMO as a treatment modality in CDH in uncertain and its use cannot be a uniform recommendation for all cases. Hence, it is reserved for those neonates with severe respiratory impairment.[45] There is considerable variation between centres for the criteria to start ECMO therapy but the following is usually used[44]:

1) Preductal saturations >85% or postductal saturations >70%
2) Requirement of MAP >17 cm H2O to achieve saturations >85%,
3) Resistant metabolic acidosis<7.15
4) Systemic hypotension resistant to fluid and pressor therapy
5) Oxygenation Index ≥ 40

Postnatal Surgery

The surgical repair of CDH leads to the question of when the optimal time for surgery is. Reducing the contents of the hernia back into the abdomen may seem to logically lead to a better outcome but most of the available evidence points to the idea that though reduction improves long-term outcomes, it does little for the immediate condition of the patient[55] as it does not result in the instant improvement of pulmonary and cardiac status. As pulmonary hypertension is the single most important variable for determining the outcomes of CDH neonates, the timing of surgery becomes a critical question when it has also been seen that surgical stress itself can induce a pulmonary hypertensive crisis and severe hemorrhage, if on ECMO.[53] For those neonates not requiring ECMO support, surgical repair is not undertaken before 2-3 days of life, that time being taken for stabilization and improvement of pulmonary status. Once a neonate is on ECMO therapy, the surgeon faces a choice between early repair, immediately after ECMO initiation (typically less than 72 hours), repair after decannulation and delayed repair as a last-ditch effort when unable to wean off

ECMO.[56] The evidence on the timing of surgery is adulterated due to smaller subject population, subject heterogeneity and study design but it has usually been seen that the neonates that do best postoperatively are those in whom repair is undertaken after decannulation, presumably due to the lower risk of hemorrhagic complications.[53]

The surgical approach for CDH can be either open or minimally invasive (thoracosopic and endoscopic). The latter has been developed with the hope of reducing surgical stress and hence improving outcomes. However, thoracoscopic surgery has been shown to have higher recurrence rates[45], may not be suitable for larger defects, has a steep learning curve and needs instruments that may not be available in all centres. It has also been seen that minimally invasive measures require a longer operative time, need intraoperative pulmonary compression and run the risk of CO2 absorption which all worsen outcomes in sick infants.[45] Hence, open surgery still remains the gold standard for repair. Small defects are primarily closed with non-absorbable sutures while larger defects need a foreign material. The most used material is a synthetic patch (Gore-Tex) while there are centres that are combining synthetic and biological derivatives to promote better incorporation of the repair and improvement in long-term outcomes.[53] Closure using autologous muscle flaps have also been described[57], with the graft consisting of the internal oblique and transversus abdominis. Observational studies have shown lower recurrence rates and better success in closing large defects[58] but higher level of evidence is not yet available to confidently make a strong recommendation on their use.

Long-term Care

The medical care that a CDH child needs does not stop with discharge from the hospital after successful stabilization and surgery. Such children have a high risk of long term medical issues and hence, need continued multidisciplinary care. Guidelines for follow-up care have been released by the American Academy of Paediatrics[55] Respiratory issues include chronic lung infections, decreased respiratory muscle strength. Persistent pulmonary hypertension and obstructive airway disease, with children who underwent ECMO and patch repair having higher rates of pulmonary morbidity.[59] Adolescent survivors often-faced mild to moderate obstructive disease requiring bronchodilator therapy along with weak inspiratory muscle strength.[60] Gastrointestinal issues such as failure to thrive, gastroesophageal reflux, need for long term tube feeds and malabsorption further complicate recovery.[61,62] Neurological issues such as neurocognitive and developmental delay[63,64] coupled with orthopaedic problems such as pectus and scoliosis[60,65], necessitate counselling and training to integrate these children into society. If these children have other associated anomalies or fit into a clinical syndrome, these problems are multiplied. Hence, it is strongly recommended to conduct a thorough evaluation of these children after stabilization in order to recognize potential problems, to sensitize and educate the parents and to plan for an appropriate rehabilitation and therapy plan.

Points to Remember

- ***Prenatal diagnosis of CDH is crucial so that the labour room team is prepared for the infant and the birth occurs in a center equipped for management of CDH.***
- ***As pulmonary hypertension is a key factor that translates into increased mortality and morbidity in CDH, addressing the same with medication and ventilation and balancing both should be the key.***
- ***Preoperative stabilization and post operative care are the two pillars of success.***

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CLIPPINGS

Baricitinib in juvenile idiopathic arthritis: an international, phase 3, randomised, double-blind, placebo-controlled, withdrawal, efficacy, and safety trial

This trial assessed the efficacy and safety of baricitinib, an oral Janus kinase 1/2-selective inhibitor, versus placebo in patients with juvenile idiopathic arthritis.

This phase 3, randomised, double-blind, placebo-controlled, withdrawal, efficacy, and safety trial was conducted in 75 centres in 20 countries. The study enrolled patients (aged 2 to <18 years) with polyarticular juvenile idiopathic arthritis, extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or juvenile psoriatic arthritis, and an inadequate response (after e”12 weeks of treatment) or intolerance to one or more conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs). After age-based dosing was established in the safety and pharmacokinetic period, patients received a once-daily 4 mg adult-equivalent dose of baricitinib (tablets or suspension) in the open-label lead-in period. Patients meeting Juvenile Idiopathic Arthritis-American College of Rheumatology (JIA-ACR) 30 criteria (JIA-ACR30 responders) at the end of the open-label lead-in (week 12) were eligible for random assignment (1:1) to receive placebo or continue receiving baricitinib, and remained in the double-blind withdrawal period until disease flare or up to the end of the double-blind withdrawal period (week 44).

220 patients were enrolled and received at least one dose of baricitinib in the study period. Time to disease flare was significantly shorter with placebo versus baricitinib (p<0·0001). Median time to flare was 27·14 weeks in the placebo group, and not evaluable for patients in the baricitinib group (<50% had a flare event.

Baricitinib was efficacious with an acceptable safety profile in the treatment of polyarticular juvenile idiopathic arthritis, extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, and juvenile psoriatic arthritis, after inadequate response or intolerance to standard therapy.

Ramanan AV, Quartier P, Okamoto N, Foeldvari I, Spindler A , Fingerhutová S et al. Baricitinib in juvenile idiopathic arthritis: an international, phase 3, randomised, double-blind, placebocontrolled, withdrawal, efficacy and safety trial. Lancet . 2023 Jul 6;S0140-6736(23)00921-2. doi: 10.1016/S0140 - 6736(23) 00921-2. Epub ahead of print.

GENERAL ARTICLE

ENTERAL NUTRITION IN PICU

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Abstract : *Nutrition is an important component of patient management in pediatric intensive care unit (PICU). Malnutrition in children hospitalized in PICU is associated with increased risk of hemodynamic instability, with the potential to adversely influence the outcome of critical illness. Enteral nutrition is preferred because it is simple, economical and relatively free of complications. Contraindications to enteral nutrition are very few, such as intestinal dysmotility, toxic megacolon, peritonitis, gastrointestinal bleeding, high output enteric fistula, severe vomiting and intractable diarrhea. Despite its simplicity, there are some complications during enteral feeding in critically ill children, such as aspiration, bacterial contamination of feeds, feed intolerance and refeeding syndrome. Nutrition is an important component of patient management in pediatric intensive care unit (PICU). Accurate assessment of energy requirements and provision of optimal nutrition support therapy through appropriate route is an important goal of pediatric critical care. Enteral nutrition is preferred in children with functioning gastrointestinal tract. Organizing a nutrition support team constituted by a pediatrician specialized or interested in nutrition and a dietician along with pharmacist and nurses within the PICU team is a wise idea to plan and execute enteral nutrition. Close monitoring is required to reduce the complications and increase the success rate.This review describes the science and challenges related to enteral nutrition prescription and delivery in critically ill children.*

Keywords: *Enteral nutrition, Children, Critical illness, PICU.*

Optimal nutrition plays a key role in the recovery of children admitted to pediatric intensive care unit (PICU). Malnutrition already existing or developing during the course of hospital stay may adversely affect the outcome including duration of hospital study. With the day-to-day challenges in management, nutrition may be overlooked in such children. Common conditions which predispose to undernutrition are congenital heart disease, chronic lung diseases, cystic fibrosis, neuromuscular diseases and genetic syndromes requiring long term nutritional support. The importance of continuous nutritional assessment of critically ill children and steps in management of enteral nutrition are discussed in this review.

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Nutritional assessment

Children admitted with critical illness are at risk of altered nutritional status and anthropometric changes that may be associated with morbidity. Hence, nutrition screening is mandatory to identify at-risk and malnourished children. Critically ill children at the greatest nutritional risk should be identified early.

Common conditions in children admitted in PICU which predispose to undernutrition are

1. Cardiorespiratory illnesses especially congenital heart disease, chronic lung diseases and cystic fibrosis
2. Traumatic brain injury requiring surgical intervention
3. Spinal cord injury
4. Burns
5. Respiratory failure or infection including acute respiratory distress syndrome
6. Gastrointestinal diseases like short bowel syndrome, biliary atresia and necrotizing enterocolitis
7. Neurological or neuromuscular diseases especially cerebral palsy, myelomeningocele with complications, spinal muscular atrophy and genetic syndromes requiring long term nutritional support

Factors that increase nutritional risk in critically ill children (with regard to underlying nutritional status, clinical course and medical management) as per American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines are given in Box 1.

Box 1. Risk factors for malnutrition in children admitted in PICU

1. Weight for age < 3rd percentile
2. Height / length for age <3rd percentile
3. Weight for length < 3rd percentile
4. Underweight children with BMI < 5th percentile for age
5. Overweight children with BMI > 95th percentile for age
6. Children with weight loss of > 10% during PICU stay
7. Critically ill children on significant vasoactive support and on muscle relaxants > 7 days
8. Critically ill children on ventilator support for > 7 days
9. Critically ill children with difficulty in weaning off the respiratory and cardiovascular support

Nutritional assessment of critically ill children should be conducted within the first 24 to 48 hours and then at least weekly and it can be quantitatively assessed by routine anthropometric measurements. Standard anthropometric measurements may be inaccurate in critically ill children with fluid shifts, edema and ascites, hence cannot be used alone to estimate nutritional goals. Adequate nutritional assessment requires assessment of energy expenditure along with nutritional markers. Accurate estimation of energy requirements is important for preventing both underfeeding and overfeeding in critically ill children. Resting energy expenditure (REE) and respiratory quotient (RQ) are used to calculate energy expenditure in critically ill children.

Resting energy expenditure (REE) is defined as amount of energy required by the body during non-active 24 hour period, accounting for 60-70% of total daily expenditure. Critically ill children experience increased REE and depletion of nutrient stores due to their catabolic state. REE is reduced significantly in sedated and mechanically ventilated children. Inhibition of anabolic role of growth hormone during inflammation in critically ill children contributes to hypo metabolism and growth impairment. The catabolic stress response following critical illness or injury varies among critically ill children based on the severity and duration of injury or illness and complications experienced during the clinical course, type of medical therapy and respiratory support used.

Indirect calorimetry is considered to be the preferred method to estimate REE in critically ill children. It is a non-invasive technique performed at the bedside and helps in determining specific energy needs on an individual basis. Its use is limited due to lack of expertise, resource constraints and its inherent difficulty for use in non-intubated children. In view of the problems caused by great variability between measurement conditions, standard prediction equations are commonly used to estimate energy and protein needs for critically ill child. Prediction equations are based on demographics from healthy children. They do not account for alterations in weight affected by body fluid status, body mass or use of sedation and neuromuscular blocking agents often used in care of critically ill children. Inaccuracies of these equations which can be influenced by the above said factors may lead to risk of either underfeeding or overfeeding as they cannot compensate for the metabolic changes that accompany critical illness or injury.

Respiratory quotient (RQ) is ratio of carbon dioxide produced (VCO_2) to the amount of oxygen (VO_2) consumed by the individual. It measures inherent composition and utilisation of various nutritional ingredients such as fat, carbohydrates and proteins as they are converted into energy yielding units. RQ provides good insight into metabolic balance. RQ for carbohydrate oxidation is 1.0 and that of fat is 0.7. RQ for protein is variable and depends on the type of amino acids being metabolised. Normal range of RQ is 0.67-1.3. RQ > 1.0 implies that more carbohydrates are used for oxidation, leading to increased CO_2 production, indicating the need to decrease the carbohydrate intake. An RQ< 0.81 implies increased fat oxidation indicating increased calorie intake or decreased carbohydrate intake, thereby allowing fat metabolism. Food sources and conditions have specific RQ values that are useful when interpreting the REE and making recommendations for changing dietary goals and feeding regimens.

Table I. Normal energy requirement based on age / weight

Age / weight	Energy requirements per day
Preterm neonates	120-150 kcal /kg
Term neonates	100-120 kcal/kg
Weight of child < 10kg	100 kcal /kg
Weight of child between 10-20kg	1000 kcal + 50 kcal/kg over 10kg
Weight of the child > 20kg	1500 kcal + 20 kcal /kg over 20kg

Table II. Percentage increase in energy expenditure (EE) in various clinical conditions

Clinical condition	Percentage increase in energy expenditure
Fever	12 % for every degree Celsius increase recorded above 37^0Celsius
Cardiac failure	15-25%
Major surgery	20-30%
Burns	Up to 100%
Severe sepsis	40-50%

Table I shows normal energy requirement based on age / weight and Table II shows the percentage increase in energy expenditure (EE) in various clinical conditions.

Energy requirements fluctuate throughout the course of illness in critically ill children. Clinicians should be aware of these dynamic states and utilise the expertise of pediatric dieticians to assist with nutritional assessments and prescription of appropriate energy and protein intake to meet individual metabolic requirements of the patient.

Enteral nutrition (EN)

Once it is decided to optimise the nutrition, the preferred method is enteral nutrition due to its various advantages.

Benefits of enteral nutrition (Box 2) are listed below.

Box 2. Benefits of enteral nutrition

1. Enteral nutrition is economical and more physiological.
2. It helps in maintaining physiological and functional integrity of gastrointestinal mucosa by nourishing the gut.
3. It helps in attenuating oxidative stress and inflammation by decreasing cytokine production
4. It prevents and decreases the risk of bacterial translocation
5. It aids in management of fluid and electrolyte balance
6. It helps in supporting gut associated lymphoid tissue
7. It reduces the length of stay in hospital

Contraindications to enteral nutrition

Absolute contraindications to enteral nutrition support include: paralytic or mechanical ileus, intestinal obstruction, bowel perforation, necrotizing enterocolitis etc. Relative contraindications to enteral nutrition include intestinal dysmotility, toxic megacolon, peritonitis, gastrointestinal bleeding, high output enteric fistula, severe vomiting and intractable diarrhea.

Under these clinical circumstances, EN should be provided to the maximum extent as tolerated by the patient, with parenteral nutrition making up to meet the balance nutritional requirement.

Administration of enteral nutrition

a)Access sites (Gastric vs post pyloric feeding)

Enteral nutrition delivery can be gastric or post pyloric. The choice of access depends on morphological and functional integrity of gastrointestinal tract, duration of EN and the risk of aspiration. Intragastric access should be used whenever possible as it is more physiological and also easier to achieve. Post pyloric access is indicated in situations like gastroparesis, gastric outlet obstruction, or previous gastric surgery precluding gastric feeding or when early postoperative feeding after major abdominal surgery is planned.

b) Routes (Tubes vs gastrostomy / enterostomy)

Enteral nutrition support can be provided by replaceable tubes (nasogastric / nasoduodenal / nasojejunal) or via gastrostomy or enterostomy. The choice of the route is influenced by duration of planned enteral nutrition support and integrity of upper gastrointestinal tract. If a shorter duration of enteral nutrition of less than 4 weeks is required, nutrition should be directly supplied to stomach, duodenum or jejunum via tube. Nasoduodenal or nasojejunal tube feeding can be performed when gastric tube feeding is difficult owing to the risk of aspiration.

