PEDI INFO

An Official Journbal of East Zone Academy of Pediatrics
Oriental Apartments, Flat H1
15C, Canal Street, Kolkata 700014
Phone : 033 2265 4072

Vol.2. No.1 & 2 January - December 2015

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Special Correspondence:
Dr Santanu Bhakta
CJ 296, Sector II, Salt Lake City
Kolkata 700091, West Bengal
Ph: 09433014193;
Email: sbhakta57@gmail.com
E mail: iapwb@rediffmail.com

Editorial

Greetings from Kolkata !!

Due to some unavoidable circumstances, the earlier issue could not be published. This annual issue is dedicated to 22nd EAST ZONE PEDICON. This annual event has now taken a good shape in terms of academics and attendance. More interest shown to this annual east zone conference will do more good to the state organizing this annual event. Last time also we enjoyed very much in Agartala, Tripura with their good hospitality and weather, not to mention about the quality of the academics proper. Now here in Imphal, Manipur, we are enjoying our stay and food. The rich culture of Manipur will definitely mesmerize all of us. Next 23rd east zone conference will be held in West Bengal. I take this opportunity to invite you all in Kolkata. Please come early and go late, so that you can enjoy your stay there.

Recent resurgence of tropical diseases like malaria and dengue are bothering the entire east zone of India for quite some time. We must be aware of the latest line of treatment to fight against these diseases. National Vector Borne Disease Control Program (NVBDCP) has laid the new guideline in 2013 to diagnose and treat malaria specially for north eastern states and we should follow that to bring down the morbidity and mortality due to malaria. In drug therapy, ACT- AL (artemether and Lumifantrene) is to be used in all Falciparum malaria in north eastern states, while ACT- SP (Artesunate + sulphadoxin and pyrimethamine) is used in other states. Primaquine, a gametocidal drug, is to be used in a dose of 0.25 mg/kg for 14 days in vivax malaria, while a single dose of 0.75 mg/kg is given on day 2 in falciparum malaria.

In dengue, we must be very watchful in fluid management than platelet management. Instead of asking how much is the platelet count, we should enquire how much is the urine output in a day. Neither dehydration nor over hydration is desirable.

Childhood TB management has become very handy now after the IAP-RNTCP guideline that has come out early this year. This guideline has given more insight in the age old armament like TST and chest x-ray. The role of CBNAAT in detecting tuberculosis has added that much more confidence amongst us. We now must be very much careful not to give empirical therapy for either malaria or tuberculosis, which will only increase the drug resistance.

Long live East Zone Academy of Pediatrics
Long live IAP
Santanu Bhakta
Editor-in-Chief

Review Article

Early Recognition And Management of Sepsis In Children

Sudip Dutta*, Srividhya, Shashank****
**Professor and Head, Department of Pediatrics, **Post Graduate*
Sikkim Manipal Institute of Medical Sciences and Central Referral Hospital,Gangtok

Abstract :

Pediatric sepsis is a major problem affecting approximately 40,000 children in united states every year. Sepsis contributes to almost two-third of admission to PICU in developing countries.This review article focusses on the prompt recognition of hemodynamic abnormalities caused by infections in emergencies and early management in the initial golden hours to avoid sepsis progressing to septic shock and multi-organ failure.

Introduction

Sepsis is a clinical syndrome complicating severe infection that is characterized by systemic inflammation, immune dysregulation, microcirculatory derangements, and end-organ dysfunction. There is a continuity of severity ranging from sepsis to severe sepsis and septic shock. Severe sepsis is characterized by sepsis plus cardiovascular dysfunction or acute respiratory distress syndrome. Septic shock is sepsis plus cardiovascular dysfunction[1]. Sepsis in children is a significant cause of morbidity and mortality worldwide[2]. The mortality rate of sepsis in children from pediatric intensive care unit (PICU) of developing countries is higher than 50%. World Health Organization statistics have shown that 80% of death in children <4 years can be classified as sepsis-related deaths[3]. Assessment of severity of illness at admission is important for effective patient management, prognostication, and optimum utilization of resources. Simple interventions such as oxygen supplementation, early rapid fluid administration, correction of electrolyte and glucose abnormalities, early initiation of antibiotics within one hour of presentation and early use of inotropes in fluid refractory cases have shown to improve the outcome of pediatric sepsis. Each hour delay in initiation of appropriate resuscitation might worsen the shock leading on to multiorgan failure which is associated with a clinically significant increased risk of death.

The mortality rate of sepsis in children from pediatric intensive care unit (PICU) of developing countries is higher than 50%. World Health Organization statistics have shown that 80% of death in children <4 years can be classified as sepsis-related deaths

Pediatric Sepsis

It is one of the very common problem faced in emergencies of both developing and developed countries. In a study by Khilnani et al., it was observed that almost half of children who expired in tertiary care PICU had multiorgan dysfunction[4].So prompt recognition is essential inorder to avoid progression of hemodynamic abnormalities.

Severe sepsis leads onto septic shock which is a unique

combination of distributive, hypovolemic and cardiogenic shock.This shock initiates an inflammatory cascade (systemic inflammatory response syndrome) that leads to hypovolemia, cardiac and vascular failure, insulin resistance,acute respiratory distress syndrome, coagulopathy, secondary infection[1].

Definitions

Sepsis – SIRS plus a suspected or proven infection.

Systemic Inflammatory Response Syndrome(SIRS):

2 out of 4 criteria, one of which must be abnormal temperature or abnormal leukocyte count.

1. Core temperature >38.5 degree Celsius or <36 degree Celsius (rectal, bladder ,oral or central catheter)
2. Tachycardia
3. Respiratory rate >2SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anaesthesia.
4. ***Leukocyte count elevated or depressed for age[1].***

Severe sepsis: sepsis plus 1 of the following

1. cardiovascular organ dysfunction,defined as despite >40 ml/kg of isotonic intravenous fluid in 1 hour, hypotension <5th percentile for age or systolic BP <2SD below normal for age.

   OR

   need for vasoactive drug to maintain blood pressure OR 2 of the following(unexplained metabolic acidosis : base defici t>5 mEq/l, increased arterial lactate->2 times upper limit of normal, oliguria, prolonged CRT>5sec, core to peripheral temperature gap >3 degree Celsius.
2. Acute Respiratory Distress syndrome (ARDS) as defined by presence of PaO2/Fio2 ratio <300mmHg, bilateral infiltrates on chest radiograph and no evidence of left heart failure

   OR

   Severe sepsis can also be called as Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic,or hepatic)[1]

Septic shock – sepsis plus cardiovascular dysfunction.

A clinical diagnosis of septic shock is made in children presenting with signs of inadequate perfusion like fever, tachycardia or bradycardia, tachypnea, bradypnea, or apnea, decreased peripheral pulses compared with central pulses, mottled, cyanotic or cool extremities capillary refill time>3sec, decreased urine output (<0.5ml/kg/hr), anuria in severe cases, hypotension, altered mental status (irritability, anxiety, confusion,stupor,coma)

Tachycardia and tachypnea are common and non-specific findings in young pediatric patients and may be due to fever, anxiety, dehydration, pain/discomfort, anemia, or agitation. However, persistent tachycardia is a sensitive indicator of circulatory dysfunction. Hypotension is a late sign of cardiovascular dysfunction and shock in pediatric patients and is not necessary to diagnose septic shock. Infants and children with sepsis often maintain blood pressure despite the presence of septic shock through compensatory mechanisms like tachycardia,vasoconstriction,increased cardiac contractility,increase in smooth muscle tone[5]. Prompt intervention is required at this stage to avoid progression to decompensated shock and cardiac arrest. Hypotensive shock within minutes can lead to cardiac arrest.

Signs of infection

Fever, cough, dyspnea, hypoxemia, rash, abdominal pain, myalgias, immunocompromising conditions (malignancies, patients on chemotherapy, sickle cell disease, primary immune deficiency, acquiredimmuno deficiency syndrome), burning micturition, dysuria (urinary tract infection), hematochezia (gastroenteritis), headache and neck stiffness (meningitis), bone or joint inflammation (Staphylococcus aureus), conjunctival

suffusion/injection (toxic shock syndrome), ecthyma (Pseudomonas species) and petechiae/purpura (meningococcemia).

For a child presenting to the emergency with shock irrespective of etiology, two peripheral iv lines should be sited as early as possible, one for the correction of shock and other for antibiotics or inotropes. Samples should be drawn for rapid blood glucose, complete blood count with differential, arterial or venous blood gas,blood lactate, Serum electrolytes, blood urea nitrogen and serum creatinine, Ionized blood calcium, serum total bilirubin and alanine aminotransferase, Prothrombin and partial thromboplastin times (PT and PTT), INR, blood culture.

Urinalysis, Urine culture, other cultures as indicated by clinical findings, diagnostic serologic testing to identify suspected sources of infection, Inflammatory biomarkers (C-reactive protein, procalcitonin) (other biomarkers-sTREM-1, suPAR, proADM, and presepsin—Studies suggest that they may have a role in future clinical developments, whether as diagnostic tests, or for stratification of patients by type of insult or severity, or to assess the therapeutic activity and efficacy and during follow-up of patients.)[6].

Early recognition of Shock with clinical findings of , tachycardia or bradycardia, tachypnea, bradypnea, or apnea, decreased peripheral pulses compared with central pulses, mottled, cyanotic or cool extremities capillary refill time>3sec, decreased urine output(<0.5ml/kg/hr), anuria in severe cases ,hypotension, altered mental status and reflected on laboratory parameters like raised serum Lactate, Dyselectrolytemia and Inflammatory markers is the key towards the approach to treatment of Sepsis.

Lab findings in favour of sepsis-anaemia,leukocytosis/leukopenia,thrombocytopenia (Platelet count <80,000/microL or a decline of 50 percent from highest value recorded over the past three days), presence of toxic granules, Lactic acidosis indicated by metabolic acidosis on blood gases and elevation of arterial blood lactate (>3.5mmol/L),disseminated intravascular coagulopathy (decreased fibrinogen with increased D-dimer, international normalized ratio, prothrombin time, or partial thromboplastin time), hypoglycemia/hyperglycemia, electrolyte abnormalities (hypocalcemia), hypoalbuminemia, renal insufficiency suggested by a serum creatinine =2 times upper limit of normal for age or twofold increase in baseline creatinine.

Liver dysfunction implied by a total bilirubin =4 mg/dLor alanine aminotransferase (ALT) >2 times upper limit of normal for age, pyuria indicating an urinary tract infection.

Mixed venous oxygen saturation (Svo2), serum lactate measurements may be used as marker for adequacy of oxygen delivery and effectiveness of the rapeutic interventions[1].

The source of infection leading onto infection can be from upper/lower respiratory tract, central nervous system, gastrointestinal system, genitourinary tract, joints, skin or soft tissues, burns/wounds, vascular catheters etc.

Therapeutic goals

Restoration of tissue perfusion, such as reversal of shock, should be targeted. Frequent monitoring of heart rate, pulses, skin perfusion,mental status ,blood pressure,urine output should be done.Target is to maintain Urine output (=1 mL/kg per hour, up to 40 mL per hour, once effective circulating volume is restored), blood pressure (systolic pressure at least fifth percentile for age: 60 mmHg <1 month of age, 70 mmHg + [2 x age in years] in children 1 month to 10 years of age, 90 mmHg in children 10 years of age or older), Lactate (<4 mmol/L or =10 percent decrease per hour until normal), Central venous oxygen saturation (ScvO2), (=70 percent), if available.

Management

Various guidelines exist for the management of paediatric sepsis. However due to the challenges in conducting clinical trials in children with sepsis-related critical illness[7] there is a lack of quality data from the paediatric population

and the guidelines are based primarily on adult studies. Early recognition of sepsis is very important; equally imperative is its early treatment. Aggressive hemodynamic resuscitation in the first few hours following recognition of severe sepsis and septic shock has been shown to improve both mortality and morbidity[8]. The Surviving Sepsis guidelines were updated in 2012 and it includes a section on paediatric sepsis[9]. Management of sepsis can be considered under the following headings.

Initial Resuscitation

Start with supplemental oxygen delivered via face mask or nasal cannula or other devices to children with septic shock even if oxygen saturation levels appear normal with peripheral monitoring devices. Infants can desaturate very quickly as they have low pulmonary functional residual capacity and for the same reason they may require early mechanical ventilatory support.

Obtain intravascular access as soon as possible. It may be difficult to find a peripheral intravenous access in hemodynamically unstable infants and young children. In such a situation early use of intraosseus access is recommended for fluid resuscitation, inotrope infusion and delivery of antibiotics when central venous access is not easily obtainable.

Septic shock needs to be recognized and managed immediately. Administer isotonic saline or colloid boluses of 20ml/kg upto and over 60 ml/kg until perfusion improves or until rales or hepatomegaly develops. Metabolic abnormalities like hypoglycemia and hypocalcemia need to be treated. For fluid refractory shock, inotropes have to be started depending upon the type of shock. For cold shock, dopamine is started and epinephrine can be added if shock does not improve. In case of warm shock, norepinephrine can be started as the first choice. Early goal directed therapy has been noted to have improved outcomes in the management of septic shock[8]. We can consider the initial therapeutic endpoints of resuscitation of septic shock as capillary refill of = 2 s, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output > 1 mL/kg/hr, and normal mental status. Thereafter, Scvo2 saturation greater than or equal to 70% and cardiac index between 3.3 and 6.0L/min/m2 should be targeted.

If shock persists despite addition of inotropes, consider risk of adrenal insufficiency and begin hydrocortisone. Rule out presence of pneumothorax or pericardial effusion and treat if required.

Initial Resuscitation primarily involves recognition of sepsis, humidified oxygen ,securing iv/io line, pushing iv bolus upto 60mL/kg or till Hepatomegaly and or rales develops correcting hypoglycemia/hypocalcemia. Broad spectrum Antibiotics within the first hour.

Antibiotics and Source Control

Once severe sepsis is suspected or confirmed, empiric broad spectrum antibiotics should be administered within 1 hour depending on the likely source of infection, the age of the child, and knowledge of local disease prevalence and drug resistant organisms. Collection of blood cultures prior to starting antibiotics should be preferred but should not delay antibiotic administration. If intravenous access is a hindrance, oral or intramuscular antibiotics may be administered. Antibiotic cover can then be rationalised later with availability of culture results and the clinical course. For toxic shock syndromes with refractory hypotension, Clindamycin and anti-toxin therapies are recommended[9]. Early and aggressive source control is essential and include drainage or debridement of infected tissues and removal of infected devices or foreign bodies.

Fluid Resuscitation

Resuscitation should begin with boluses of 10-20ml/kg of crystalloid or 5 % albumin over 5-10 minutes with further aliquots titrated to clinical condition (e.g. heart rate, urine output, CRT and level of consciousness). Aggressive fluid resuscitation is a key stage to improved survival, provided there is also access to inotropic therapy and

mechanical ventilation. Large fluid deficits are common and volumes of over 40-60ml/kg can often be required.

Special care should be taken in malnourished children as aggressive fluid resuscitation could lead to greater risk of congestive heart failure from over-hydration. It is challenging to recognize and treat septic shock in these patients. They should be given slow iv rehydration with careful and regular observation (every 5-10minutes). 15ml/kg Ringer's lactate can be given over one hour; a repeat bolus can be given slowly if there are signs of improvement, followed by oral or nasogastric rehydration. If the patient does not improve after one hour, a blood transfusion should be considered (10ml/kg slowly over three hours). If the child deteriorates during treatment (increased respiratory rate or heart rate) the infusion should be stopped[10].

A recent study challenged the practice of high-volume fluid resuscitation in sepsis. 'Fluid Expansion As Supportive Therapy' (FEAST) study investigated fluid resuscitation in children with a diagnosis of sepsis (but without hypotension), in a large cohort of children in Uganda, Kenya, and Tanzania[11]. It compared resuscitation with a fluid bolus of 20-40 ml/kg saline or albumin to the local practice of no fluid bolus resuscitation. The results showed that the fluid bolus groups had increased mortality at 48 hours and a 4% higher risk of death and neurologic sequelae at four weeks compared to the children who did not receive a fluid bolus. Most deaths were early, (87% occurring in the first 24 hours). The study included many children with malaria (57%), severe anaemia (32%), hypoxia (25%) or coma (15%), and 6% had hypotension. This may represent a population in whom over hydration will not be well-tolerated, particularly if mechanical ventilation and inotropic support are not available. These results suggest that the traditional recommendation of aggressive bolus fluid resuscitation should not be used in children with severe anaemia or malaria, or other common febrile illness associated with a significant stress response but not hypotension (i.e. associated with ADH release and fluid retention).

The decision on the type of fluid to be used is controversial. Recently a systematic review of resuscitation fluid in children was unable to find evidence to support the use of colloid over crystalloid[12].

Inotropic and vasoactive drug therapy

In fluid refractory shock, persistent hypotension is treated with either inotropes, vasopressors or a suitable combination of both. Regular re-assessment of the child with appropriate changes to the choice and rate of cardiovascular drug used is essential.

Apart from the clinical therapeutic end points we can use other methods to assess our treatment. Cardiac output monitoring in the form of echocardiography, trans-oesophageal Doppler, pulse contour analysis, or supra-sternal ultrasound cardiac output monitors can be helpful. However till date there is no data to prove that these measures improve survival. A large multicentre randomised controlled trial is needed for the same.

Mechanical ventilation

Early intubation and mechanical ventilation is recommended in severe sepsis and septic shock because it helps to reduce the work of breathing and thereby oxygen consumption. Lung protective strategies should be used during mechanical ventilation[9].