If enteral nutrition support is expected to be required for long term, feeding via gastrostomy or enterostomy is the preferred route. Chronic diseases associated with nutritional imbalance or neurological abnormalities such as cerebral palsy and neuromuscular disorders are indications for percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ). PEG (J) is also considered for feeding and decompression if malignant tumors of head, neck and esophagus or chronic intestinal pseudo obstruction is present. PEG(J) is contraindicated if the patient has terminal illness with limited life expectancy,

uncorrectable coagulopathy, inability to perform UGI endoscopy, or failure to transilluminate the abdominal wall.

Composition of enteral formulations

EN is predominantly offered as liquid ready-to-feed formulations. It supplies a balanced mix of all the essential nutrients needed to meet physiological requirements and growth. When pediatric formulas are not available, an adult formulation can be used preferably beyond the age of 8 to 10 years. An energy density of 1 kcal/mL feed is appropriate for most children and it also supplies sufficient fluid intake. Children with increased energy requirements in a limited volume should receive feeds with a high energy density (1.5 kcal/mL). Supplemental PN should be used if nutritional requirements cannot be fully met by EN alone.

Polymeric feeds are usually based on cow's-milk protein. Low-molecular formulas are feeds with oligopeptides derived from protein hydrolysates, and elemental feeds are based on free amino acids. Low molecular formulas are indicated in children with intolerance to polymeric feeds and those with severe impairment of intestinal absorption. It is expensive and usually delivered by tube feeding due to poor palatability. Enteral formulations are generally gluten free and also contain only low amounts of lactose. Isoosmolar feeds (osmolality: 300-350 mOsm/kg) is always preferable as feeds with high osmolality may induce diarrhea in patients with intestinal pathology. Feeds rich in fiber have beneficial effects on intestinal physiology and prevent both diarrhea and constipation. Feeds rich in lipid content and low in carbohydrate is beneficial to children with stress metabolism like insulin resistance, hyperglycemia, septicemia and burns and can also reduce CO2 production.

Medium-chain triglycerides (MCT oils) are beneficial in patients with fat malabsorption, severe short bowel syndrome and disorders of lymphatic system. Random use of MCT oil should be avoided as it contains 15% less energy per gram than natural oils and also reduces essential fatty acid intake. Diets rich in mono-unsaturated fatty acid seem to improve insulin resistance, but clinical evidence in children is lacking. Long-chain omega-3 polyunsaturated fatty acids provides anti-inflammatory and immune modulating effects, but needs further research to prove its efficacy.

Disease-specific formulas

Disease specific formulations can be prepared in hospital kitchens or at home or available as ready-made and it includes the following.

1. Feeds with reduced protein contents are used for patients with renal disease or hyperammonemia
2. Feeds rich in lipid content provided by MCT and fat-soluble vitamins are used in children with severe cholestasis and short bowel syndrome.
3. Carbohydrate -modified formulas are used in children with galactosemia or glucose galactose malabsorption
4. Formulas based on extensively hydrolyzed protein or amino acids are used in children with cow's milk protein allergy or food allergy

Barriers to enteral nutritional support

Barriers that are unavoidable include

1. Critically ill children with hemodynamic instability on multiple vasoactive agents
2. Need for fluid restriction especially in children with acute or chronic kidney injury and congenital heart disease.
3. Critically ill children demanding extracorporeal membrane oxygenation
4. Patients at risk for necrotizing enterocolitis.
5. Feeding intolerance

Hypoxia, hypovolemia or hemodynamic instability may result in shunting of blood from splanchnic vascular bed leading to ischemia of gastrointestinal tract. Feeding a potentially ischemic gastrointestinal (GI) tract increases risk of severe progressive mucosal injury and tissue death. Vasoactive agents commonly prescribed in PICU also compromises splanchnic perfusion resulting in ineffectiveness of EN.

Feeding intolerance in critically ill pediatric patients occurs secondary to GI dysmotility driven by sympathetic nervous system stimulation, immobilization, use of sedation and muscle relaxants. It manifests as abdominal distension or discomfort, persistent emesis or diarrhea or high gastric residual volumes (GRV). Practical application of GRV to assess feeding intolerance and aspiration risk is questionable as the lower limit of GRV that protects from risk of aspiration is unknown. In addition there are also other reasons for EN interruptions are failure to place nasogastric tube (NGT), dislodgement of NGT, feeding tube blockage, and lack of standard approach to delivery of nutrition.

Critically ill children experiencing unavoidable EN interruptions should be initiated on parenteral nutrition and effectively advanced to meet nutritional needs.

Complications of enteral nutrition

Enteral nutrition in critically ill children carries significant risks and complications. Most important of which is considered in detail below. Tables III and IV list the mechanical and gastrointestinal complications associated with enteral nutritional support in critically ill children respectively.

Metabolic complications: Children with chronic nutritional imbalance are at risk of refeeding syndrome during abrupt feeding of high energy nutrition.

Refeeding syndrome

Refeeding syndrome is a potential metabolic complication occurring in malnourished children as a result of implementation of nutritional support. Starvation causes adaptive reductions in cellular activity and organ function accompanied by micronutrient, mineral, and electrolyte deficiencies and stores of nitrogen, phosphate, magnesium, and potassium are depleted. Sudden reversal of catabolism through nutritional support (particularly excessive carbohydrate) leads to a surge of insulin secretion, which causes massive intracellular shift of phosphate, magnesium, and potassium with a subsequent fall in their serum concentrations. These electrolyte imbalances can lead on to development of hemolytic anemia, muscle weakness, and impaired cardiac function, leading potentially to cardiac failure, fluid overload, arrhythmia and death.

Children with severe chronic weight loss such as anorexia nervosa and cancer cachexia are at greater risk especially during the first week of feeding. Assessing the baseline nutritional status and hydration before initiating nutritional support, checking baseline serum electrolytes,

Table III. Complications associated with nasoenteral feeding tubes

Complications	Possible Cause	Prevention / Treatment
Tube related complications 1. Plugging	Improper tube care	1. Flush the tube before and after each feed 2. Open clogged tubes using warm water 3. Replace the tube
2. Tube dislodgement	Coughing , sneezing, vomiting or unintentional removal	1. Tube position to be checked before each feed 2. Reposition the tube if dislodgement noted
3. Nasopharyngeal discomfort	Larger tubes or flexible tubes	Use smaller and soft tubes
4. Tracheo-esophageal fistula	Pressure necrosis occurring secondary to presence of large nasoenteric and nasotracheal or tracheostomy tubes	Use small and soft tubes
5. Tube misplacement (endobronchial / intrapleural / intrapericardial / intracranial)	Altered consciousness with absence of cough and gag reflex Mechanical ventilation	Tube position to be checked after insertion and before each feeding
6.Visceral perforation with associated complications • Pneumothorax • Empyema • Mediastinitis • Pneumatosis intestinalis	Misplacement of the tube	1. Gentle insertion 2. Check position after insertion and before securing the tube

Table IV. Gastrointestinal complications

Complication	Possible causes	Prevention / treatment
Diarrhea	Increased rate of infusion	Decrease the rate of infusion and gradually increase as tolerated
	High osmolar feeds	Build up the strength of feed slowly and give it by continuous infusion
	Impaired gut function	Use hydrolysed formula or modular feed
	Bacterial contamination of feeds	Use sterile, commercially prepared feeds
	Drugs like antibiotics and laxatives	Review drug prescription
Nausea or vomiting	Increased rate of infusion	Decrease the rate of infusion and increase it as tolerated
	Delayed gastric emptying	Encourage lying on right side Use prokinetics
	Constipation	• Adequate fluid intake • Provide diet rich in fiber
	Medications given along with the feed	Increase time gap between feeds and medications
	Psychological factors	
Regurgitation or aspiration	Gastroesophageal reflux	• Give thick feeds • Deliver the feed by continuous infusion • PPI • Feed through nasojejunal tube
	Tube dislodgement	Correct the tube position and check the position before each feed
	Increased rate of infusion	Decrease the rate of infusion
	Intolerance to bolus feeds	Give frequent small feeds or deliver the feed by continuous infusion

magnesium, and phosphate and monitoring them daily, monitoring the cardiovascular status clinically and by ECG and echocardiography are essential strategies of prevention.

Enteral feeding regimen

- Initial enteral feeding regimen should be limited in terms of volume and energy content to provide around 75% of requirements in severe cases

  <7 years:60 kcal/ kg/ day

  7-10 years:50 kcal/ kg/ day

  11-14years: 45 kcal/ kg/day

  15-18 years:40 kcal/ kg/ day

- If initial intake is tolerated, this may be increased over 3 to 5 days

- Frequent small feeds is recommended with an energy density of 1 kcal/mL to minimise fluid overload
- Protein intake may start at 0.6 to1g/ kg/ day and increase to 1.2 to 1.5 g/kg/day
- Supplements are given as follows:

  Sodium: 1 mmol/ kg/day

  Potassium: 4 mmol / kg/ day

  Magnesium: 0.6 mmol/ kg/ day

  Phosphate up to 1 mmol/ kg/ day intravenously and up to 100mmol/ kg/ day orally for children older than 5 years of age
- Hypocalcemia should be corrected
- Thiamine, riboflavin, folic acid, ascorbic acid, pyridoxine and fat-soluble vitamins must be supplemented and additional trace elements may also be added.

Bacterial contamination of feeds[4]

Microbiological contamination of enteral tube feeds in hospital is common. The organisms isolated from feeds include coagulase-negative staphylococci, streptococci and Gram-negative bacilli. Inadequate hand washing techniques and poor attention to hygiene while handling the feed containers are the risk factors involved. Vulnerable population includes immuno compromised children and those with impaired gastric acid barrier. Bacterial contamination of commercial products may occur while opening and decanting feeds from source containers. Hence, frequent feeds may be unwise unless the administration sets are also changed. Commercially available ''ready to hang'' closed enteral feeding systems are designed to limit handling. Though it reduces the risk of microbial contamination due to poor handling procedures, retrograde contamination of the set may still occur and the risk of contamination increases with the duration of feed. Based on limited evidence, it is suggested that feed hang time should not exceed 4 hours. Bacterial contamination of feeds can be prevented by preparing feeds and setting up feeding systems in a clean environment with scrupulous attention to hygiene.

Drug-nutrient interactions

Medications to be taken orally are often given via an enteral feeding tube in critically ill children. Crushing or dissolving medications for administration through enteral feeding tube can affect drug bioavailability and also leads to tube occlusion. Absorption, metabolism and the excretion of drug may be affected by enteral feeds and its components. Bioavailability of the medications is improved by flushing the feeding tube with water before and after drug administration. Liquid drug preparations with high osmolality can provoke diarrhea when given via a jejunal tube if not first diluted.

Recommendations for administering medications via enteral feeding tube in critically ill children:

- Prefer alternate route of drug delivery if possible
- Avoid giving enteric coated and slow-release tablets via feeding tube.
- Prefer liquid preparation if the tube is the only route available.
- Tablets must be thoroughly crushed and mixed with water and the contents of gelatin capsules can be dissolved in warm water.
- Flush the tube with water before and after administration of each medication.

Table V. Comparison of bolus feeding and continuous feeding

Bolus feeding	Continuous feeding
• More physiological, economical and does not require a feeding pump for infusion	• Requires feeding pump for accurate delivery and to aid intestinal adaptation.
• Provides cyclical surges of gastrointestinal hormones and hence has trophic effect on intestinal mucosa	• Has lower probability of emesis compared to bolus feeding
• Allows the feeding patient to freely perform his activities	• More effective at enteral balance and weight gain
• Carries risk of osmotic diarrhoea and emesis.	• Can be given overnight to avoid disruption of day time schedule and oral intake.

Table VI. Feeding volume according to bolus and continuous feeding

	Bolus feeding			Continuous feeding		
	0-12 mo	1-6 Yrs	>7Yrs	0-12 mo	1-6 Yrs	>7Yrs
Initiation	10-15 mL/kg every 2-3 hours	5-10 mL/kg every 2-3 hours	90-120 mL/kg every 3-4 hours	1-2 mL/kg every hour	1 mL/kg every hour	25 mL/kg every hour
Advance	10-30 mL per feeding	30-45 mL per feeding	60-90 mL per feeding	1-2 mL/kg every 2-8 hours	1 mL/kg every 2-8 hours	25 mL every 2-8 hours
Suggested tolerance volumes	20-30 mL/kg every 4-5 hours	15-20 mL/kg every 4-5 hours	330-480 mL every 4-5 hours	6 mL/kg every hour	1-5 mL/kg every hour	100-150 mL every hour

Bolus versus continuous feeding

Each has its own indications and advantages which are listed in Table V.

Feeding volumes in various age groups for both bolus and continuous feeding is shown in Table VI.

Role of pre-biotic, probiotic and symbiotic organisms

Probiotics are viable bacteria or yeast microorganisms that can benefit patients when added as dietary supplements Prebiotics are fermentable and soluble dietary fibers such as inulin and fructo oligosaccharides which stimulate the growth or activity of beneficial bacteria in the gut, thereby improving host health. Symbiotic formulations contain both products. The inclusion of symbiotics in enteral formula resulted in an increase in faecal bacterial groups, previously reported to have beneficial effects. But, evidence is still lacking to recommend the use of prebiotics, probiotics, or symbiotics in critically ill children.

Use of prokinetic agents

Abnormal gastric motility is common in critically ill children and it prevents the achievement of nutritional goals. Large gastric residual volume with increased risk of aspiration of gastric contents occurs secondary to delayed gastric emptying. Role of prokinetics in management of feed intolerance still remains unclear. Agents like erythromycin, metoclopramide and domperidone have been used alone or in combination with variable results and their use is not risk free. Domperidone use is associated with long QT syndrome. Evidence is limited to support the use of prokinetic drugs for feed intolerance or to facilitate enteral access device placement as per A.S.P.E.N guidelines on pediatric nutrition. Methyl naltrexone, mitemcinal, ghrelin agonists and dexloxiglumide are newer agents available with potential advantages but further research is needed to prove their efficacy and safety.

Role of nutrition support team (NST) in PICU

Nutrition therapy in PICU should be guided by NST, which is constituted by a pediatrician specialized or interested in gastroenterology or nutrition and a dietician along with pharmacist and nurses. They will plan and execute the following aspects of care: nutritional status assessment at admission and during PICU stay, estimation of nutritional requirements, route of administration of nutrition, use of insulin and establishing a day-to-day nutritional prescription. NSTs can provide knowledge updates for clinical staff to improve the delivery of nutrition in critically ill children.

Role of feeding protocols

Feeding protocols aid in implementing early enteral feedings in critically ill children. Its implementation could be assisted by a specialized nutrition support team. Feeding protocols may identify caloric goals, route and time of initiation of EN, type of formulation, rate of increase in infusion rate and time to reach caloric goal. Evidence is lacking to support the use of feeding protocols in PICU.

Immuno-nutrition in critically ill children

Immuno-nutrition are specific nutrients aimed at modulating the inflammatory or immune response. Nutrients with immune modulating effects include arginine, glutamine, aminopeptides, omega 3 fatty acids and antioxidants. RCTs employing immune nutrition in critically ill children have not demonstrated positive treatment effect till date, and hence its routine use in critically ill children is not recommended with available data.