Steroids

There is no role for routine administration of steroids in pediatric sepsis. Current retrospective studies of steroids in children with severe sepsis have shown their use to be an independent predictor of increased mortality[13]. However timely hydrocortisone therapy in children with fluid-refractory, catecholamine-resistant shock and suspected or proven absolute (classic) adrenal insufficiency is important[9]. Approximately 25% of children with septic shock have absolute adrenal insufficiency. Patients at risk for absolute adrenal insufficiency include children with severe septic shock and purpura, those who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal

abnormalities. Initial treatment is hydrocortisone infusion given at stress doses (50mg/m2/24hr); however, infusions up to 50mg/kg/d may be required to reverse shock in the short-term. Death from absolute adrenal insufficiency and septic shock occurs within 8 hrs of presentation. Adrenal insufficiency can be identified by random blood cortisol levels < 18 mcg/dl or a cortisol level increase of < 9 mcg/dl after an ACTH stimulation test.

DVT prophylaxis[9]

Older post-pubertal children may be considered for unfractionated or low molecular weight heparin or mechanical prophylactic devices such as compression stockings. However there are no recommendations for use in young children. The majority of thrombotic events are associated with the use of central venous catheters.

Stress ulcer prophylaxis[9]

Early enteral feeding should be initiated wherever possible. Stress ulcer prophylaxis with H2 blockers or proton pump inhibitors can be used in patients with severe sepsis. This is aimed at reducing the risk of GI bleeds and at the prevention of ventilator-associated pneumonia.

Glycaemic control[9]

Controlling hyperglycemia using a similar target as in adults (= 180mg/dL). Glucose infusion should accompany insulin therapy in newborns and children

Transfusion

During resuscitation of low superior vena cava oxygen saturation shock (< 70%), hemoglobin levels of 10 g/ dL are targeted. After stabilization and recovery from shock and hypoxemia, then a lower target > 7.0 g/dL can be considered to reduce potential risks and complications The transfusion strategies in paediatric intensive care units (TRIPICU) study looked at transfusion thresholds in stable, critically ill children[14]. They found that a haemoglobin threshold of 7 g/dl decreased transfusion requirements without increasing adverse outcomes.

Renal replacement therapy

With large volumes of initial resuscitation fluid being given and often an on-going fluid requirement due to capillary leak, there can be significant tissue oedema and fluid overload. Diuretics, peritoneal dialysis or renal replacement therapy may be required once the child has been stabilised. Early implementation of continuous renal replacement therapy is associated with improved survival compared to late implementation[15].

Protein C and Activated protein C (APC)

Use of APC in children is not recommended due to a lack of evidence of benefit and an increase in bleeding complications[16].

Extra-corporeal membrane oxygenation (ECMO)

ECMO may be considered in those cases of severe septic shock, which have not responded to all conventional treatment strategies[9], where it may be associated with improved survival.

The optimum treatment of sepsis is an evolving process[9] and as more data come into light the treatment guidelines may change.

Summary

Intotropes- Indicated in fluid resistant shock, followed by regular re-assessment and cardiac monitoring.

Mechanical Ventilation- Early intubation and ventilation indicated to reduce the work of breathing.

Steroids-Indicated only in Fluid Resistent, Catecholamine resistant Shock with Adrenal insufficiency.

DVT prophylaxis has no role in pre-adolescent children.

Glycemic control less than 180mg/dL is suggested.

Transfusion-Hemoglobin target of 7gm%

Choice of Empirical Antibiotic in patients with Septic Shock. (17)

Clinical Setting	Usual Pathogens	Preferred Therapy	Alternate Therapy
Unknown source from the community	Salmonella typhi/paratyphi S.pneumoniae H.influenza Enterobacteriaceae Malaria/dengue also should be thought in indian settings	Ceftriaxone with aminoglycoside	Piperacillintazobactum OR newer Quinolone(levofloxacin/ Gatifloxacin)
Lung source	S.pneumoniae H.influenza Staphylococcus aureus M.pneumoniae	Ceftriaxone/cefotaxime/ amoxclav and azithromycin/ clarithromycin	Substitute new fluoroquinolone (levofloxacin/gatifloxacin/ moxifloxacin) For macrolides
Iv line sepsis	S.epidermidis S.aureus(MSSA) Klebsiella Enterobacter Serratia	Vancomycin PLUS Meropenem OR Imipenam OR Cefepime OR Piperacillintazobactum	May substitute linezolid for vancomycin. Add antifungals if fungal infection suspected.
Urosepsis	Enterobacteriaceae	Ceftriaxone OR Cefotaxime OR Quinolone AND aminoglycoside	Aztreonam OR Ampicillin+Amikacin
Meningitis	S.pneumoniae H.influenza Meningococci	Ceftriaxone OR Cefotaxime	Add vancomycin if drug resistant pneumococci suspected.
Intra-abdominal source	Enterobacteriaceae B.fragilis Enterococci	Ceftriaxone PLUS Metronidazole OR Piperacillintazobactum OR Meropenam OR Imipenam	Quinolone(ciprofloxacin/ levofloxacin) PLUS either Metronidazole OR Clindamycin

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An Appeal

Shubho Vijaya and Happy Diwali to you all.

This is third time, I am getting the opportunity to communicate with you through this official journal of East Zone Academy of Pediatrics, "Pedi- Info". On the eve of this 22nd East Zone PEDICON 2015, I would like to welcome you all in the writing panel of this journal.

In spite of repeated request, there is a very poor response in contributing the articles for the journals. It becomes increasingly difficult for me to bring out this journal without your active cooperation. My request to all of you to please send articles for the regular publication of journal otherwise its future may be in jeopardy.

Review Article

Oxygen Therapy in PICU

Rashna Dass Hazarika
Medical Director and Chief of Pediatrics, Midland Hospital and Rigpa Children's Clinic, Guwahati, Assam

Introduction

Oxygen therapy is the delivery of oxygen at FiO_2 of more than 21% (0.21). It is a critical drug in the management of various illnesses. It is colourless, odourless and tasteless and even today there are many aspects of oxygen therapy which are poorly understood. It is a drug that is inappropriately used or in some instances abused in a hospital setting thus leading to some inadvertent errors.

Indications of oxygen therapy:

Oxygen is indicated in any sick patient leading to the following situations:

1. Hypoxemia: This is defined by inadequate amount of oxygen in the blood and clinically objectively identified when the saturation (SpO_2) is < 90% or the partial pressure of oxygen (PaO_2) < 60 mmHg in an arterial blood gas (ABG) sample.
2. Hypoxia
3. Excessive work of breathing
4. Excessive myocardial load

The main causes of hypoxemia are:

1. Presence of a shunt in the cardio-respiratory system
2. Hypoventilation due to any cause leading to a rise in carbon dioxide and fall in oxygen
3. Ventilation perfusion (V/Q) mismatching as in pneumonia, pulmonary edema or acute lung injury
4. Increased diffusion gradient as in early pulmonary edema

Assessment of the need for oxygen: The need for oxygen in a particular patient is done by three ways:

1. Clinical assessment
2. Pulse oxymetry
3. ABG

The clinical symptoms of hypoxia are presence of impaired judgement, agitation or restlessness, disorientation, confusion, and in extreme conditions lethargy and coma. Clinical signs include tachypnea, tachycardia, dysarrhythmias, elevated blood pressure, diaphoresis and central cyanosis. Pulse oxymetry is a readily available tool that can be used both in hospital as well as clinic settings for assessment of the hypoxia. A lot of reliable and portable including finger tip oxymeters are readily available to the astute clinician and is a good objective way of confirming tissue hypoxia. ABG is the most reliable as it gives us the partial pressure of oxygen in figures but may not be easily available because of its cost.

Sources of oxygen

The main source of oxygen is the oxygen cylinders which contain compressed oxygen and come in different

sizes from portable to the big jumbo cylinders for hospital use. The other sources are liquid oxygen and oxygen concentrators or in hospital settings from the central gas pipe line systems.

Oxygen delivery devices

Many devices are available in the market for delivery of oxygen to the patient such as:

1. Nasal cannulae
2. Nasal prongs
3. Nasal masks
4. Face masks
5. Through ventilators, continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) devices.

Oxygen delivery systems

There are three kinds of oxygen delivery systems:

1. *Low flow* – Gas flow is insufficient to meet all the inspiratory requirements
2. *High flow* – Gas flow is sufficient to meet all inspiratory requirements
3. *Reservoir* – Stores a reserve volume that exceeds or equals the patient tidal volume

Low flow systems:

These contribute partially to the inspired gas taken in by the patient. It is a variable mix of air and oxygen and delivers oxygen at a flow of = 8 litres per minute. The common low flow devices in use are the nasal cannulae, simple mask and rebreather masks.

A. Nasal cannulae – These are used for stable patients and use 100% oxygen but this gets mixed with air during inspiration. They are able to deliver FiO_2 of 0.22 to 0.44 which is again affected by flow rate, respiratory rate and minute ventilation. The usual flow rate required in this device is 1-6 L/min. The concentration of inspired oxygen in the nasal cannulae can be increased by 4% by increasing the flow rate by 1 L/min.

(a) 1 L/min=24%

(b) 2 L/min=28%

(c) 3 L/min=32%

(d) 4 L/min=36%

(e) 5 L/min=40%

(f) 6 L/min=44%

There are some reservoir nasal cannulae which have a reservoir at the site of the cannulae. The reservoirs store oxygen during expiration and deliver 100% oxygen during the next inspiration. They deliver a higher FiO_2 than the nasal cannula and do not require humidification. It has the advantage that the patient can do activities like talking, eating and spirometry while on the device.

B. Simple mask – This is the most commonly used device and delivers FiO_2 of 0.35 to 0.5. The minimum flow rate required in order to wash out the CO_2 is 5 L/min. The disadvantages are that it causes dryness of the nasal and oral mucosae at high flow rates and also irritation of the skin on prolonged use.

C. Partial rebreather mask – This is a mask with a reservoir. It delivers FiO_2 of 0.4 to 0.7 at a flow rate of 6-10 L/min and the reservoir should be ½ full on inspiration. It is not commonly used.

D. Blow by oxygen – Here the oxygen is delivered in a non threatening way by putting the tubing or the tubing attached to a baby mask and placing it near the baby's face (Fig 1). It delivers $FiO_2 < 30\%$ and is not a reliable way to deliver oxygen but comes in handy in agitated babies or in those who require a very small amount of oxygen to maintain $SaO_2 > 90\%$.

High flow systems :

These systems deliver oxygen at high flows and consists of the following devices:

1. Venturi mask
2. Non rebreather mask
3. Aerosol masks

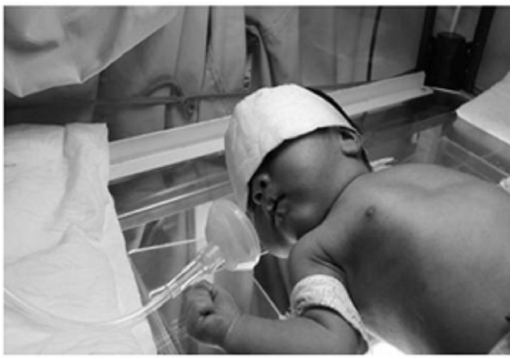

Fig 1: Oxygen delivered by blow by method

4. T Tubes
5. Face tents
6. Oxygen hood
7. Humidified high flow nasal cannula (HHFNC)

A. Venturi mask – These consists of 5-7 interchangeable air entrainment devices which delivers FiO_2 of 0.25 to 0.5 (Flow rate independent). The oxygen concentration that can be achieved is maintained by color coded valves which deliver a fixed FiO_2 (Fig 2). The FiO_2 delivered by the different colour coded valves are as follows:

(a) 24% blue
(b) 28% white
(c) 31% orange
(d) 35% yellow
(e) 40% red
(f) 60% green

B. Non-rebreather masks – These are masks which can deliver a high concentration of oxygen and are the preferred mode of delivery of oxygen to very sick but conscious patients. The device (Fig 3) consists of a one way valve which prevents reentry of exhaled air. It delivers FiO_2 of 0.6 to 0.8 at flow of 10 L/min. the reservoir should be 1/4 to 1/2 full on inspiration and the mask should fix snugly on the face for ensuring a maximum FiO_2 delivery. It is ideal for use in the emergency room. Starting at 6 L/min, an increase of 1 L/min will ensure an increase of the inspired oxygen concentration by 10% as indicated below:

Fig 2: Colour coded Venturi Masks

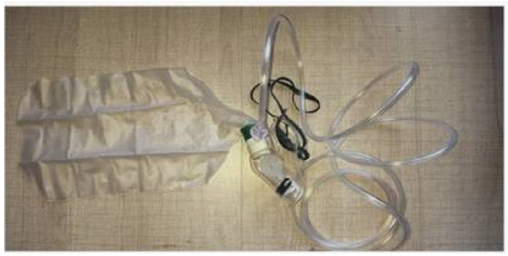

Fig 3: Non rebreathing mask

(a) 6 L/min=60%
(b) 7 L/min=70%
(c) 8 L/min=80%
(d) 9 L/min=90%
(e) 10 L/min= almost 100%

C. Oxygen hood – This is another commonly used device in the newborn unit. What one has to remember while using this device is that it requires a minimum flow rate of 7 L/min (2 to 3 L/kg/min) to prevent the accumulation of CO_2 inside the hood and rebreathing of CO_2 by the infant. It can deliver Fio2 ranging from 0.21 to 1.0 depending on the flow rate and how many ports are kept open. It can deliver FiO_2 of 0.8 to 0.9 at flow rates of 10-15 L/min.

D. Humidified high flow nasal cannula (HHFNC) – HHFNC is nowadays the preferred mode of oxygen delivery used in patients with high O_2 requirements. It is being increasingly used as an alternative to CPAP or non invasive ventilation (NIV). The use of this modality requires that the oxygen should be humidified and the flow rates of oxygen exceed patient inspiratory flow rates.

The device works by targeting different aspects in the respiratory cycle. The high flow rate ensures the wash out of the anatomical dead space and helps in washing out of CO_2 and delivers 100% oxygen and maintains positive airway pressure throughout the respiratory cycle (Fig 4). The humidified oxygen flowing at a high flow rate also ensures that the nasopharyngeal wash out occurs along with optimized mucocilliary clearance. The recommended flow rates for HHFNC are:

(a) 6-8 L/min in smaller children

(b) 10-15 L/min in bigger children

(c) >30 kgs: 45-50 L/min

With these flow rates, the FiO_2 can be titrated to maintain SaO_2 of 92-95%. The indications of HHFNC are as follows:

(a) An FiO_2 requirement of >40%

(b) Increased work of breathing as manifested by tacypnea and retractions

(c) Presence of thick secretions

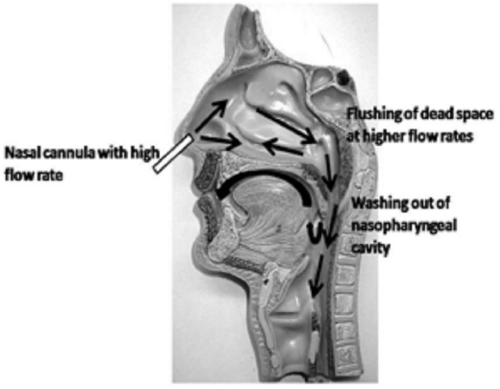

Fig 4: Mechanism of action of HHFNC

The basic requirements for using HHFNC are a standard heated humidifier, oxygen blender, respiratory circuit and appropriately sized nasal cannulae. The optimal weaning strategies from HHFNC are not very clear but usually weaning is done when the FiO_2 requirement goes below 40% along with improvement in recessions as well as reduction of secretions. Patient can then be put on the conventional nasal prongs.

E. Other devices like the face tents, aerosol masks and T-tubes deliver high oxygen concentration in a similar fashion but are applied differently. Aerosol masks are most commonly used during nebulization and T-pieces are used during weaning in an intubated patient. For an aerosol masks, a flow of 10-15 L/min is required and can deliver FiO_2 of 0.28 to 1.0.

F. Ventilators – This is for intubated and ventilated patients and has the advantage of delivering FiO2 from 0.21 to 1.0.

Which method of Oxygen delivery to choose from?

There are no clear answers on which method of oxygen delivery to choose from. It all depends on patient condition and morbidity, available infrastructure, expertise and patient response.

Evaluation of patient on oxygen

This can be done clinically by assessing the improvements in the blood pressure, respiratory rate, pulse rate, capillary refill time, work of breathing and consciousness level. Objective assessments can be done by looking at the SpO_2 by pulse oxymetry or by measuring the PaO_2 on an ABG.

Weaning off from oxygen

The decision to wean off a patient from oxygen depends on the clinical status of the patient and decreasing oxygen requirements. The FiO_2 is gradually titrated to maintain SaO_2 of >92%. Once a minimum FiO_2 is reached then one can put off oxygen and see how well the child maintains SaO_2 > 92% on room air with no respiratory distress. Once a patient is able to maintain SaO_2 > 92% on room air in the absence of respiratory distress, then it is time to stop oxygen therapy.

Side effects of oxygen therapy

Many a times in clinical practice, oxygen is used rampantly without considering the fact that it is also a drug and has equal potential as other drugs to cause harm to the human body. The various side effects of undue or excessive use of oxygen are as follows:

1. Physiological effects such as vasoconstriction, V/Q changes and CO_2 narcosis
2. Ventilator depression in the spontaneously breathing child because of CO_2 wash out and loss of the ventilator drive
3. Absorption atelactasis
4. Depression of cilliary clearance and leucocyte dysfunction occurring with FiO_2 >0.5
5. Retrolental fibroplasias and retinopathy of prematurity on prolonged use
6. Chronic or acute lung injury on high FiO_2
7. Free oxygen radical induced damage to the brain and lung tissues esp. in case of newborn babies and more so in the preterm newborns

Conclusion:

There is no doubt that oxygen forms an important drug in the management of sick patients in the hospital, clinic or even at home. There are a number of devices to deliver the optimum oxygen required by a patient in different clinical conditions right from the newborn to the older child and adult. Clinical monitoring as well as use of simple tools like pulse oxymetry can guide oxygen therapy. The art behind the science of oxygen therapy is to assess the requirement of oxygen in a particular individual, choose the most appropriate deliver device as per the age and clinical situation, keep the patient under continuous monitoring and decide when and how to wean off oxygen at the appropriate time so as to prevent the various side effects of excess and prolonged oxygen use.