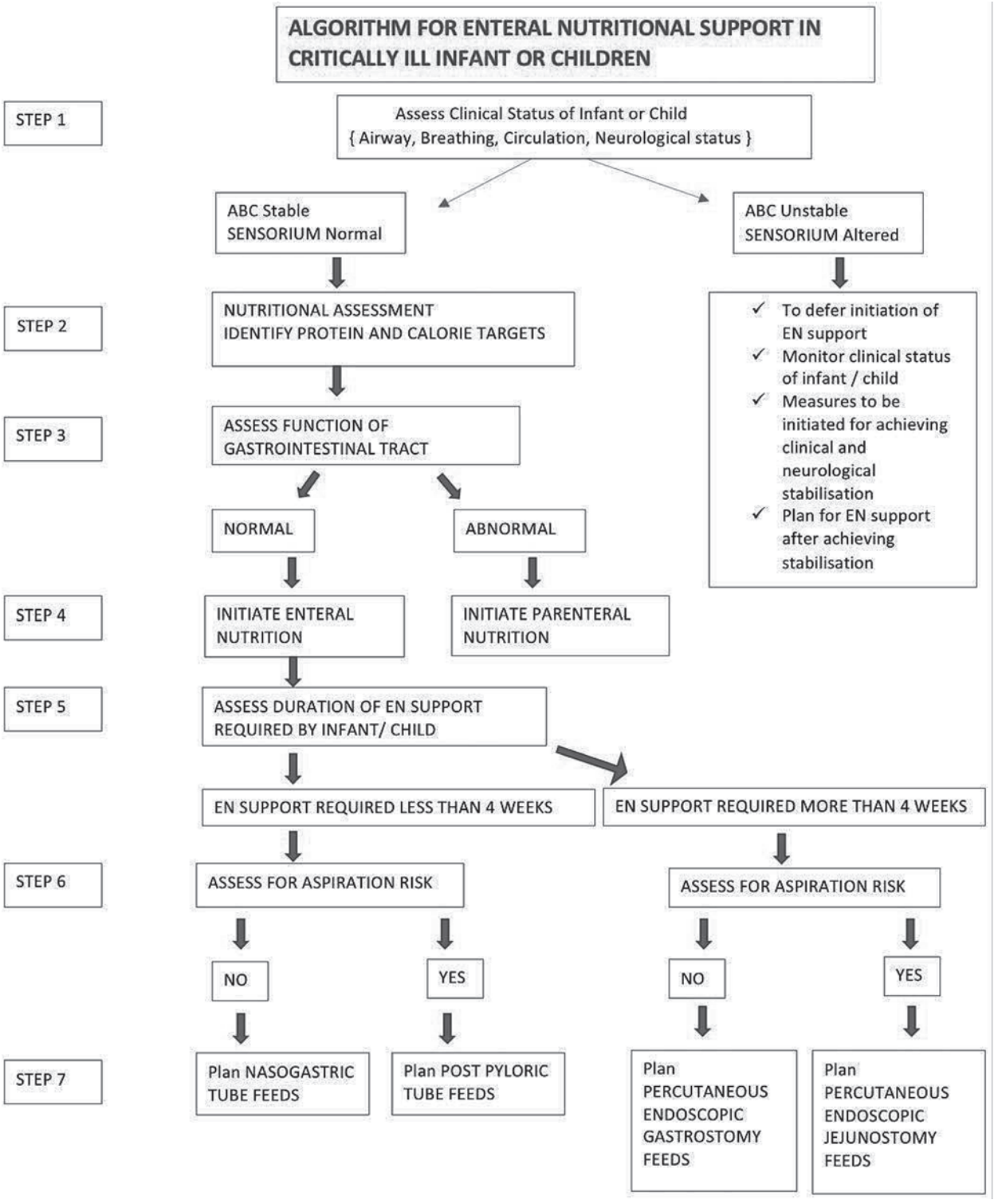

Fig.1. Algorithm for enteral nutritional support in critically ill infant or children

Monitoring during EN

- Monitor weight of the child daily as it is a valuable indicator of nutritional status. Document height or length of the child whenever possible. Interpretation of weight should be done in the context of fluid therapy, volume overload and diuresis.
- Monitor daily calorie and protein intake with guidance from dieticians to decide on appropriate protein and caloric intake.
- Monitor abdominal girth periodically following feeds as it is a good indicator of feed intolerance.

- Measurement of gastric residual volume(GRV) before next feed is an indirect indicator of feed intolerance. Evidence is lacking to guide this practice and its use can lead to unnecessary feed interruptions. GRV should always be interpreted only in context of other signs of feed intolerance like abdominal distension and vomiting. No evidence supports that monitoring GRV can prevent aspiration in pediatric patients.
- Document stool frequency , consistency and quantity daily
- Confirm and document the placement and position of nasogastric tube before each feed
- Serum levels of electrolytes, protein, triglycerides, urea, lactate, ammonia and blood gas should be monitored at least once a week.
- The role of Critical Care Enteral Nutrition (EN) Practice Bundle comprising nutrition assessment at admission, identification of individual caloric goal, early initiation of EN, elevation of head of bed and use of an institutional guideline to maintain optimal EN is being studied.

Algorithm for enteral nutritional support in critically ill infant or children is shown in Fig.1.

Points to Remember

- ***Among children admitted in PICU, common conditions which predispose to under nutrition are congenital heart disease, chronic lung diseases and cystic fibrosis, neuromuscular diseases and genetic syndromes requiring long term nutritional support***
- ***Benefits of enteral nutrition include its simplicity and ability in maintaining physiological and functional integrity of gastrointestinal mucosa.***
- ***Absolute contraindications to enteral nutrition include, paralytic or mechanical ileus, intestinal obstruction, bowel perforation and necrotizing enterocolitis.***
- ***Disease specific formulations are available for specific conditions such as renal disease or hyperammonemia and cow's milk protein allergy (with reduced proteins, extensively hydrolyzed protein or amino acid formulas).***
- ***Complications are minimal and include tube dislodgement, aspiration and refeeding syndrome.***
- ***Monitoring of vital signs, growth parameters, abdominal girth and biochemical parameters are essential to identify the complications***

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NEWS & NOTES

DRUG PROFILE

DOSAGE ADJUSTMENTS IN PATIENTS WITH RENAL IMPAIRMENT - ANTIBIOTICS - PART 1

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Abstract: *Dosages of commonly used antibiotics need to be modified in renal impairment to ensure antimicrobial efficacy and to avoid toxicity. Based on the pharmacodynamics of the antibiotic, modifications may be either by adjusting dosage itself or by adjusting the the interval between doses . With antibiotics exhibiting time dependent killing properties, dosage adjustment is required Whereas,with those exhibiting concentration dependent bacterial killing like aminoglycosides, dosing interval needs to be adjusted. In this article, dosage adjustments for beta lactams, cephalosporins, carbepenems and macrolides are discussed.*

Keywords: *Renal impairment, Glonurelar filtration rate, Creatinine clearance, Dosage adjustment.*

Dose adjustment of antibiotics in renal impairment is usually stressed in the intensive care settings. But commonly used antibiotics in general practice also need dose adjustments in renal impairment. In this article we discuss the renal dose modifications of antibiotics used in pediatric general practice. This is essential to maintain the antimicrobial efficacy and at the same time, to prevent toxicity.

There are two ways of adjusting the dosage-interval adjusting or dose adjusting. They are utilised depending on the antibiotic characteristics. Concentration-dependent killers like aminoglycosides needs interval adjustment whereas time-dependent killers like fluroquinolones need dose adjustment. Some less toxic antibiotics like beta lacatams can be either dose or interval adjusted whereas few do not need any dose modification.

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Beta lactam antibiotics

Benzyl penicillin

Benzyl penicillin is water soluble and 60-90% of dose is excreted by renal elimination, 10% by glomerular filtration and 90% by tubular secretion. 10-30% of a dose is metabolized in the liver to penicilloic acid. Sixty percent is protein bound, its molecular weight is 3 334.39 daltons and half-life (t½): Infants and children: 0.5-1.2 hours, neonates >14 days old: 0.9-1.9 hours, 7-13 days old: 1.2-2.2 hours, < 6 days old: 3.2-3.4 hours, and in renal impairment it is 10 hours. The dosage for severe infection more than 4 weeks of age is 50 mg/kg (max 2.4g) IV every 4-6 hours and that of mild infection is 25 mg/kg IV 6th hourly.[1]

In GFR>50 mL/min - no dose adjustment is needed; between 10 to 50 mL/min, give normal dose at 8th hourly interval and in GFR <10, give normal dose at 12 hrly interval.

It is dialysable and is removed by HD, PD and CRRT- Give normal dose every 12 hrly, post dialysis in case of HD. Increased incidence of neurotoxicity (seizures) is reported with renal impairment.[2]

Ampicillin

Ampicillin is a semisynthetic aminopenicillin and is widely used. It is excreted mainly in the bile and urine and 60-80% is excreted unchanged in the urine. The conventional dosage is 50 mg/kg 6th hourly. The t½ of ampicillin in children is 1-1.8 hour, neonates 8-14 days old - 2.8 hours, 2-7 days old - 4 hours and in renal impairment - 7-20 hours. No dose adjustment is needed above GFR of 20. Between a GFR of 10 and 20, give normal dose 8 hourly and if below 10, give 12 hourly. Ampicillin is dialyzed, around 40% of the dose is removed by HD. Give normal dose every 12 hours, administered after dialysis session. It is not removed through PD. In CRRT, give normal dose over 6 to 8 hours.[3]

Cloxacillin

Infections with beta lactamase producing staphylococci warrant usage of cloxacillin. It is metabolized and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. Biliary excretion is minimal.

Dosage - Newborn <7 days: 50-100mg/kg/day IV/oral in 2 divided doses; 7-21 days 75-150mg/kg/day in 3 divided doses, > 21 days 100-200 mg/kg/day in 4 divided doses. May be increased to 100mg/kg/dose in severe infection (meningitis, cerebral abscess, staphylococcal osteitis). Orally used only for minor infections. Children 50-100 mg/kg/day IV/IM in 4 divided doses (max single dose 1 gm - may be doubled in severe infection); < 1 yr 250mg/day Oral, 1-5 yr 500mg/day, 5-18 yr 1gm in 4 divided doses. Doses may be doubled in severe infection.

Cloxacillin is not dialyzed and no dose adjustment is needed till GFR of 10. Use normal dose every 8 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m^2 .

Co-amoxiclav(Amoxycillin Clavulanic acid)

The pharmacokinetics of amoxicillin and clavulanic acid are similar - both have low levels of serum binding; about 70% remains free in the serum. Amoxicillin is largely excreted through the kidneys unchanged and a small fraction is excreted in the bile. Clavulanic acid is 50-70% metabolized, with approximately 40% eliminated via the kidneys, primarily by glomerular filtration.

Dose is calculated on amoxycillin content. Neonates - 30mg/ kg/day in 2 divided doses. Children 20-45 mg/kg in 2-3 divided doses.

No dose adjustment is required till GFR of 30. Between 10 -30 ml/min, give normal dose initially followed by 50% dose 12 hourly. In GFR<10, give normal dose initially followed by 50% dose 24 hourly.[4] Regarding oral administration, in GFR<10, give 100% of dose at 12 hrly intervals.

In the setting of HD/PD - give normal initial dose followed by 50% of dose 24 hourly and in CRRT, after normal initial dose, 50% dose, 12th hourly.

Piperacillin Tazobactum

Piperacillin is excreted unchanged in the urine. It also undergoes metabolism to a minor microbiologically active metabolite. Tazobactam is metabolized to a single inactive metabolite, with 80% of a dose appearing in the urine unchanged. Both piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion. The t½ of piperacillin in children 2-12 years: 0.7 hours; and of tazobactum 6-12 years: 0.9 hours, 2-5 years: 0.8 hours; while in renal failure in adults it is 4-6hours for piperacillin and 7 hours for tazobactum.

Dosage - Hospital-acquired pneumonia, septicemia, complicated infections involving the urinary-tract, skin and and soft tissues: IV infusion - Neonate: 90 mg/kg 8 hrly; 1 month - 12 years: 90 mg/kg 6th-8th hourly (max.4.5 g/dose once in 6 hrs); 12-17 yrs: 4.5 g 8 hrly; increased if necessary to 4.5 g 6 hrly. For acute exacerbation of bronchiectasis used above I/12 age in same doses as mentioned and for infections in neutropenic child at 90 mg/kg 6 hrly (max. per dose 4.5 g). Complicated intra-abdominal infections: IV infusion - 2-11 yrs: 112.5 mg/kg 8 hrly (max. per dose 4.5 g); 12-17 yrs: 4.5 g 8th hrly; increased if necessary to 4.5 g 6th hrly. Note: Piperacillin with tazobactam is not licensed for use in children under 12 years (except for children 2-12 years with neutropenia).

In GFR above 50 mL/min, no dose adjustment is required.[5] Between 30 and 50 mL/min GFR, administer 50 mg/kg 6th hourly and in GFR<30,administer 50 mg/kg 8th hourly. It is removed through HD/CRRT but not through PD. Administer supplementary dose post HD (50-75 mg/kg 12 hourly). In PD give 50-75 mg/kg 12 hourly. In CRRT, administer dose of 35-50 mg/kg 12 hourly.

Ticarcillin clavulanic acid

The major route of elimination for both ticarcillin and clavulanic acid is renal excretion.[6] Approximately 60-77% of a dose of ticarcillin and 35-45% of clavulanic acid is excreted unchanged in the urine.

The dosage in infections due to Pseudomonas and Proteus spp-IV infusion: preterm (< 2 kg): 80 mg/kg 12 hrly; preterm (>2 kg): 80 mg/kg 8hrly, increased if necessary to 6hrly; term newborn and child upto 40kg: 80 mg/kg 8 hrly; increased if necessary to 6 hrly; child > 40kg: 3.2 g 6th to 8 hrly, increased to 4 hrly for treated more severe infections.

Between GFR of 30-60 mL/min, give normal dose at 8 hourly intervals; between 10 and 30 mL/min, give dose of 50 %-100% dose 8 hourly and in GFR <10 ml/min, give 50% to 100% dose 12 hourly.

It is removed through HD and CRRT but not removed through PD. Give 50% -100% of normal dose 12 hrly in HD /PD and 8 hourly in CRRT.

Cephalosporins

Cephalosporins are chemically related to penicillins; the nucleus consists of a beta lactam ring fused to a dihydrothiazine ring. They are divided into 4 generation and lately added members have been designated 5th generation.

1st generation cephalosporins

Cephalexin

Well absorbed from GI tract. Bioavailability of 75-100% - only slightly reduced by food. Reduced absorption in young children - upto 50% in neonates. Peak levels appear 1 hour after dose in older children, within 2 hours in children 9-12 months of age, and 3 hours in infants <6 months old. Half-life: 1 hour in older children, 2.5 hours in infants aged 3-12 months, 5 hours in neonates. Widely distributed in body. Does not enter CSF. Not metabolized. Appears in bile in therapeutic concentration, 80% excreted in urine within 6 hours of a dose.

Dosage: Children 25-100 mg/kg/24 hr in 3-4 divided doses; adolescent 250-500 mg 4 times daily (maximum 4 gm/24 hr.

Reduce dose in severe renal impairment (creatinine clearance <10mL/minute/1.73m^2) by reducing dose frequency. Removed by dialysis thus an additional dose may be required after dialysis.

Cefazolin

Peak serum concentrations attained 1-2 hours post intramuscular injection; it is 74-86% protein bound and is excreted unchanged in the urine. In the first six hours approximately 60% of the drug is excreted in the urine and this increases to 70%-80% within 24 hours. The t½ is approximately 1.8 hours following IV administration and approximately 2.0 hours following IM administration.

Dosage: 7 days or younger: 25 mg/kg IV or IM every 12 hours; 8 to 28 days: Up to 2 kg: 25 mg/kg IV or IM every 12 hours; > 2 kg: 25 mg/kg IV or IM every 8 hours; 1 month or older: mild to moderate infections: 25 to 50 mg/kg/day IV or IM in 3 divided doses (maximum dose: 3 g/day); severe infections: 100 to 150 mg/kg IV or IM in 3 divided doses (maximum dose: 6 g/day).

Renal impairment: CrCl 40 to 70 mL/min: 60% of usual daily dose given 12th hourly, CrCl 20 to 40 mL/min: 25% of usual daily dose given 12th hourly, CrCl 5 to 20 mL/min: 10% of usual daily dose every 24 hours.

2nd generation cephalosporin

Cefuroxime

Peak levels reached 35-40 minutes after IM injection and the drug is excreted unchanged in the urine. Oral absorption is poor and requires presence of food to maximize absorption.

Dosage: Infections due to sensitive Gram-positive and Gram-negative bacteria - Orally (as cefuroxime axetil) - 3 months-2 years 10 mg/kg (max. 125 mg) twice daily; 2-12 years 15 mg/kg (max. 250 mg) twice daily; 12-18 years 250 mg twice daily; double the dose for severe lower respiratory-tract infections; 125 mg twice daily in lower UTI. IV, IV infusion, IM - <7 days age - 25 mg/kg 12 hrly; 7-21 days age 25 mg/kg 8 hrly; 21-28 days age - 25 mg/kg 6th hrly; severe infection in neonates give IV at double these doses. 1month-18 years 20 mg/kg (max. 750 mg) 8 hrly; increase to 50-60 mg/kg (max. 1.5 g) 6-8 hrly in severe infection and cystic fibrosis. Lyme disease - Orally - 3 mths-12 yrs 15 mg/kg (max. 500 mg) BD for 14-21 days (for 28 days in Lyme arthritis); 12-18 years 500 mg BD for 14-21 days (for 28 days in Lyme arthritis) Surgical prophylaxis - IV - 1 month-18 years 50 mg/kg (max. 1.5 g) up to 30 min before procedure; up to 3 more doses of 30 mg/kg (max. 750 mg) may be given IM/IV 8 hrly for high-risk procedures.

No dosage modification is needed for GFR of 30-50 mL/min; 25-50 mg/kg /dose 12 hrly and 24 hrly if GFR is 10-30 and <10, respectively.

3rd generation cephalosporin

Ceftriaxone

Ceftriaxone is 90% protein bound and eliminated mainly unchanged, approximately 60% being excreted in the urine, by glomerular filtration. The rest of the dose is excreted via the biliary and intestinal tracts.

Dosage: Neonates 50-75 mg/kg once daily IM/IV. Infuse over 10-30 min. Avoid in premature, neonates with acidosis or hyperbilirubinemia . Children 50-75 mg/kg once daily IV/IM. Meningitis loading dose 75mg/kg followed by 80-100mg/kg/24 hrs once or divided 12hrly. Maximum 4gm/day.

There is no dose adjustment in GFR>10. In GFR <10 mL/min, usual dose given at 24 hourly. Ceftriaxone is not dialyzed and the dose on HD, PD and CRRT is same as above.[6]

Cefotaxime

Cefotaxime is partially metabolized and is predominantly eliminated by renal excretion. Approximately 60% of a dose is excreted unchanged in the urine, whereas rest is excreted as the microbiologically active metabolite desacetyl-cefotaxime. The usual dosage is 50 mg/kg/dose 6 hourly.

No dose adjustment is needed above GFR of 5 mL/min. In GFR below 5 mL/min, give 1st dose as normal and continue the subsequent doses as 50 % at the same frequency. It is partially removed in HD and so continue the dosages as suggested for less than 5 mL /min GFR. In CRRT give normal dose at 8 hourly intervals. Administration of high-dose cephalosporins in patients with renal impairment may result in encephalopathy. The dose adjustments of the rest of 3rd generation cephalosporins are given in Table I below.[7-9]

Fourth generation cephalosporin

Cefepime

Cefepime is metabolized to N-methylpyrrolidine and later in to its oxide. This undergoes renal excretion mainly through glomerular filtration.[10]

Children > 2 yrs age: IV 50 mg/kg every 8 h (maximum 2 g/dose). Intraperitonial 15mg/kg/dose. In peritoneal dialysis associated with peritonitis 1000mg/24hrs.

Between GFR 50-10 mL/min, give 50 mg/kg 24 hourly and below 10 ml/min, give 50 mg/kg 48 hourly. The dose on HD and PD are 50 mg/kg 24 hourly and on CRRT is 50 mg/kg /dose 12 hrly (the regular dose). Cefepime is known to cause neurological manifestations including seizures and myoclonus when administered in renal impairment. This is considered to be due to concentration related GABA antagonism.[11]

Monobactam

Aztreonam

Approximately 6 to 16% metabolized to inactive metabolites by hydrolysis of the beta-lactam bond, resulting in an open-ring compound; protein binding of 56% independent of dose; t ½ of 1.7 hours (1.5 to 2.0) and 2.1 hours with normal renal function, independent of the dose and with renal impairment, respectively and excreted in the urine about equally by active tubular secretion and glomerular filtration, complete after single IV administration within 12 hours.

Dosage: IV over 3-5min or IV infusion - <7day old-30mg/ kg 12th hrly; rest of neonatal period and upto 12yr - 30mg/ kg 6-8th hrly. In severe infection and cystic fibrosis in 2-12yr olds - may increase upto 50mg/kg 6-8th hrly (max 2gm 6th hrly); 12-18yr - 1gm 8th hrly or 2gm 12th hrly (severe infection with P aeruginosa or pulmonary infection in cystic fibrosis). Nebulisation for P. aeruginosa pulmonary infection in cystic fibrosis 6-17 years: 75 mg 3 times a day for 28 days, doses to be administered at least 4 hours apart.

Renal impairment - No dose modification required in GFR above 30 mL/min. In GFR between 10-30, administer 15-20 mg/kg/dose 8 hourly. In GFR <10 mL/min give 7.5-10 mg/kg/dose 12 hourly

In HD and PD give dose as suggested for GFR <10, In CRRT, give normal dosage.

Carbapenems

Imipenem-cilastin

Cilastatin is the enzyme inhibitor which blocks the metabolism of imipenem in the kidney thereby increasing the plasma concentration. When imipenem and cilastatin are administered concurrently, approximately 50-70% of the imipenem dose and 75% of the cilastatin dose is

Table I. Dosage adjustment as per GFR

Drug	Normal dose	GFR 30-50mL	GFR 10-30mL	GFR <30 mL
Ceftazidime (IV)	25-50 mg/kg 8 hrly	1st normal dose then 50 mg/kg 12 hrly	1st normal dose then 50 mg/kg 24 hrly	1st normal dose then 50 mg/kg 48 hrly
Cefoperazone (IV)	25-50 mg/kg 6th hrly	same dose q8hrly	same dose 12 hrly	same dose 12 hrly
Cefixime (Oral)	5 mg/kg/dose 12 hrly	no change	no change	4mg/kg/dose 12 hrly

excreted unchanged in the urine by both glomerular filtration and tubular secretion. Imipenem also undergoes hydrolysis of the beta-lactam ring to form a microbiologically inactive metabolite. Half-life is approximately 1 hour in healthy older children, 1.5-2 hours in younger children and up to 3 hours in premature infants. Imipenem is widely distributed in many body tissues but levels are low in the CNS.

Dosage: Newborn IV 20mg/kg/dose in the frequency - < 7days, 7-21 days and >21 days at 2 times, 3 times and 4 times daily respectively. Children - IV <3months 80mg/kg/day, 3month - 12 yr 60mg/ kg/day, 12-18 yr 2gm/ day in 4 divided doses. (max/dose <12 yr 500 >12 yr 1gm). Children - IV <3months 80mg/kg/day, 3month - 12 yr 60mg/ kg/day, 12-18 yr 2gm/day in 4 divided doses. (max dose <12 yr 500 >12 yr 1gm).

In GFR, 30 give 50% dose 12 hourly. Avoid in GFR <10 unless dialysis is planned. In HD, give normal dose 12 hourly. In PD give 50% of dose 24 hourly. In CRRT, give normal dose 8 hourly. Imipenem has seizure potential and has to be carefully used in renal impairment.

Meropenem

Approximately 70% of Meropenem is excreted unchanged in the urine over 12 hours. The only metabolite of meropenem is microbiologically inactive. Half-life is approximately 1 hour in healthy older children, 1.5-2 hours in younger children and up to 3 hours in premature infants. 2% is plasma protein bound.

Dosage: Newborn - 40mg/kg/day in 2 divided doses <7 days and in 3 divided doses >. 7 days. Double dose in meningitis and severe infection. Children UTI, gynecological, skin and soft tissue infection - 30mg/kg in 3 divided doses (max 500mg/dose) Pneumonia, peritonitis, neutropenia, septicemia - 60mg/kg/ day in 3 divided doses (max 1gm/dose) Meningitis and life threatening infections - 120mg/kg/day in 3 divided doses (max 2gm/dose).

No dose adjustment above GFR of 50 mL/min. In GFR between 20-50, administer normal dose at 12 hourly intervals. In GFR 10-20, give 50% of dose at 12 hourly intervals. In GFR <10, give 50% dose 24 hourly. In HD and PD, administer as in GFR <10. In CRRT, administer normal dose 12 th to 8th hourly depending on the severity of infection.

Macrolide antibiotics

These antibiotics have a macrocyclic lactone ring with attached sugars. Erythromycin is the first member, Clarithromycin, Roxithromycin and Azithromycin are the new additions.

Erythromycin

Erythromycin is 905protein bound and is metabolized principally by demethylation in the liver and excreted in the bile. Around 12-15% is excreted in the active form in the urine.Regular dosage is 10-15 mg/kg/dose 6th hourly. No dose adjustment needed above GFR of 10. In GFR<10, HD and PD, administer 50-75% of normal dose 6th hourly. No dose change in CRRT. Despite being predominantly hepatically metabolized,ototoxicity has been seen in patients with severe renal impairment and caution is warranted. Erythromycin may markedly elevate levels of other medications with hepatic metabolism by inhibiting CYP3A4.

Clarithromycin

Clarithromycin is 80% protein bound and undergoes first-pass metabolism to form a microbiologically active metabolite (14-hyroxyclarithromycin). Approximately 33% of clarithromycin and 11% of the active metabolite is excreted unchanged in the urine. The usual dose is 7.5-15 mg/kg/dose 12 hourly.No dose modification till GFR of 30.Below 30, administer 50% dose 12 hourly. No dose adjustment needed in HD, PD or CRRT

Azithromycin

Azithromycin has a long t1/2 and is largely excreted unchanged in the bile. Urinary excretion is around 10%. Normal dosage is 10-15 mg/kg/dose on day 1, then 7.5 mg/ kg/dose q 24 h on day 2-5 PO.No dose adjustment needed at any GFR or in any form of dialysis.

Points to Remember

- ***No dose modification is required with GFR > 30mL/min, while with lower GFRs, dose alteration or spacing out of doses is recommended. Modifications depend on the individual antibiotic.***
- ***Beta-lactam antibiotics are hydrophilic molecules and most beta-lactams are eliminated primarily through the kidneys.***
- ***For macrolides like erythromycin or azithromycin which are predominantly excreted in the bile, there is no dosage change in renal impairment.***

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CLIPPINGS

Pharmacokinetics and tolerability of intranasal or intravenous administration of nalbuphine in infants

Nalbuphine, an opioid analgesic agent, is often used to treat moderate to severe pain in children. It is used in children aged over 1.5 years at a dose of 0.1-0.2 mg/kg (maximal 10 mg) intramuscularly, intravenously or subcutaneously every 3-6 hours. Nalbuphine is also being frequently used in infants and neonates for good analgesia and a lower ceiling effect on respiratory depression in comparison with other opioid analgesic agents due to its unique pharmacological properties as a κ-receptor antagonist/μ-receptor agonist.

This prospective open-label study enrolled infants 1-3 months of age admitted to the emergency department, receiving nalbuphine for procedural pain management. Patients were allocated either to a single nalbuphine dose of 0.05 mg/kg intravenously or 0.1 mg/kg intranasally.....Neonatal Infant Pain Score was assessed during nalbuphine administration and the following interventions: venous access, urinary catheterisation, lumbar puncture.

Out of 52 study subjects receiving nalbuphine, 31 were eligible for analysis (11 intravenous, 20 intranasal).....Maximum serum concentration was observed 30 min after intranasal administration. During intravenous and intranasal nalbuphine administration, mild to no pain was recorded in 71% and 67% of study subjects, respectively.

This is the first study reporting clinical pharmacokinetics of intranasal nalbuphine in infants 1-3 months of age. It suggests an intranasal bioavailability close to 50% and was well tolerated.

Pfiffner M, Gotta V, Pfister M, Vonbach P, Berger-OlahE .Pharmacokinetics and tolerability of intranasal or intravenous administration of nalbuphine in infantsArchives of Disease in Childhood 2023; 108:56-61.

RADIOLOGY

SIGNS IN CHEST X-RAY

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Signs in chest X-ray, are described patterns in radiological images that bring to mind a specific condition or diagnosis. These descriptions are usually a word or phrase that either recounts or characterises a thing that is generally familiar. This makes it easy for the reader to memorise and learn to recognize image patterns leading to quick and easy diagnosis. Rarely it is in the name of the person who first made the observation. In this article some common signs are discussed.

Sail sign: The thymus is an important organ in childhood which assumes varying shapes. It is seen as a bulge in the upper mediastinum symmetrically on both sides or more prominent on one side. Since it is a very soft organ it can insinuate into the minor fissure giving a sharp edged triangular appearance on the right side. This is called the sail sign (Fig.1).

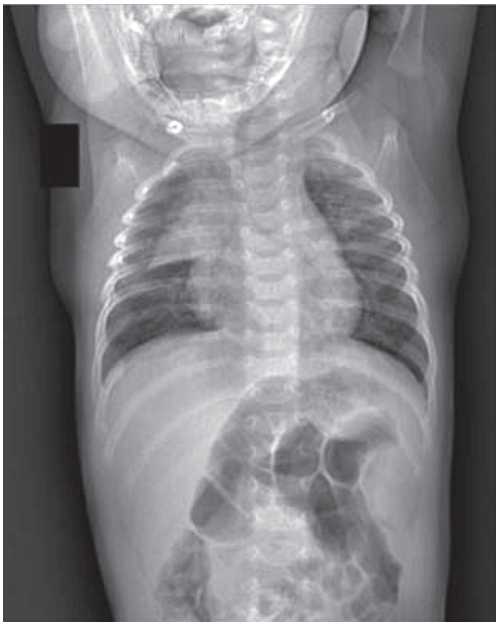

Fig.1. Sail Sign - Thymus

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Spinnaker sail sign: The thymus shadow is flush with the heart and both are referred together as the cardiothymic shadow. When the thymus is lifted away from the heart it denotes pneumomediastinum. Then it is called a spinnaker sail sign (Fig.2).