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Answer to the quiz:

BCG Adenitis: it may be nonsuppurative and suppurative.

Simple or nonsuppurative BCG lymphadenitis: It is usually best managed with expectant follow up only. Regresion occurs spontaneously over a few weeks or months. Medical treatment with erythromycin or ATD does not hasten the regression or prevent suppuration.

Suppurative BCG Adenitis: Consider needle aspiration to hasten resolution and prevent spontaneous perforation and sinus formation. Surgical excision is rarely needed and is meant for failed needle aspiration or draining BCG nodes.

Fact Sheet

Improving Outcome In Chronic Kidney Disease In Children: What Can Pediatricians Do?

Ripan Debbarma*, Himesh Barman**
Senior Resident, and Assistant Professor**, Department of Pediatrics, NEIGRIHMS, Shillong*

Introduction

Previously the term chronic renal insufficiency and chronic renal failure were used to characterize patients who had progressive decline in renal function. Chronic kidney disease (CKD) is the new term defined by the National Kidney Foundation – Kidney Disease and Outcome Quality Initiative (KDOQI) Group to classify any patient who has kidney damage lasting for at least 3 months with or without a decreased GFR or any patient who has a GFR of less than 60 mL/min per 1.73 m^2 lasting for 3 months with or without kidney damage[1,2]. The KDOQI Group classified CKD into five stages (table 1).

Burden of chronic kidney disease

Burden of CKD is increasing worldwide. The magnitude of adult CKD varies from one geographical area to another due to genetic and environmental factors. The exact prevalence of CKD in India is not known due to lack of adequate data recording systems. Three studies from different parts of India have found the prevalence of CKD in adults, ranging from 7.85 to 13.5 per 1000 population. The incidence of End Stage Renal Disease (ESRD) was estimated to be 181 per million populations in 2005 in central India[3-6]. The data on prevalence of chronic kidney diseases in children is even more scary. Recently with the Support of the Indian society of Nephrology, a CKD registry has been set up with the hope of generating adequate information about patients in India. As 38 centers of Indian Society of Pediatric Nephrology centers also enrolled into the registry it is likely to give some insight into status of CKD in Indian children[6].

Survival and quality of life

In last three decades there is improvement in care of children with kidney diseases owing to development of

Table 1: Classification of chronic kidney disease

Stages	Description	Corresponding estimated GFR
Stage 1	Kidney damage with normal or increased GFR	Greater than 90 ml /min/1.73m^2
Stage 2	Mild reduction in the GFR	60-90 ml/min /1.73m^2
Stage 3	Moderate reduction in the GFR	30-60 ml/min /1.73m^2
Stage 4	Severe reduction in the GFR	15-30 ml/min /1.73m^2
Stage 5	Kidney failure	Less than 15 ml/min /1.73m^2

medical technology and better understanding of disease biology. This has allowed long term survival of children with end stage renal disease is possible. Advances in organ transplant have allowed transplant recipients to lead a near normal life. The advances in technologies in continuous ambulatory peritoneal dialysis (CCAPD) and maintenance hemodialysis allow them to be used effectively as bridge therapy till transplant and occasionally as destination therapy. However despite all that advances the mortality of kidney disease in children is thirty times more compared to healthy children[7]. Precise survival data from India is not available but diagnosis of end stage renal disease in children is a literal death sentence with most of them surviving only few months and that too with a poor quality of life. It has been documented all round the world that the outcome of ESRD in disadvantaged population is poorer. Health seeking behavior, access to health care and various biological factors and environmental factors may be responsible for this[8].

Poverty and chronic kidney disease: Bidirectional relationship

In addition to having a higher disease burden, the poor have limited access to resources for meeting the treatment costs. A large proportion of patients who are forced to meet the expensive ESRD treatment costs by incurring out-of-pocket expenditure, get pushed into extreme poverty. In one Indian study, over 70% patients undergoing kidney transplantation experienced catastrophic health care expenditures[9]. Entire families felt the impact of this, including job losses and interruptions in education of children. Once a child is diagnosed to have ESRD it comes a shock to the parents. Despite all the development in medical technology, these children do not survive for long after having diagnosed as ESRD and the quality of life for the period of survival in not good. In the mean while the family exhausts all their resources in treatment. This makes ESRD in children in resource poor country an ethical rather than medical issue. Whether to offer maintenance dialysis/ or palliative care is a tough and decision

Etiology of chronic kidney disease (Table 2)

In 2003 study of 305 children, diagnosed to have chronic renal failure over a 7-year period, obstructive uropathy was the commonest cause of CRF present in 97 (31.8%) children. Other causes included chronic glomerulonephritis in 84 (27.5%), reflux nephropathy in 51 (16.7%), hereditary nephritis in 20 (6.6%), renal dysplasia in 15 (4.9%) and hemolytic uremic syndrome in 5 children. The commonest causes of CRF were obstructive uropathy and reflux nephropathy[10].

Preventive measures: Importance and feasibility

It has been outlined that the ESRD has a devastating consequences and once diagnosis is made the survival and quality of life is not good. What is noteworthy that many of the conditions, if detected and treated early may prevent occurrence of end stage kidney disease in these children later. Also children with chronic kidney disease if detected in earlier stages, remedial actions can be

Table 2: Etiology of chronic kidney disease

India (AIIMS) (10)	NAPRTICS (11)
Obstructive uropathy (31.8%)	Obstructive uropathy (22%)
Chronic glomerulo nephritis (27.5%)	Aplasia/hypoplasia/dysplasia (18%)
Reflux nephropathy (16.7%)	Glomerulonephritis (10%)
Heridetery nephritis (6.6%)	Focal glomerulosclerosis (9%)
Renal dysplasia (4.9%)	Reflux nephropathy (9%)
Hemolytic uremic syndrome (1.6%)	

taken to delay progression into end stage kidney disease. This will prolong quality life in these children with a favorable socioeconomic impact.

It is apparent that most causes of ESRD in children are potentially remediable if detected early. In conditions like obstructive uropathy and reflux progressing to higher stage of CKD is largely preventable by timely detection and referral. The progression of CKD in chronic glomerulonephritis can also be delayed if detected early. This underscores the importance of early detection of CKD.

Improving outcome in chronic kidney disease: what can a pediatrician do?

Primary prevention :

Awareness about kidney health among general population as well as pediatrician is very important. This is likely to help avoid practices which may have negative impact of kidney health. Attention to following aspects may be helpful

(1) Prevention of acute kidney injury – It is usually believed that acute kidney injury is distinct from chronic kidney disease as AKI is often reversible. However it is important to appreciate that a proportion of AKI may lead to a irreversible renal damage of varying proportion and lead to persistent renal dysfunction which over time may progress to ESRD.

(2) Drug induced nephrotoxicity – Over the counter drug use especially in chronic disease requiring nephrotoxic (e.g, NSAIDs) drug may be dangerous. In acute conditions also when a nephrotoxic drug is chosen, due consideration should be given to risk benefit ratio. If there is risk of AKI or pre existing CKD an alternate drug should be considered. Maintenance of hydration should be actively monitored if nephrotoxic drug needs to be given.

Early diagnosis:

The data from the North American Pediatric Renal Transplant Co-operative Study (NAPRTCS) reveals that children with stage 1 constitute 28% and stage 2 or 3 constitute 70% of children registered for CKD[11]. However, in India the children are often diagnosed in stage of end stage renal disease and the therapeutic window is lost.

(1) High index of suspicion – We need to have a high index of suspicion, as chronic kidney diseases in its early stages may be asymptomatic. Table 3 and 4 shows the situations where CKD should be suspected. It is recommended that all children above 3 years needs to undergo blood pressure measurement during hospital visit. High index of suspicion should be kept for children with short stature or slow growth velocity.

Table 3: When to suspect chronic kidney disease[12]

Abnormal renal imaging
Unexplained anemia
Failure to thrive, not explained by under nutrition or gastrointestinal disorders
Bony deformities
Recurrent urinary infection
Polyuria
Systemic disease with known renal involvement
Hypertension
Persistent proteinuria and abnormal urine analysis
Positive family history of kidney disease
Exposure to nephrotoxic drugs

(2) Estimation of GFR – Whenever a child is suspected to have chronic kidney disease and serum creatinine is ordered, estimation of glomerular filtration rate needs to be calculated by the Schwartz formula. This simple step allows one to assign a stage of CKD to these children, which help decide what needs to be done. Relying on serum creatinine alone may allow early stages of CKD to skip our radar. It should be realized that kidney damage even without drop of glomerular filtration rate is qualifies for CKD stage 1 remedial action be taken and be followed up for progression to higher stages.

eGFR= k x length / serum creatinine.

The value of k = 0.45 in infants, 0.55 in children and 0.7 in adolescent male.