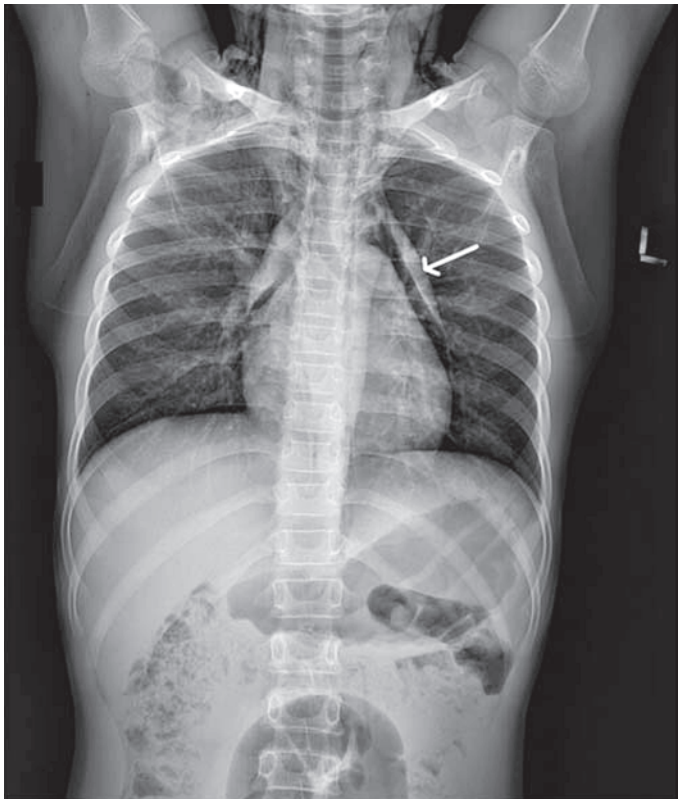

Fig.2. Spinnaker sail sign - Pneumomediastinum

The spinnaker sail (Fig.3) is the colourful triangular sail seen billowing out in the wind, as the yatch sails easily in the same direction as the wind. Sometimes the sign is a subtle and isolated finding in a child with dyspnea without the presence of more obvious subcutaneous emphysema. In such a situation appreciation of this sign is useful to make the diagnosis of pneumomediastinum.

Continuous diaphragm sign: Just as the thymus merges with the heart shadow, so also the inferior border of the

Fig.3. Spinnaker Sail

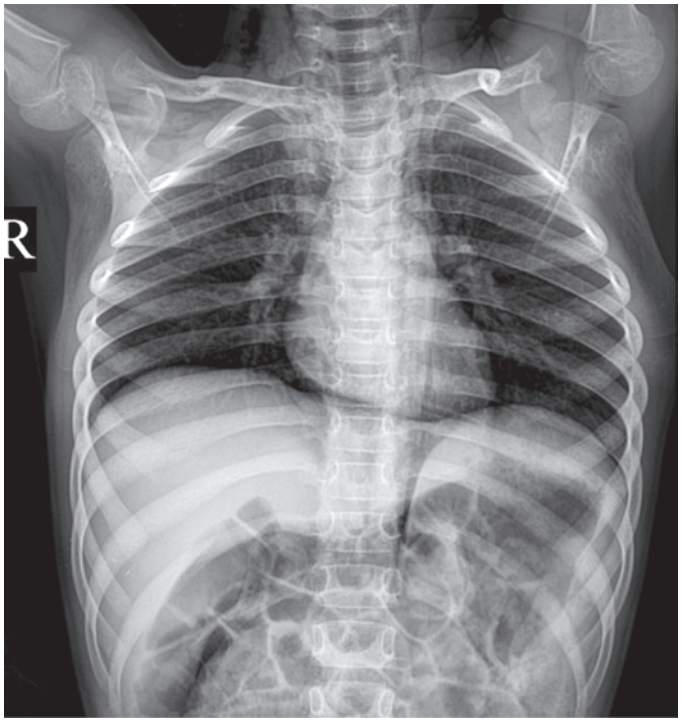

Fig.4. Continuous diaphragm sign - Pneumomediastinum

heart is merged with the diaphragm. The entire outline of the diaphragm is not normally seen. In case of pneumomediastinum, air insinuates in between and outlines the inferior border of the heart separate from the diaphragm. This is called the continuous diaphragm sign (Fig.4).

Air bronchogram sign: When the alveoli are opacified because they are filled with exudate or transudate air within the airways is called the air bronchogram sign, one of the first signs described in radiology (Fig.5). It should be remembered that the air bronchogram is also seen in

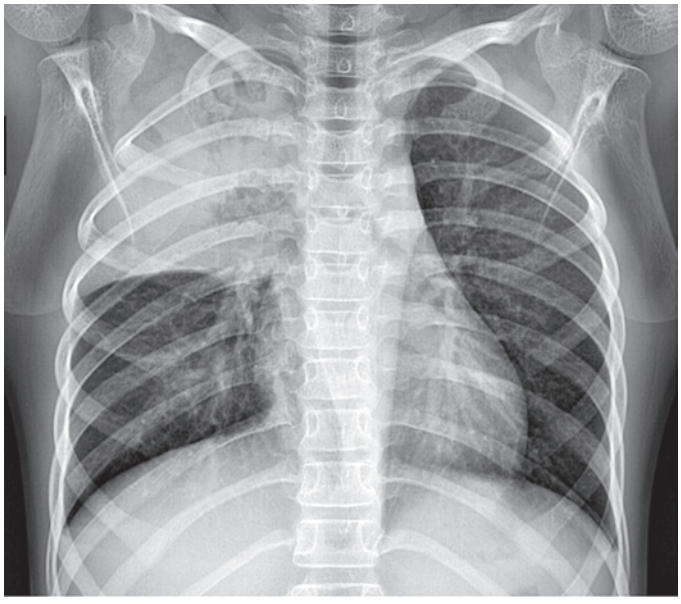

Fig.5. Air bronchogram - Seen within the white consolidation

atelectasis where black air in the airways are outlined against white airless lung.

Silhouette sign: Obliteration of outlines made by air as seen previously is known as the silhouette sign. The silhouette sign is useful for localising the plane of lesions. The word means outline in French, but as a sign it is used with the meaning of a loss of outline. Two adjacent shadows will merge with each other if they lie in the same plane. This can be seen in Fig.6 where the shadow of middle lobe pneumonia obscures the right heart border.

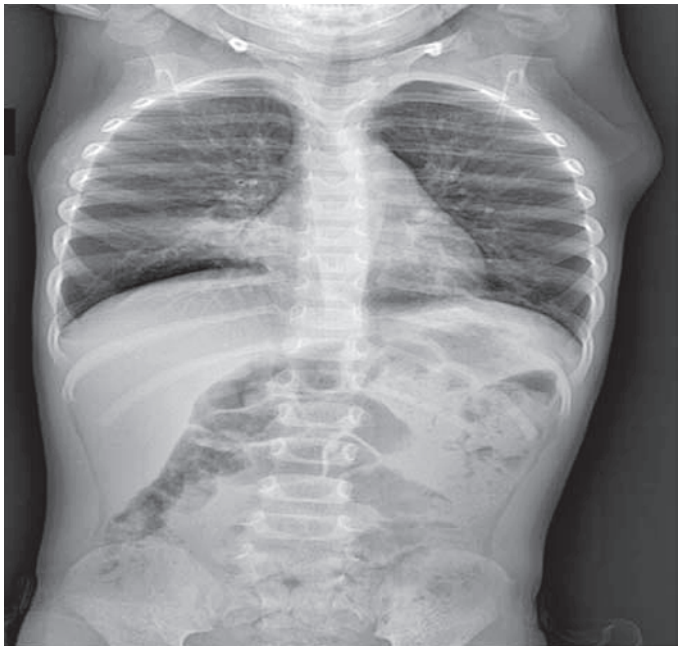

Fig.6. Silhouette sign-Middle lobe pneumonia

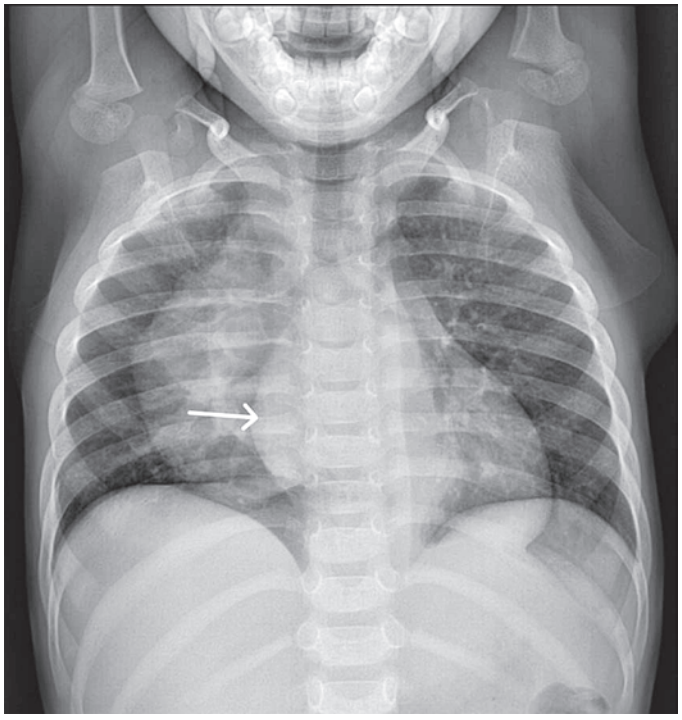

Fig.7.Silhouette sign- Not silhouetted because not in same plane

In Fig.7 the right heart border is seen to the right of the midline and there is another rounded shadow outer to the right heart border. Both outlines are seen, so the round mass shadow is clearly not in the same plane as that of the heart. ie it is not in the middle mediastinum. We infer that the mass is either in the anterior or posterior mediastinum. This is a thoracic neuroblastoma.

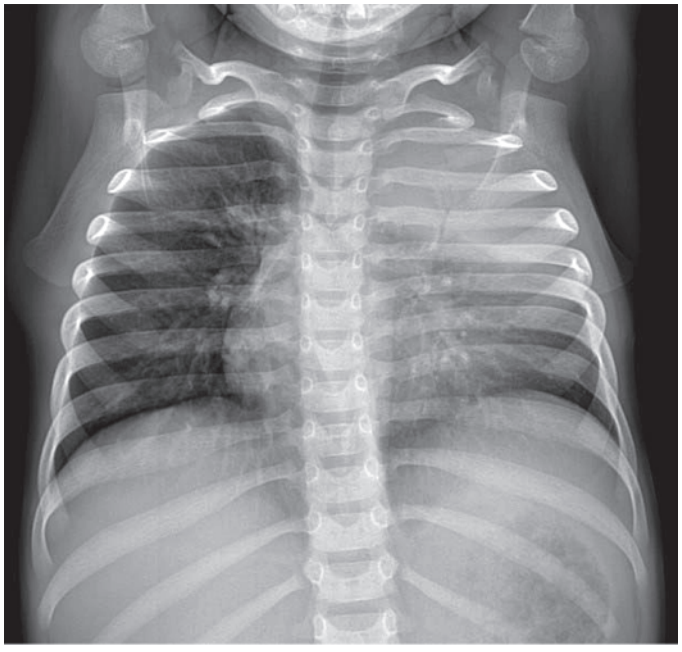

Fig.8. Silhouette sign- Left upper lobe and heart have lost their separate outlines

Likewise, the left upper lobe consolidation in Fig.8 has obscured the superior part of the left border of the heart.

Triangular sign: Fig.9 shows a triangular dense shadow internal to the left heart border. This is a classical sign of a collapsed left lower lobe. Collapse of the right lower lobe produces a similar picture on the right.

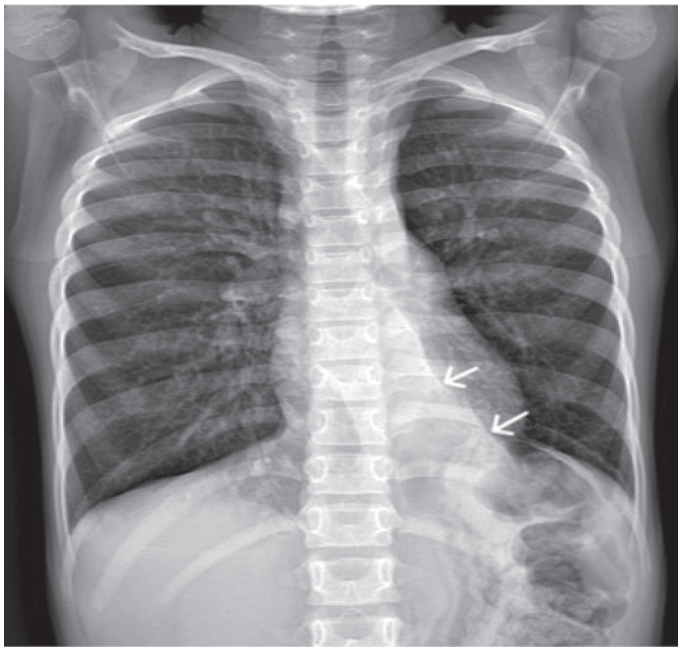

Fig.9.Triangular sign–Left lower lobe collapse

Bulging paraspinal stripe: the paraspinal line is the outlining of the paraspinal tissue by the air in the lung. A lateral displacement of this line indicates a paraspinal abscess or a paraspinal mass like a thoracic neuroblastoma (Fig.10). Routine chest X-rays have sometimes picked up serious pathology with the help of this sign.

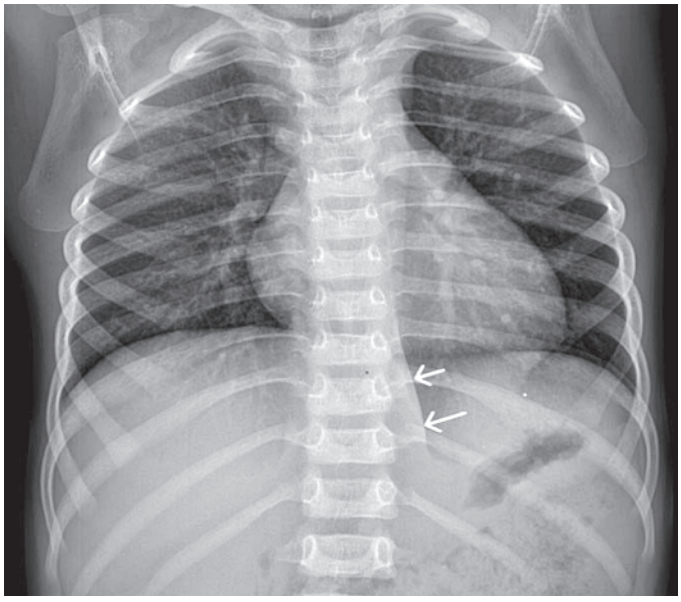

Fig.10. Bulging para spinal stripe - Note normal paraspinal line on right

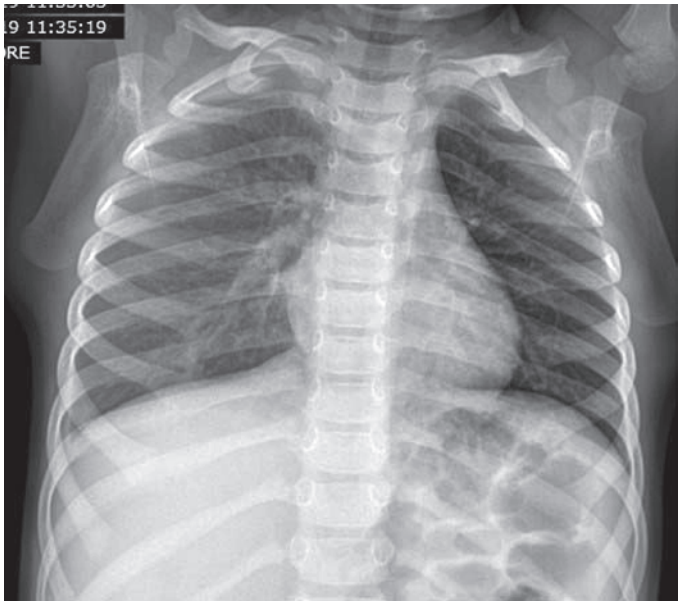

Fig.11. Hazy hemithorax - Little fluid in supine film

Meniscus sign: Little pleural fluid blunts the costo-phrenic angle in an erect chest film. In the supine film the fluid forms a thin film layering posteriorly causing a hazy hemithorax (Fig.11).

Moderate fluid accumulation in the erect chest X-ray assumes an upward concave margin that rises up towards the lateral chest. This is the meniscus sign (Fig.12). Massive fluid causes an opaque hemithorax.

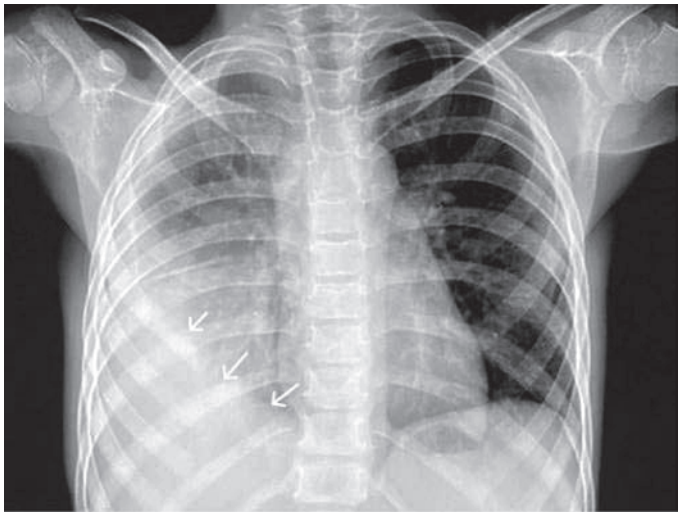

Fig.12. Meniscus sign - Pleural fluid in erect film

Deep sulcus sign: In a supine film pleural air collects in the non-dependent portions of the lung, anteriorly and basally. The air which has collected laterally deepens the lateral costophrenic angle producing the deep sulcus sign

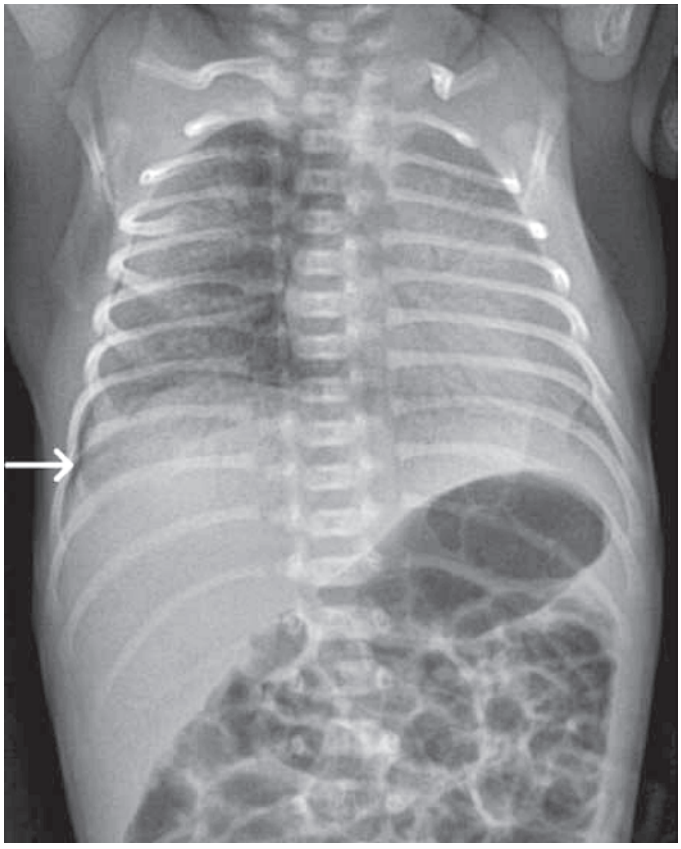

Fig.13. Deep sulcus sign - Pneumothorax in supine film

(Fig.13). This is especially useful in the neonate or in the critically ill patient as it is often difficult to identify pneumothorax in the supine position. The pitfall in this sign is hyperinflated chest in a rotated film.

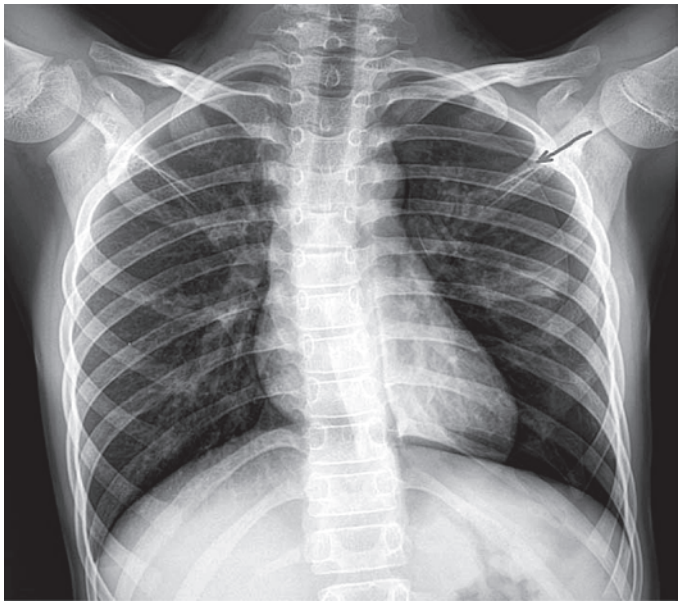

Fig.14. White line of pleura - Pneumothorax in erect film

Visceral pleural white line sign: Air in the pleural cavity separates the visceral and parietal pleura and outlines the visceral pleura that is seen as a white line in an upright film (Fig.14). Lateral to that there is air, without any bronchovascular markings, which is the hallmark of pneumothorax.

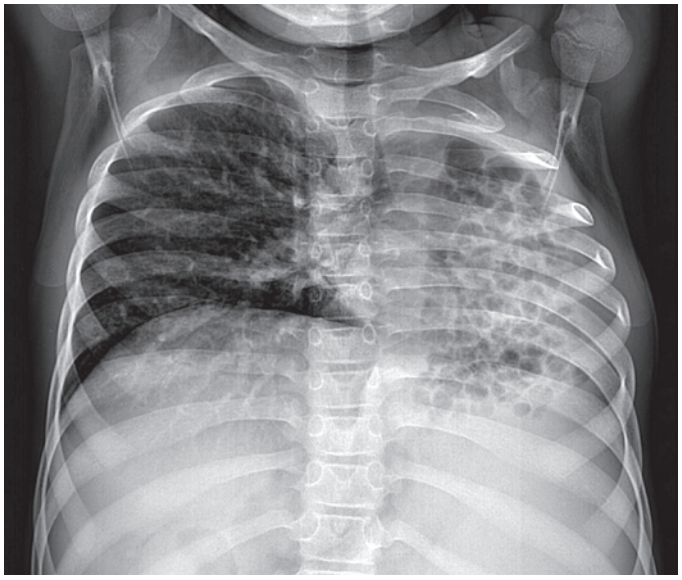

Fig.15. Honeycomb lung - Destroyed lung parenchyma

Honeycomb lung: Fig.15 shows the left lung that is replaced by multiple small round cystic spaces. There is no normal parenchyma on that side, but only the dilated air filled airways. This is the end stage of chronic inflammation and fibrosis.

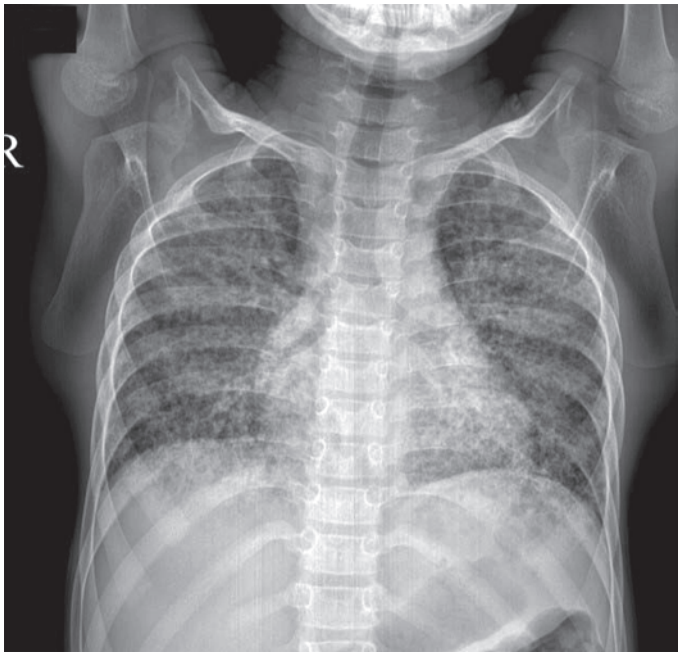

Fig.16. Snowstorm appearance - Miliary TB

Snowstorm appearance: In Fig.16 both lungs show multiple uniformly small nodular shadows likened to a snowstorm. This is a picture of miliary tuberculosis. The nodules represent tuberculous granulomas arising out of a sudden shower of bacilli distributed widely due to hematogenous spread. This sign is also used in metastases due to thyroid carcinoma.

Open mouth of a hippo: The hilum of the lung (Fig.17) is likened to the open mouth of a hippopotamus (Fig.18), the upper jaw being the upper branch of the pulmonary artery and the lower jaw being the descending branch of the pulmonary artery with lucent lung in between. In case of a hilar node this appearance is lost and a round shadow of the node is seen in the mouth of the hippo (Fig.19).

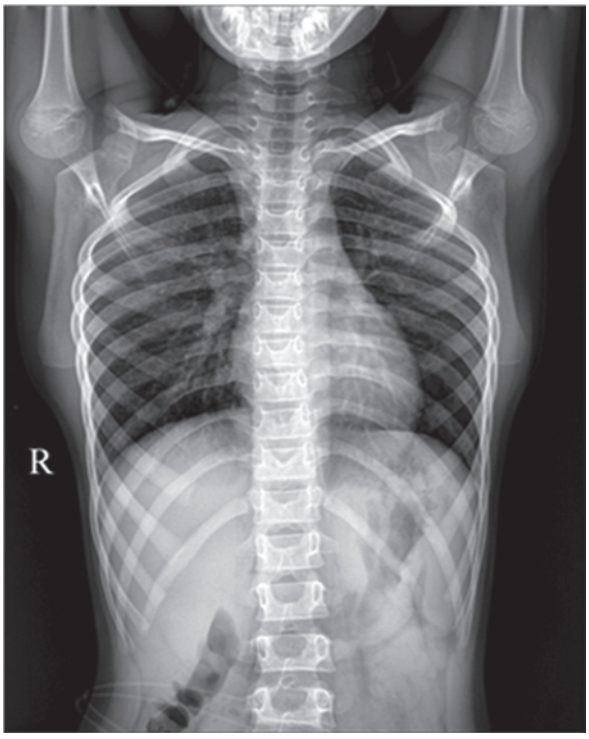

Fig.17. Open mouth of hippo appearance-Normal hilum

Fig.18. Open mouth of hippo

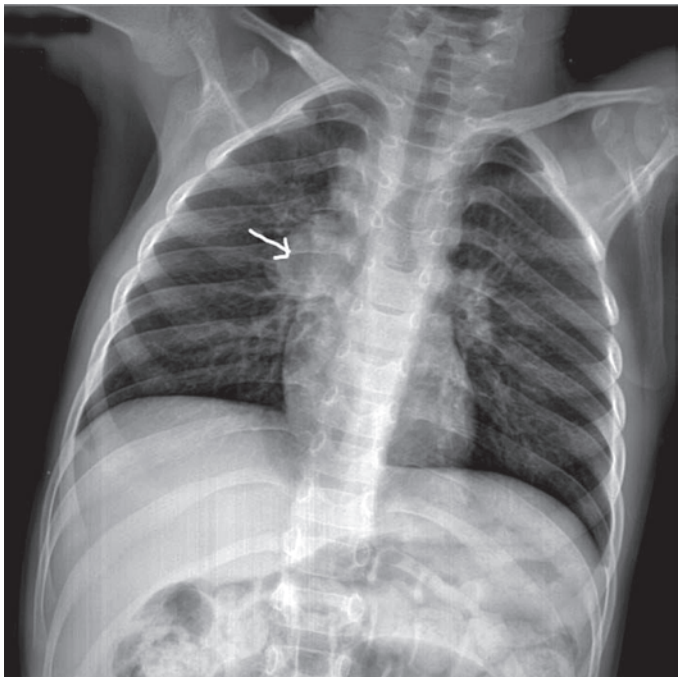

Fig.19. Hilar node

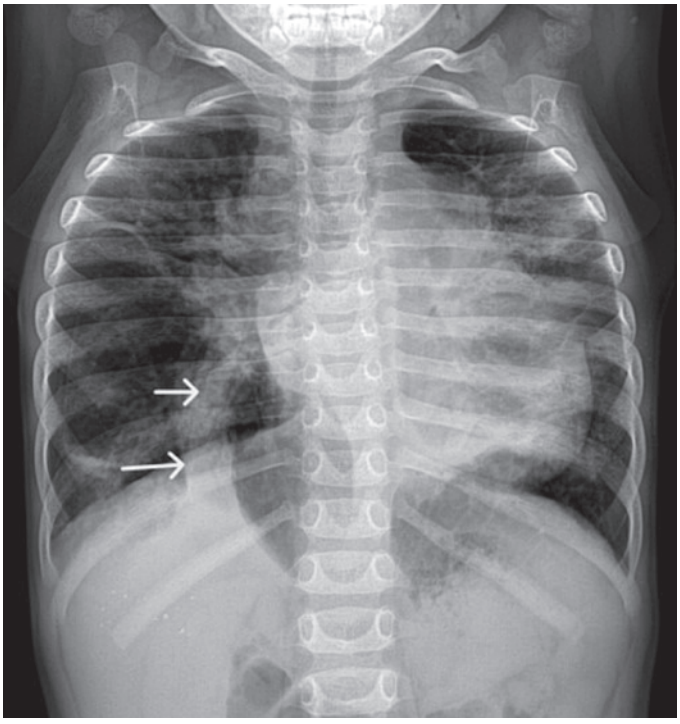

Fig.20. Scimitar sign - Partial anomalous pulmonary venous drainage

Scimitar sign: The descending pulmonary artery branch (Fig.17) tapers peripherally as it courses downwards parallel to the right heart border. In Fig.20 there is a different curvilinear shadow in the paracardiac region extending downwards to the diaphragm. It does not taper. This is called scimitar sign. The scimitar is a sword with a curved blade. It indicates partial anomalous pulmonary venous drainage into the systemic venous system. The anomalous inferior pulmonary vein travels posteriorly and inferiorly to empty into the IVC.

Signs are a trick used by the human mind to improve memory. Let us use them and become familiar with the various conditions and their appearance.

CLIPPINGS

Utility of genetic testing in children with leukodystrophy

Leukodystrophies are monogenic disorders primarily affecting the white matter. The researchers aimed to evaluate the utility of genetic testing and time-to-diagnosis in a retrospective cohort of children with suspected leukodystrophy. 67 patients were included (F:M - 35:32). Time from symptom onset to a confirmed genetic diagnosis was 15months. Pathogenic variants were identified in 60/67 (89.6%) patients, classic leukodystrophy (55/67, 82.1%), leukodystrophy mimics (5/67, 7.5%). Seven patients (10.4%) remained undiagnosed. Exome sequencing showed the highest diagnostic yield (82.9%), followed by single-gene sequencing (54%), targeted panels (33.3%) and chromosomal microarray (8%). Familial pathogenic variant testing confirmed the diagnosis in 7 patients. They concluded that next generation sequencing carries the highest diagnostic yield in children with suspected leukodystrophy. Access to advanced sequencing technologies accelerates diagnosis, which is crucial as targeted treatments become available.