Table 4: Clinical clues to early diagnosis of chronic kidney disease (adopted from reference 12)

Clues in history	Clues in examination
Antenatal events:	***At birth:***
Hydronephrosis – seen with obstruction	Single umbilical artery
Oligohydramnios – secondary to renal dysfunction/obstruction	Palpable bladder
Polyhydramnios – secondary to polyuria	Spinal defects
	Ambiguous genitalia
At birth:	Dysmorphic features
Intrauterine growth restriction	
Respiratory distress – associated with lung hypoplasia	***Older Children:***
Perinatal asphyxia	Short stature
	Pallor
Infancy/childhood:	Edema
Failure to thrive	Hypertension
Easy fatigability	Rickets/bony deformities
Developmental delay	Spinal defects
Polyuria/polydipsia or edema	External genital defects
Recurrent fever – suggesting urinary tract infections	Quite tachypnea
Recurrent seizures – secondary to hypocalcemia, hypertension, and uremia	ascites, and abdominal mass (renal, bladder)
Refractory anemia	***Eye:***
Recurrent vomiting – seen with metabolic acidosis and uremia	Hypertensive retinopathy
Bony deformities	Cystine crystals
Poor urinary stream	Chorioretinitis (congenital infections causing nephrotic syndrome)
Incontinence	Aniridia (Denys–Drash syndrome)
	Optic atrophy
	Retinitis pigmentosa (nephronophthisis)
	Sensory neural deafness (Alport's syndrome, renal tubular acidosis)

Management plan

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease in Children has proposed an action plan for each stage of CKD. For a child with stage 1 CKD, treatment of the primary and co-morbid conditions with measures to slow the progression and reduce the cardiovascular disease risk factors are recommended. At stage 2 and 3 it is important to regularly estimate the rate of progression of CKD while ensuring a constant evaluation and treatment for co-morbid conditions. At stage 4, preparations for renal replacement therapy are initiated, since by CKD stage V it is imperative to provide renal replacement therapy[13].

Retarding progression

Early identification of factors with a potential to accelerate the progression of renal disease helps plan the course of action in a child with CKD. The key points to retard the progression of CKD is shown in table 5. The stage specific interventions are shouwn in figure 1. All attempts should be made to determine the aggravating factors for worsening renal functions. Simple measures like avoiding nephrotoxic drugs when alternatives are available can help prevent further damage, e.g. in a child with CKD,

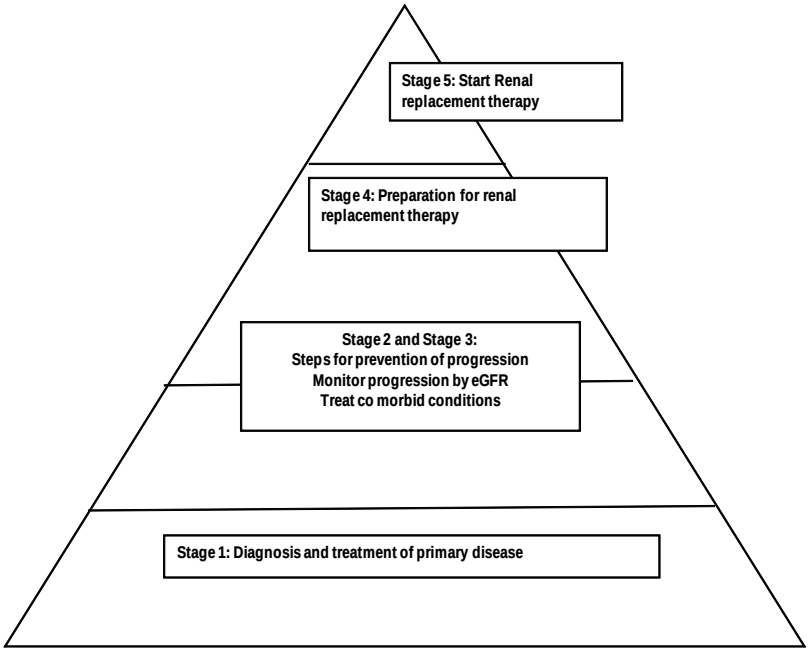

Figure 1: Stage specific interventions in a child with CKD

fever and pain can be treated with paracetamol instead of ibuprofen. It is important to avoid dehydration especially in children with tubulopathies and polyuria states. The use of nephrotoxic medications in a setting of sepsis and dehydration has a cumulative nephrotoxic effect. Urinary tract infections need early diagnosis and treatment[14].

Table 5: Key points to retard progression of CKD[14]

Control of hypertension
Reduction of proteinuria
Management of anemia
Prevention of dyslipidemia
Prevention of acidosis
Non- hypercalcemic doses of vitamin – D analogs

Early referral of chronic kidney disease to pediatric nephrologists

Stage 1 to stage 3 is the therapeutic window as in these stages certain remedial actions can be taken (table 3). Therefore, it is important that chronic kidney disease once diagnosed early should be referred early to a pediatric nephrologist for optimization of therapy. Thereafter the pediatrician may jointly follow up the child with the pediatric nephrologists. Late referrals to pediatric nephrologists (in stages 4 and 5) are futile as little can be done in these stages to delay further decline in GFR.

School health screening program

Urine screening for school children as a strategy for early diagnosis of chronic glomerulonephritis (eg. IgA nephropathy) has worked well in many south east asia countries. Feasibility of such program has been demonstrated in India. School health screening program as a strategy to adopt into rest of the world for early diagnosis of renal diseases is under debate

Conclusion

End stage renal disease in children is a devastating clinical condition. Many of the conditions leading to ESRD in children are remediable. Pediatricians sensitive to picking up these conditions before occurrence of any drop in GFR or in early stages of CKD can delay/avoid occurrence of end stage kidney disease in these children.

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Announcement

Fact Sheet

Scrub Typhus – The Meghalaya Experience

Richard Mario Lurshay*, Palash Ranjan Gogoi, Santanu Deb***

DNB trainee, Consultant,***Senior Consultant and HOD, Department of Pediatrics, Nazareth Hospital, Shillong*

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*. The pathogen is an obligate intracellular gram-negative bacterium. Even though it is recognised as one of the tropical rickettsioses, *O. tsutsugamushi* has a different cell wall structure and genetic composition than that of other rickettsiae.

The term scrub is used because of the type of vegetation (terrain between woods and clearings) that harbours the vector; however, the name is not entirely correct because certain endemic areas can also be sandy, semi-arid and mountain deserts[1].

Scrub typhus, a dreaded disease in pre-antibiotic era, is a militarily important disease that caused thousands of cases in the Far East during the Second World War.It was suspected to be the leading cause of pyrexia of unknown origin (PUOs) in forces of the United States of America during the Vietnam conflict. Scrub typhus is essentially an occupational disease among rural residents in the Asia-Pacific region.An increase in the prevalence of scrub typhus has been reported from some Asian countries, which coincides with the widespread use of ß-lactam antimicrobial drugs and urbanization in rural areas[1].Scrub typhus is endemic to a part of the world known as the "tsutsugamushi triangle". As shown in fig 1. It extends from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan in the west[2].Approximately 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk[3].

Fig 1: Tsutsugamushi Triangle

Outbreaks are being reported with increasing frequency from different parts of India in the past decade[4].

2001 to 2002 – An outbreak (28 cases, 3 fatal) was reported in Tamil Nadu.

2003 – An outbreak (225 cases, 19 fatal) was reported in Himachal Pradesh.

2006 to 2008 – An outbreak (50 cases) was reported in Pondicherry.

2007 – An outbreak (38 cases) was reported in Bishnupur district, Manipur.

2009 to 2010 – An outbreak (80 cases, 5 fatal) was reported in Meghalaya.

2011 – Outbreaks were reported in Himachal Pradesh (200 cases, 13 fatal) and Nagaland (9 cases, 3 fatal).

Disease transmission

O. tsutsugamushi is transmitted via the bite of the larval

stage (chigger) of a trombiculid mite (Leptotrombidium), which serves as both vector and reservoir.The mite is very small (0.2 – 0.4mm) and can only be seen through a microscope or magnifying glass.Humans are accidental hosts and acquire this zoonotic disease from the bite of an infected chigger. The trombiculid mite is shown in fig 2 and the life cycle in fig 3.

Fig 2: Chigger mite (larva of trombiculid mite)[5]

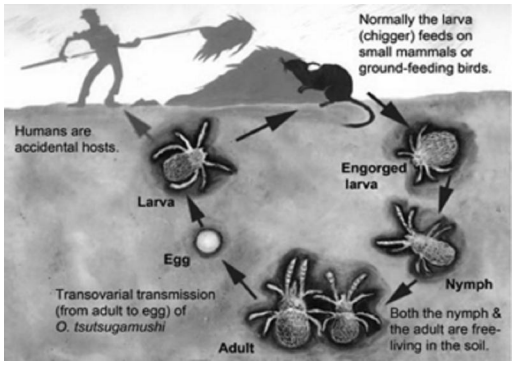

Fig 3: Life cycle of trombiculidmite[6]

Pathogenesis

Rickettsial microorganisms appear to exert their pathologic effects by adhering to and then invading the endothelial lining of the vasculature (microvasculitis) within the various affected organs[7].