Zerem A, Libzon S, Ben Sira L, Meirson H, Hausman-Kedem M, Haviv N et al Utility of genetic testing in children with leukodystrophy. Eur J Paediatr Neurol. 2023 Jul;45:29-35. doi: 10.1016/j.ejpn.2023.05.008. Epub 2023 May 27. PMID: 37267771.

CASE REPORT

COATOMER ASSOCIATED PROTEIN COMPLEX SUB UNIT ALPHA GENE SYNDROME PRESENTING AS INTERSTITIAL LUNG DISEASE IN AN INFANT

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Abstract: *Childhood interstitial lung disease encompasses a heterogeneous group of innate, genetic, infectious and inflammatory diseases, quite different from that seen in adulthood. Although histopathological evidence along with clinical assessment and radiology have helped in making specific diagnoses, wider availability of genetic studies has made noninvasive diagnosis a possibility in these children. Coatomer associated protein complex subunit alpha gene syndrome is a rare genetic autoimmune disorder where new evidence is emerging as a cause of interstitial lung disease in young children.*

Keywords: *COPA syndrome, Interstitial lung disease, Infant.*

Childhood interstitial lung diseases (ILD) are a group of heterogenous chronic lung disorders associated with high morbidity and mortality. Typical features include tachypnea, dyspnea, diffuse pulmonary infiltrates in chest X-ray or computed tomography with evidence of a restrictive ventilatory defect (in older children) in pulmonary function test and impaired gas exchange. Pulmonary interstitial glycogenosis, neuroendocrine cell hyperplasia of infancy and genetic disorders of surfactant metabolism are the predominant causes of infantile ILD. Here we report a rare etiology of infantile ILD caused by the coatomer associated protein complex sub unit alpha (COPA) syndrome.

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Case Report

A 7 month old female child 2nd born to 3rd degree consanguineous parents presented with breathing difficulty and failure to gain weight noticed by the mother since 4 months of age. There was no history of significant cough, fever or cyanosis. The child also had feeding difficulty in the form of suck - long rest cycle along with forehead sweating during feeding. Child had been taken to several hospitals and was treated with multiple courses of oral antibiotics and bronchodilators; however, the breathing difficulty persisted. The antenatal and natal period were uneventful with a birth weight of 2.5kg. The family history was negative for any premature death or chronic lung disease, nor were there any significant environmental exposures. She had been exclusively breastfed till the age of six months and was immunized appropriately for age.

On examination, the child was alert, playful but tachypneic with a respiratory rate of 66/ minute with minimal chest retractions and oxygen saturation of 90 to 92% in all limbs which improved to 100% with oxygen administration (1 to 2 L). There was no pallor, cyanosis, clubbing, or dependent edema. BCG scar was present. There were bilateral fine crepitations heard all over the chest. There was baseline tachycardia with a heart rate of 160/ min and no audible murmur. The rest of the vitals were stable. The child's weight for age. length for age, and weight for length were less than 3SD. X ray chest showed bilateral diffuse infiltrates with normal cardiac silhouette. Baseline investigations and echocardiogram were normal. Hemoglobin was 12gm%.

A provisional diagnosis of childhood interstitial lung disease [chILD] was made in view of the prolonged clinical course, tachypnea, and hypoxia improving with oxygen and diffuse lung infiltrates. High resolution computerized tomography revealed bilateral ground glass opacities which was suggestive of interstitial lung disease (ILD). Further work up was done including immunoglobulin profile, nitro blue tetrazolium (NBT) test and screening for tuberculosis which were negative.

Clinical exome sequencing was done for elucidation of etiology of ILD which showed heterozygous mutation in the COPA gene exon 7 with autosomal dominant inheritance.

Discussion

COPA syndrome is named because of the mutated gene, which encodes the alpha subunit of the coatomer complex-I (coatomer protein complex subunit alpha), that is responsible for retrograde movement of vesicles from the Golgi apparatus to endoplasmic reticulum. COPA syndrome is autosomal dominant with variable expressivity and results from mutations affecting a narrow amino acid stretch in the COPA gene-encoding COPα protein.[1]

It is a disease characterized by immune dysregulation with autoinflammation and autoimmunity. This affects multiple systems including lungs, kidneys and joints, and usually appears in childhood. The COPA syndrome is a distinctive clinical phenotype including pulmonary haemorrhage / interstitial lung disease, renal disease and arthritis. Pulmonary disease is universally present in children affected by COPA syndrome with atleast some manifestations before age of five years. Chest X-rays are frequently notable for the presence of diffuse alveolar opacities. CT scans of the chest exhibit a unique pattern marked by diffuse ground glass opacities with septal thickening and cyst formation. Although the index case did not manifest the typical CT picture (Fig.1), it may be an evolving stage in the disease and on further follow up these changes may be observed. The age of onset of arthritis and renal disease is usually in the late teens.

With reference to the reports earlier, Grijalba CQ, et al have reported a similar presentation of COPA syndrome with complaints from 2 months of age.[2] Among the first five families in which this mutation was first elucidated the average age of presentation was 3.5 years with a range of 6 months to 22 years.[3] To our knowledge, this is the first case of COPA syndrome to be reported from India presenting as interstitial lung disease in an infant.

COPA is classified as both disorder of both autoimmunity and autoinflammation, where children may manifest various autoimmune manifestation affecting the hematological and other systems. Auto antibodies such as anti nuclear antibody, anti neutrophil cytoplasmic antibodies, anti citrullinated peptide testing, rheumatoid factor (ANA, ANCA, anti-CCP, RF) in this child were negative. ESR was 30 mm in 1 hour and C reactive protein was negative.[4]

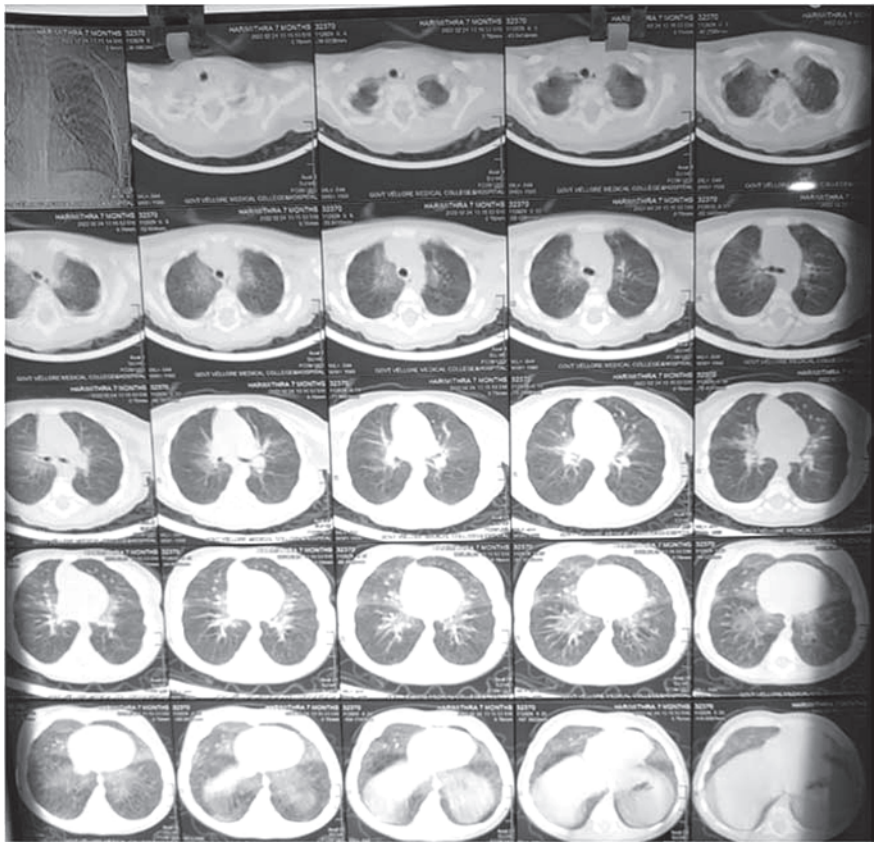

Fig.1. HRCT chest showing bilateral diffuse ground glass opacities of the lung

Till date, treatment regimens with corticosteroids, immunosuppressant and biological agents have been tried to treat COPA. Since this child did not manifest autoimmunity, the child was managed with home oxygen along with tablet azithromycin and hydroxychloroquine added as possible immuno modulators. Currently, the child is on home oxygen and asymptomatic with good weight gain.

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CLIPPINGS

FDA Approves RSV Monoclonal Antibody for Infants and Young Children

The authors assigned infants who had been born at a gestational age of at least 35 weeks to receive a single intramuscular injection of nirsevimab or placebo before the start of an RSV season. The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection.

Medically attended RSV-associated lower respiratory tract infection occurred in 12 infants (1.2%) in the nirsevimab group and in 25 infants (5.0%) in the placebo group; these findings correspond to an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; P<0.001) for nirsevimab. Hospitalization for RSV-associated lower respiratory tract infection occurred in 6 infants (0.6%) in the nirsevimab group and in 8 infants (1.6%) in the placebo group (efficacy, 62.1%; 95% CI, "8.6 to 86.8; P=0.07).

For term and preterm infants, who would not be eligible for vaccination, the single-dose monoclonal antibody nirsevimab might be an option for preventing illness and hospitalization due to RSV infection, according to updated findings from another phase 3 trial.

Hammitt LL, Dagan R, Yuan Y, CotsMB., Bosheva M, Madhi SA,et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. N Engl J Med 2022; 386:837-846.

First Ever Malaria Vaccine to Be Distributed in Africa

Eighteen million doses of the first malaria vaccine to become available will be allocated over 2 years across 12 African countries, including Benin, Democratic Republic of the Congo, and Uganda, the World Health Organization (WHO) recently HYPERLINK "https://www.who.int/news/item/05-07-2023-18-million-doses-of-first-ever-malaria-vaccine-allocated-to-12-african-countries-for-2023-2025-gavi-who-and-unicef"announced. In addition, parts of Ghana, Kenya and Malawi will continue receiving doses of the vaccine, known as RTS,S/AS01, which protects against Plasmodium falciparum malaria, after participating in a pilot program that illustrated the vaccine's safety and efficacy.

Doses will arrive in Africa as early as the end of 2023, according to the WHO, which collaborated with Gavi, the Vaccine Alliance; the United Nations Children's Fund (UNICEF); and other partners to make the vaccine available. The vaccine will then be distributed HYPERLINK "https://cdn.who.int/media/docs/default-source/immunization/mvip/first_malaria_vaccine_allocation_explained_may2023.pdf?sfvrsn=248c4624_4"according to the rate of disease transmission and child mortality, among other factors.

Harris E. First Ever Malaria Vaccine to Be Distributed in Africa. JAMA. 2023 Jul 19. doi: 10.1001/jama.2023.12549. Epub ahead of print. PMID: 37467002.

CASE VIGNETTE

INFANT WITH RECURRENT INFECTIONS

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A three month old female infant, second born to second-degree consanguineous parents with uneventful neonatal period was brought for complaints of cough, difficulty in breathing and refusal of feeds. She was on exclusive breastfeeds. Examination revealed a well-thriving infant with no BCG scar, extensive papular skin lesions all over the body without any significant lymphadenopathy or organomegaly. She was tachypneic and hypoxic. A clinical diagnosis of bronchiolitis and infantile scabies was made and was treated symptomatically and the child improved.

She was admitted after one month for fast breathing and high grade fever of five days duration. During this admission, complete blood counts showed Hb-11 g/dL, total white blood cell counts - 11600 cells/mm^3, neutrophil of 83% and lymphocyte of 9%, and platelets- 5 lakhs/mm^3. Chest X-ray done showed right middle lobe consolidation. Another striking feature noted in the chest X-ray was the absence of thymic shadow.

In view of recurrent respiratory infections within a short span and infantile scabies along with lymphopenia and absent thymic shadow the possibility of inborn errors of immunity was considered and workup was done for the same. Serum immunoglobulin levels showed immunoglobulin G of 634 mg/dL, Immunoglobulin A of 22mg/dL and Immunoglobulin M of 98mg/dL which were normal for the age. Flow cytometry showed reduced T and B lymphocyte counts (T cell-65/uL, CD4 – 61/uL, CD8 - 2/uL, B cell- 70/uL, natural killer cell- 310/uL) suggestive of T-B-NK+ severe combined immunodeficiency(SCID). Whole exome sequencing detected homozygous mutation for RAG 1 gene. A final diagnosis of SCID (RAG 1+) was made and she underwent haploidentical hematopoietic stem cell transplantation (HSCT) at 6 months of age and doing well.

Inborn error of immunity in young infants is suspected when there is a serious infection with an unusual pathogen, infection in multiple anatomic locations(extensive distribution of scabies in the upper torso above root of neck in an infant and also absence of lymphadenopathy should raise suspicion for immunodeficiency), increasing frequency and severity of infections with increasing age, recurrent sino-pulmonary infections and positive family history.[1]

SCID is a serious disease which needs immediate attention. A high degree of clinical suspicion is essential for early diagnosis. Absent thymic shadow, persistent lymphopenia(<1500/uL), T lymphocyte count of <300/uL and hypogammaglobulinemia are pointers to the diagnosis.[2] Initial management includes isolation, immunoglobulin replacement, anti-microbial prophylaxis and avoidance of live virus vaccines. HSCT has excellent overall survival with reconstitution of T cell and B cell immunity. Early diagnosis through newborn screening will improve the survival rate.

References

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LEARNING TOGETHER

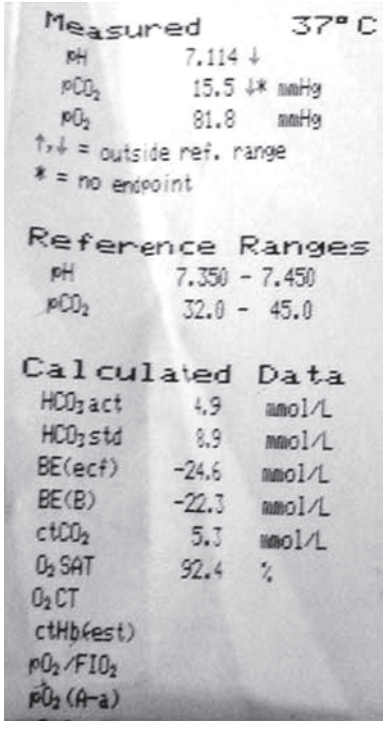
ARTERIAL BLOOD GAS ANALYSIS MIXED DISTURBANCE

**** Annamalai Vijayaraghavan***
***** Thangavelu S***

Questions

1. Basics of ABG

Look at this ABG strip and answer the following questions



a) In ABG analysis, which parameters are directly measured and which are derived?

b) What are the important data to be collected and documented in the ABG strip when taking the arterial sample for blood gases?

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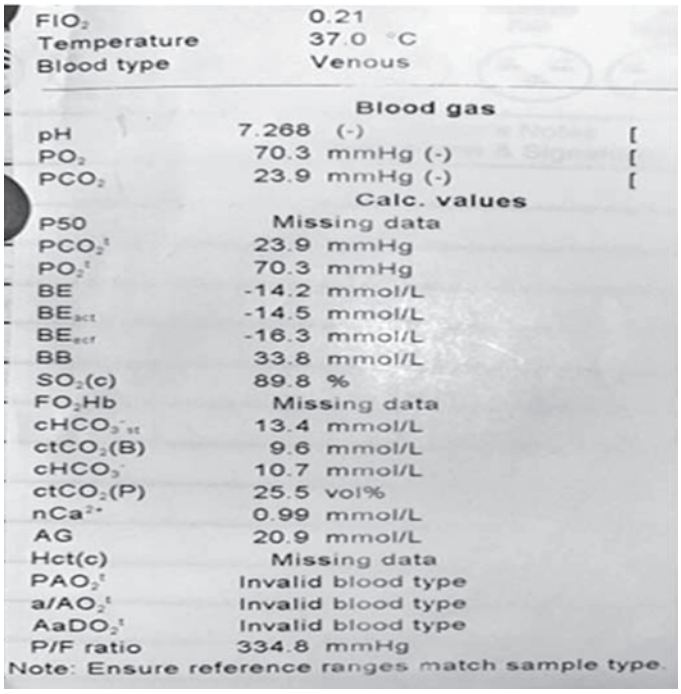
c) If one is planning for sampling at the radial artery, Allen test should be performed before pricking the radial artery. Describe the modified Allen's test

d) What is the inference one gets from the ABG data?

2.a) Interpret the data using the 6 steps



b)How to make out whether it is simple or mixed disturbance?

3. A eight years old girl is brought with history of polyuria, polydipsia of 2 weeks duration. On examination, child is dehydrated, comatose with deep and rapid breathing.

Sodium 136 mEq/L, Chloride 99 mEq/L, HCO3 12 mEqL, CBG 600 mg, Ketonuria present. Anion gap is 136 – (99+12) = 25

pH 7.12

BE -15

PCO_2 16 mm/Hg

HCO3 12 mmol/ L

PO_2 90 mm/Hg. SaO_2 95%

Interpret the data using the 6 steps

4. A five years old child brought in cardiac arrest following fever and respiratory distress of 4 days duration.

Arterial blood gas report.

pH	6.86
HCO3	12.7 mEq / L
BE	- 18.3
$Paco_2$	75 mm/Hg
Pao_2	38.6 mm/Hg
Sao_2	75%
Anion gap	20

Interpret the data using the 6 steps

5.What are simple or mixed disturbances? Quote examples.

6. When will you suspect mixed disturbances?

7. What are the types of mixed disturbances?

8. When should one apply delta ratio or delta gap, how will you interpret using

a) delta delta ratio and b) delta delta gap?

9. Interpret the following

a) pH-6.99 pCO_2 -34 mm Hg, HCO3-8 mEq/L Anion gap is 28

b) pH-7.30 PCO_2-40 mm Hg HCO3-16 mEq/L Anion gap is 29

Answers

1.a) Parameters that are directly measured are : pH, $PaCO_2$ and PaO_2 - these three values are directly measured and other data like bicarbonate, arterial or venous oxygen saturation are calculated by Henderson-Hasselbalch equation.

1.b) Documentation of FiO_2 & SaO_2: Whenever ABG analysis is done there should be a documentation of FiO_2 (Fraction of inspired oxygen concentration) and SpO_2 (oxygen saturation by pulse oximeter or peripheral oxygen saturation) to determine whether it is a venous or arterial sample.

If sample O_2 saturation is 70% and the recorded SpO_2 (oxygen saturation by pulse oximeter or peripheral oxygen saturation) is 97%, one should presume the source is a venous example. If the reverse situation is observed i.e lower SpO_2 and normal SaO_2 (oxygen saturation from arterial blood source) indicates the presence of an abnormal hemoglobin such as methemoglobin. Apart from these data, general information such as name, In patient (IP) number, time, date and hemoglobin level needs to be documented.

1.c) Modified Allen test[1]

This test attempt to measure arterial competency, and should be performed before taking an arterial sample.

- Patient is instructed to clench his fist; in a young child, medical or para medical personnel should close the person's hand tightly, so that the palm and finger tips are completely blanched.
- Then the paramedic should use his fingers, to apply occlusive pressure to both the ulnar and radial arteries, to obstruct blood flow to the hand.
- While applying occlusive pressure to both arteries, patient should be requested to relax his hand, and check whether the palm and fingers have blanched. If this is not the case, it indicates that the arteries are not completely occluded and occlusive pressure should be reapplied using the fingers.
- Next step is to release the occlusive pressure on the ulnar artery only, continuing the compression over radial artery, to determine whether the modified Allen test is positive or negative.
- Positive modified Allen test - If the hand flushes within 5-15 seconds it indicates that the ulnar artery has good blood flow to maintain the blood supply to hand; this normal flushing of the hand is considered to be a positive test. One can proceed with the test, as inadvertent block of the radial artery will not affect the hand.
- Negative modified Allen test - If the hand does not flush within 5-15 seconds, it indicates that ulnar artery circulation is inadequate or non-existent; in this situation, the radial artery supplying arterial blood to that hand should not be punctured

1.d) Objectives of ABG measurement: The inference we get from the ABG data is to assess the i) acid base status and ii) oxygenation status.

2. a) Interpretation of the data using the 6 steps

Step 1. Is the pH in the normal range? - pH is 7.268 which is below the normal range (Normal 7.35-7.45) and denotes acidosis

Step 2. Is it respiratory or metabolic? In acidosis we expect low HCO3 or high PCO2. Observed HCO3 is 10.7 mmols (Normal 22-26) - probable metabolic acidosis, however PCO2 is also low (23.9 mm/Hg), not high to consider respiratory acidosis.

Step 3. Is metabolic acidosis compensated? If compensated, is it appropriate? Apply Winter's formula, to derive the expected PCO2 - 1.5 x HCO3 +8 (+/- 2). 10.7x1.5 +8 =24.05mm (22mm to 26mm) is the expected PCO2. The measured PCO2 is 23.9 mms which denotes an appropriate compensation.

Step 4. Is it a simple metabolic acidosis or a mixed disturbance? Impression is compensated metabolic acidosis.

Step 5 & 6: As it is a venous blood sample, saturation and PaO2 are not taken into account.

Note: Previously compensation is expressed in different stages - Uncompensated, partially compensated and fully compensated. Currently, interpretation is expressed as simple or mixed acid base disturbance, instead of the stages of compensation. One should also express as normal anion gap (AG) or high anion gap acidosis, if electrolyte results are also available. The answer - it is a simple acid base disturbance - metabolic acidosis.

2.b) To make out whether simple or mixed disturbance.

HCO3 level	Expected PCO2 as per Winter's formula	Inference
10.7 mmols	22-26 mm/Hg	Appropriate. Simple metabolic acidosis
	21 mm/Hg or < 21 mm/Hg	Overcompensated. Metabolic acidosis with respiratory alkalosis
	27 mm/Hg or > 27 mm/Hg	Undercompensated. Metabolic acidosis with respiratory acidosis

Similar calculations can be done for all other simple disturbances, metabolic alkalosis, respiratory acidosis or respiratory alkalosis by applying the rules of compensation for each condition.

3. A eight years old girl is brought with history of polyuria, polydipsia of 2 weeks duration. Interpretation of the data using the 6 steps.

Step 1. Is the pH in the normal range? pH is 7.12 below the normal range (Normal 7.35-7.45) denoting acidosis

Step 2. Is it respiratory or metabolic?. Here HCO3 is 12 mmols (Normal 22-26) hence metabolic acidosis. PCO2 is low (not high to consider respiratory acidosis)

Step 3. Is metabolic acidosis compensated? If compensated, is it appropriate? Winter's formula is applied, to know the expected PCO2. PCO2 = 1.5 x HCO3 +8 (+/- 2). Here HCO3 is 12 mmol/L. PCO2 = **1.5X12 +8 =26 +/- 2**. Hence 24 to 28 mm/Hg will be the expected PCO2. Here the measured PCO2 is 16 mms, which is higher fall than expected value. Hence, it is partially compensated or metabolic acidosis with respiratory alkalosis

Step 4. Is it a simple metabolic acidosis or a mixed disturbance? Impression is mixed disturbance (Partially compensated metabolic acidosis or metabolic acidosis with respiratory alkalosis)

Step 5 & 6: SaO2 is 95% and PaO2 is 90 mm/Hg, hence no hypoxia. As glucose (CBG) 600 mg ketonuria present and anion gap is 25 final diagnosis is diabetic keto acidosis with high anion gap metabolic acidosis with respiratory alkalosis with no hypoxia

4. **A five year old child brought in cardiac arrest. Interpretation of the data using the following steps**

Step 1. Is the pH in the normal range? pH is 6.86 hence denotes acidosis

Step 2. . Is it respiratory or metabolic?. Here HCO3 is 12.7 suggestive of metabolic acidosis

Step 3. Is metabolic acidosis compensated? No, here expected PCO2 for the given HCO3 is 12.7.X1.5+8+/-2 = 27+/-2. Expected PCO2 is 27 (25mm -29 mm). Actual PCO2 is 75 mms which is higher.

Step 4. Is it a simple metabolic acidosis or a mixed disturbance? It is a mixed disturbance - mixed respiratory and metabolic acidosis

Step 5 & 6. Hypoxia, both SaO2 and paO2 are low.Final impression: High anion gap metabolic acidosis and respiratory acidosis with hypoxia Note: In the presence of metabolic acidosis, if anion gap is high the next step is to calculate delta ratio and delta gap (Refer to Answer 8)

5. Simple and mixed disorders

A simple acid-base disorder includes the following four disorders - metabolic acidosis, metabolic alkalosis, respiratory acidosis and respiratory alkalosis and the appropriate degree of compensation for that disturbance.

Mixed acid-base disorder means there is simultaneous presence of more than one acid-base disturbance which is suspected from the a) patient's history, b) from a lesser or greater than the expected compensatory response and c) from analysis of the delta anion gap and delta HCO3. e.g. metabolic acidosis with respiratory acidosis, metabolic acidosis with respiratory alkalosis, respiratory acidosis with metabolic alkalosis. In addition there are double metabolic disturbances which are high anion gap and normal anion gap metabolic acidosis. Based on the duration they are categorized as acute or chronic.

6. Situations when one suspects mixed disturbance

i) When both HCO3 and PCO_2 independently account for the change of pH or both move in opposite direction. e.g. pH-7.0 HCO3 -15mEq/L PCO_2 - 50 mm Hg.

Both variables (PCO_2 and HCO3) claim responsibility for acidosis. In general during compensation both the variables move in same direction, here they move in opposite, HCO3 falls and PCO_2 rises.

ii) A truly normal pH with distinctly abnormal HCO3 and $PaCO_2$.

e.g. pH 7.40, $PaCO_2$ 20 mm Hg, HCO3- 12mEq/L

In simple disturbances with appropriate compensation, pH will be just close to the lower range of normal pH i.e. 7.34 or 7.33. Natural compensation never crosses the midline, so pH will never be in the normal range. Here a paradoxical situation is observed. Distinctly normal pH but, both (HCO3 and PCO_2) are clearly abnormal. This raises the suspicion of mixed disturbance.

iii) Under or over compensation, means that actual PCO_2 or HCO3 are out of the range predicted by rule of compensation.

Rules for compensation predict the HCO3 for a given change in $PaCO_2$ or vice versa.

A substantially reduced or excessive (inappropriate) compensation is indicative of a mixed acid-base disorder.

If the $PaCO_2$ or HCO3 is higher or lower than expected, then there is mixed disturbance

e.g. pH 7.32, $PaCO_2$ 39 mmHg, HCO3 18 mEq/ L.

Expected $PaCO_2$ using Winter's formula is (18x1.5) + 8 =35 ± 2 = (33 to 37mm). Actual PCO_2 is higher the predicted range hence mixed disorder.

7. The types of mixed disturbances

i). Mixed disturbance with similar effects: e.g Double acidemia i.e. Metabolic and respiratory acidosis.

Inadequate compensation leads to severe degree of acidemia or alkalemia.

Eg: Metabolic acidosis and respiratory acidosis

e.g. pH 7.0 HC03 15mEq/L PCO_2 50mm /Hg

ii). Mixed disturbance with opposite effects: e.g. Metabolic acidosis with respiratory alkalosis. Over compensation leads to this sort of disturbances.

pH may be low, normal or high

e.g. Metabolic acidosis and respiratory alkalosis (pH 6.98, HCO3 6mEq/L, PCO_2 7mm Hg). Applying Winter's formula. For a given HCO3 of 6, expected PCO_2 is

15-19 mms. Here it is out of range and is lower than expected. Metabolic acidosis and respiratory alkalosis

iii). Double metabolic disturbances.

e.g. High anion gap metabolic acidosis (HAGMA) with normal anion gap metabolic acidosis (NAGMA).

High anion gap metabolic acidosis (HAGMA) with metabolic alkalosis.

Delta gap or delta ratio is calculated and analyzed wherever HAGMA is identified, not routinely in all situations.

However both respiratory acidosis and respiratory alkalosis can never occur together.

8. It is applied only when there is HAGMA and not applied in other disturbances which is calculated by a 3 step process.

(i) Calculate the anion gap (AG) and delta AG, which is the difference between measured and normal AG.

e.g. if measured AG is 18, and normal AG is considered as 12. The delta AG gap is calculated as 18-12 = 6. In other words, it is estimated that, how much it is higher than the normal value.

(ii) Calculate the delta bicarbonate gap: e.g. if measured HCO3 is 18 and the normal value is 24, the delta bicarbonate gap is 24-18 is 6.

(iii) Estimate the ratio or gap between delta anion gap and delta bicarbonate gap.

8. b) Delta delta gap:[3]

Here delta AG and delta bicarb gap are calculated as

8. a) Delta delta ratio:[2]

It is analysed and interpreted in the following way.

e.g. in the above example delta AG is 6 and delta HCO3 gap is 6 the ration is Delta ratio = (change in anion gap) / (change in bicarbonate). Here it is 1.

Interpretation of delta delta ratio

Less than 0.4 = pure normal anion gap acidosis.

0.4-0.8 = mixed high and normal anion gap acidosis.

0.8-2.0 = pure high anion gap acidosis.

More than 2.0 = high anion gap acidosis and a pre-existing metabolic alkalosis.

Interpretation of delta delta gap

If D gap is negative (< -6) :Mixed (HAGMA +) and a normal anion gap metabolic acidosis

If D gap -6 to 6 : consider only a HAGMA

If D gap is positive (>6) : Mixed (HAGMA +) & metabolic alkalosis

mentioned above, ie both are 6. Now one should estimate the gap, here it is 6 - 6 - 0

9.a) pH - 6.99 PCO_2 - 34 HCO3 - 8. Anion gap 28

Because of the presence of HAGMA delta-delta ratio has to be calculated

Delta anion gap is 28 -12 = 16

Delta bicarbonate gap is 24 - 8 = 16

Delta delta ratio is 1.0. Hence it is pure HAGMA

When winter's formula is applied, expected PCO_2 is 18 - 22. Actual PCO_2 is 34. Hence there is respiratory acidosis

Final impression: HAGMA with respiratory acidosis

9.b) pH is 7.30 PCO_2 - 40 HCO3 - 16 Anion gap is 29

Delta anion gap is 29-12 = 17

Delta HCO3 is 24 - 16 = 8

Because of the presence of HAGMA delta-delta ratio has to be calculated

Delta delta ratio is 17/8 = 2.1

High anion gap metabolic acidosis and a pre-existing metabolic alkalosis.

Winter's formula: expected PCO_2 for HCO3 16 = 30-34. Actual PCO_2 is 40. So associated respiratory acidosis.

Final Impression: High anion gap metabolic acidosis, with metabolic alkalosis and respiratory acidosis.

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