Clinical features

Scrub typhus may be mild or severe. After an incubation period of 6-21 days, the rickettsiae proliferate at the site of the chigger bite to form in less than 50% of cases, a necrotic eschar with an erythematous rim. An eschar, if found, is pathognomonic of scrub typhus[7]. Eschars are found with difficulty in dark skinned individuals and when small. The common sites for finding an eschar are groin, axilla, waist and other damp and moist areas of the body.

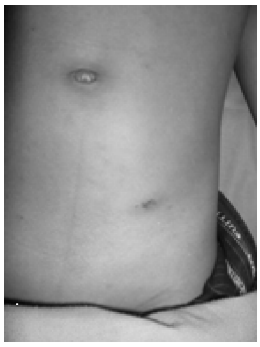

Fig 4 (i)

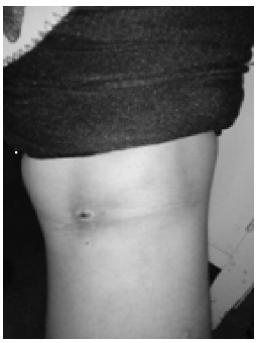

Fig 4 (ii)

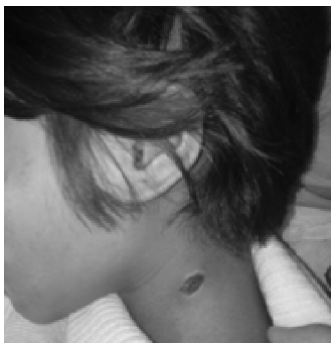

Fig 4 (iii)

Fig 4[8]: Eschars in the (i) abdomen, (ii) popliteal fossa and (iii) neck

Eschars resemble skin burn of cigarette butt and has an erythematous rim.

The onset of illness usually becomes manifest by fever, headache, and sometimes myalgia, cough, and gastrointestinal symptoms. Regional or generalized lymphadenopathy is common. A maculopapular rash is present in <50% of patients and involves the trunk and

extremities and infrequently the hands or face. Most patients have such mild to moderate symptoms which resemble viral fever and are treated as such. In fact, these signs and symptoms mimic many common causes of fever such as typhoid, meningococcal disease or malaria. Untreated patients may go on to develop complications or severe scrub typhus.

Complications – Severe scrub typhus

1. *Respiratory* – Interstitial pneumonitis and noncardiogenic pulmonary edema secondary to pulmonary microvascular leakage are occasionally observed[9].
2. *Neurological* – Meningoencephalitic syndrome is known to occur with rickettsial infections. In fact, rickettsial infections should be included in differential diagnosis of aseptic meningitis and encephalitis in patients exposed to endemic areas specially when accompanied by renal insufficiency and/or jaundice[10].
3. *Renal* – Acute renal failure is associated with bad prognosis and can be a presenting feature of rickettsial disease. The possibility of scrub typhus should be borne in mind whenever a patient of fever present with varying degree of renal insufficiency particularly if eschar exists along with history of environmental exposure[11].
4. Disseminated intravascular coagulation like syndrome, hepatic failure, gangrene and myocarditis are sometimes seen in rickettsioses[9].
5. *Gastrointestinal* – Upper gastrointestinal bleeding associated with scrub typhus
6. *Cardiac* – In one study[12] myocarditis with cardiogenic shock at presentation was the most common complication (34% of the cases). Most cases of myocarditis (75%) occurred during the second week of illness.

Laboratory findings

Laboratory findings are usually non-specific[9]. No single laboratory finding is specific for early diagnosis.

1. Normal WBC or leukocytosis may be seen. Total leukocyte count may be initially normal or low but leukocytosis develops as the disease progresses[7]. Thrombocytopenia may occur[13]. Erythrocyte sedimentation rate is usually high.
2. Hyponatremia and hypoalbuminemia, reflecting increased vascular permeability are sometimes helpful in differentiating rickettsial infections from other acute infections. Thrombocytopenia, hyponatremia and normal to low leukocyte count are certain clues to early diagnosis. Hepatic transaminase values are frequently elevated. Blood urea is elevated due to prerenal mechanisms[9].

Diagnosis

1. *Serology* – The mainstay in scrub-typhus diagnostics remains serology[14]. Micro-immunoflorescence, immunoperoxidase assay, latex agglutination, indirect hemagglutination, enzyme-linked immunosorbent assay, dot blot immunoassay (including dipstick test) and Weil-Felix test are the various serological methods available for diagnosis of rickettsial diseases[9].Of these, only Weil-Felix test is easily available inIndia. As all these tests detect antibodies, they would be able to make diagnosis only after 5-7 days of onset of disease and hence play no role for initiation of therapy in a suspected case.
2. *Weil Felix test* – The cheapest and most easily available serological test; but is notoriously unreliable. The Weil-Felix test is based on the detection of antibodies to alkali based carbohydrate antigen which are shared by some rickettsiae and certain strains of Proteus species, *P.vulgaris* OX19, and OX2 and *P.mirabilis* OXK. The poor sensitivity of the WF test is now well demonstrated but a good correlation between the results of the WF test and detection of IgM antibodies by an indirect immunofluorescence assay (IFA) is often observed[15].

In spite of all its drawbacks, Weil-Felix test still serves as a useful and cheap diagnostic tool for laboratory diagnosis of rickettsial disease. Either fourfold rise in agglutinin titre in paired sera or single titre of more than

1:320 is considered diagnostic for infection. The use of this test is accepted in conditions where definitive investigations are not available[16].

1. *Indirect Immunofluorescence Antibody (IFA)* – IFA is the gold standard and is used as a reference technique in most laboratories. Detection of rickettsiae by using immunofluorescence allows the confirmation of infection in patients prior to their seroconversion. It has been recommended previously that the "IFA should be considered a technique for sero-epidemiology only in areas where the seroprevalence of rickettsial disease has already been established"[15].
2. *Rapid diagnostic test* – A solid phase immunochromatography assay for the rapid, qualitative detection of IgG, IgM or IgA antibodies to *Orientia tsutsugamushi* in human serum, plasma or whole blood. Sensitivity of this test is 66.7% and specificity 98.4%. Available in India (SD Bioline)[18].

Management

1. The recommended treatment regimen for scrub typhus is doxycycline (2.2 mg/kg/dose bid PO or IV, maximum 200 mg/day)[3].
2. Alternative regimens include tetracycline (25–50 mg/kg/day divided every 6 hr PO, maximum 2 g/day) or chloramphenicol (50–100 mg/kg/day divided every 6 hr IV, maximum 3 g/24 hr)[3].
3. Azithromycin 10mg/kg/day for 3-5 days

The therapy should be continued for a minimum of 5–7 days and for at least 3 days until the patient is afebrile in order to avoid relapse. Patients treated with one of these regimens usually become afebrile within 48 h and thus the entire therapy lasts for less than 10 days[3].

Diagnosis

No rapid laboratory tests are available to diagnose rickettsial infection early in the course of disease. It is emphasized again that the only crucial factor for early diagnosis is high index of suspicion. Following five factors taken together should help in diagnosis, which can then be confirmed with serology[9].

1. *Compatible clinical presentations* – Fever without source, pyrexia of unknown origin (PUO), fever with rash, fever with eschar, meningoencephalitis or aseptic meningitis, acute renal insufficiency with eschar, and infective vasculitidis.
2. *Tick bite or tick exposure*– History or physical evidence of tick bite
3. *Epidemiological data* – Residing in or travel to an endemic area
4. Suggestive laboratory features
5. *Rapid defervescence with appropriate antibiotics* – It is so characteristic that it can be used as a diagnostic test for rickettsial disease. In fact if fever fails to respond in 48 hours, one should review the diagnosis. Severely ill patients with multiple organ dysfunction may take a longer period of time to respond.

Our experience

Since the 2009 - 2010 outbreak, cases are being continuously diagnosed and reported with increased prevalence in the winter months in Meghalaya.

In one study[17] carried out in Nazareth Hospital, Shillong, we found fever with cough (50%), fever with headache(18%) and fever with diarrhea (15%) to be the commonest presenting complaints in children with mild to moderate scrub typhus. In patients who had severe scrub typhus[8], common symptoms included headache (58.7%), loss of appetite (46.7%), cough (46.7%), vomiting (45.3%), abdominal pain (32%), breathing difficulty (25.3%), myalgia (24%), altered sensorium (24%), loose stools (16%), convulsions (14.7%), swelling of the body (14.7%) and facial puffiness (13.3%). Eschar was present in only 1 of 67 patients with mild scrub typhus[17] whereas it was present in 16 of 75 (21%) of patients with severe scrub typhus(8). 44% patients were found to have conjunctival redness[8].

Amongst 75 patients with severe scrub typhus[8], most (58.6%) had predominantly CNS involvement (meningoencephalitis), 34.6% had gastro intestinal involvement, 33% had respiratory system involvement

and 16% had cardiovascular system involvement.

Of the 25(33%) patients who had respiratory involvement, 10 had interstitial pneumonia, 4 had pleural effusion, 8 had consolidation and 3 had ARDS. 6 of 75 children had metabolic acidosis with increased arterial lactate on ABG. 3 children had hypotension below the 5th percentile for age and 3 children required a vasoactive drug to maintain blood pressure within the normal range.

Laboratory evaluation[8] showed that 78.7% of the children had a raised ESR; 74.6% of the patients had anemia. C-Reactive Protein was elevated in 82.7%. Leukocytosis was seen in 46.7% of children and of these neutrophilia was found in 22.7%. Thrombocytopenia was documented in 49.3%. Raised serum SGPT levels, hypoalbuminemia, hyponatremia, hyperkalemia and hypocalcemiawere commonly found in the patients who had severe scrub typhus. Serum creatinine was found elevated in 9.3% children.

Lessons learnt

Mortality rates in our institution have come down significantly because of early diagnosis and prompt institution of therapy because of high index of suspicion. The preferred drug is Doxycycline. A randomized control trial[17] has found no difference between Doxycycline and Azithromycin in bringing about defervescence in patients with mild scrub typhus. Alternative medications being used in our institute is intravenous Chloramphenicol for meningoencephalitis.

Conclusion

Physicians should consider scrub typhus when caring for patients with acute febrile illness in endemic areas. Identification of clinical signs like neck stiffness, hepatosplenomegaly and respiratory distress would help in timely recognition of complications such as meningoencephalitis, pneumonia and ARDS. This is of paramount importance to ensure a favorable outcome in pediatric patients with scrub typhus.

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East Zone Academy of Pediatrics

Executive Board 2015

Update on Pertussis Vaccination

Shafi Kolhapure
Head of Medical Affairs, Novartis Vaccines, India

1) **What are the issues and challenges in the pertussis vaccination, globally and in India?**

Current status of global pertussis resurgence:

- The recent phenomenon of pertussis resurgence is an important global problem and is being witnessed across the developed countries.
- In Australia, there is an ongoing epidemic since 2008, with >38,000 cases in 2011; similarly, in New Zealand, there is an ongoing epidemic since 2011.
- In Latin America (viz. Argentina, Brazil, Chile, Colombia and Uruguay) pertussis epidemics have been reported in 2011-2012.
- In UK (England and Wales), >8,000 cases were reported in 2012, while the USA reported >40,000 cases in 2012.

Issues with aP vaccine :

- There is growing evidence that aP vaccines have sub-optimal efficacy in primary series; they do not provide long-term protection; and even after repeated boosters aP vaccines do not provide adequate protection.
- Also it should be noted that the activation of type of immune response is different for both vaccines; and wP vaccination mimics natural infection mainly driven by Th1 biased immune response (whereas aP vaccination induces predominantly Th2 biased immune response). The Th2 biased immune response generated by aP vaccines in the primary series has serious implications; as this lead to the non-booster response to subsequent aP vaccine's booster doses (especially after 5/6 booster doses). It significantly contributes to create a vulnerable cohort of children and adolescents in any community; despite multiple boosters.

Issues and challenges in the pertussis vaccination in India:

- In the Indian context, there are numerous issues and challenges such as there is virtually non-existent Vaccine Preventable Diseases (VPDs) surveillance system, pertussis is not considered an important health problem, the diagnosis of pertussis remains exclusively clinical (due to lack of modern diagnostic modalities), the incidence of pertussis along with mortality is underestimated and underreported; and a large heterogeneity exits in terms of vaccination coverage across states with high rate of movement of individuals.
- Also, in India, the major challenge is of choosing the 'right' wP pentavalent vaccine, with well documented proven immunogenicity, efficacy and safety based on Evidence Based Approach (EBA) from the all available DTwP pentavalent vaccines.

2) Why field-based efficacy trials are the only

way to prove protective efficacy of pertussis vaccines?

- As till date there is no known 'correlate of protection' for pertussis, nor there are any established protective antibody levels; the real-time field-based vaccine efficacy study is the only way to prove protective efficacy of any wP or aP pertussis vaccine.
- Also, any wP or aP pertussis vaccine showing high immunogenicity in the controlled clinical trial; may not have same vaccine efficacy in the real-time field usage.

3) What are the global and Indian health association's recommendations for pertussis vaccination?

Efficacy of aP vaccines:

- A recent study by Misegades et al. following outbreak of pertussis in California in US, showed that even the 5-component aP vaccine efficacy was 88.7%.
- In another systematic review of 49 RCCTs of 3 component aP vaccines, Jefferson et al. showed higher absolute efficacy (80-84%) of 3C vaccines than 1 or 2 components (67-70%).
- Also, the Cochrane Review of 6 aP vaccine efficacy and 52 vaccine safety trials showed that the efficacy of one- and 2-component vaccines in preventing typical whooping cough was 59 - 75%; while in preventing mild disease was further lower at 13 - 54%.

WHO SAGE recommendations about pertussis vaccines:

- Considering all the currently available evidences, World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) on pertussis recommend use of wP vaccine for primary infantile vaccination series. WHO-SAGE pertussis working group recommends that countries where less than 5 doses of pertussis are used, wP vaccines should be used for primary early infant vaccination. SAGEgroup also mentioned that, switch from wP vaccines to aP vaccines will result in resurgence of pertussis after some years with increased risk of neonatal deaths and magnitude of such resurgence is difficult to predict.

IAP recommendations about pertussis vaccines:

- The Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) recommends that the primary immunization series to be completed with 3 doses of wP vaccines, and DTaP vaccine/combinations should preferably be avoided for primary series.
- Also, the 1st and 2ndboosters may also be of DTwP; however, considering relatively higher reactogenicity DTaP vaccines can be considered for the boosters.
- ACVIP also reinforces that all the currently available wP pentavalent vaccines are not same on parameters like pertussis immunogenicity, safety, reactogenicity, WHO-PQ and global usage.

IAP and JCVI recommendations about 2 component aP vaccines:

- As mentioned earlier, the vaccine efficacy of 2 component aP vaccines is unacceptably low and the available evidence does not favor use of 2-component aP vaccines in primary series.
- The ACVIP of IAP have evaluated all the available evidence and recommended to avoid aP vaccines in primary series.
- Also, the latest recommendations from Joint Committee on Vaccination and Immunization (JCVI), UK (released on 1st October, 2014) favors use of 3 component aP vaccines; particularly given the recent increase in pertussis incidence in UK.
- In fact many other developed countries (especially USA and Canada) use 5-component aP vaccines; and still they all are having the pertussis resurgence problem.

4) Why globally no other country has not

recommended not to use aP vaccines in the primary series?

- The developed countries facing pertussis resurgence or outbreaks have no other option of using wP or wP combination vaccine products as no wP vaccines is currently licensed in these countries.
- Also, for shift from aP to wP vaccines the regulatory or licensure pathway of wP or wP combination vaccine will take many years for developing new wP candidate vaccines for clinical trial evaluation.
- Furthermore, as there is also strong resistance against wP vaccines from population, which can lead to the reduced compliance to overall immunization.

5) Why developed countries (viz. US, Canada, Australia, etc.) are not getting back to wP?

- These countries have temporarily circumvented the recent pertussis outbreak by initiating repeated boosters every 10 years (mainly targeted at adolescents) and cocooning strategy (i. e. maternal immunization in pregnancy, HCP, adult and elderly immunization).
- As mentioned earlier, as wP vaccines are not currently licensed in these countries, the newly formulated wP vaccines will be treated as new vaccines; and their clinical trials will require many years.

6) In India as only a small portion of children receive aP vaccines, so will it lead to pertussis resurgence?

- It is an established fact that aP vaccines have sub-optimal efficacy, they only prevent serious disease, they have lower efficacy against milder disease; and aP vaccines don't prevent colonization of the respiratory tract. Therefore,aP vaccine using countries are at higher risk of increased carriage and transmission of B. pertussis in the vaccinees, despite of 5 or 6 doses of aP vaccines.
- As mentioned earlier, the Th2 biased immune response generated by aP vaccines has implications of creatinga vulnerable cohort of children in a community with high prevalence of pertussis in India. Furthermore, as currently 500,000 babies receive aP or aP combination vaccine every year in India, and with this rate there will be a cohort of 5,000,000 -7,500,000 vulnerable babies in next 10-15 years (which is not a small number to overlook).
- Also, as aP vaccines do not prevent B. pertussis colonization of the respiratory tract, there is significant risk of increase in unimmunized pockets of 'reservoirs of infection'. When it comes to India, our current usage is wP/wP combination vaccines in more than 95% babies as compared to 100% babies getting vaccinated with aP vaccines in developed countries; hence, in India it is easy to stop using aP vaccines in the primary series and shift to better option of wP vaccines.

7) As the pediatricians are more concerned on safety, reactogenicity due to wP vaccines (as compared to the aP vaccines), why they should recommend wP vaccines for primary series vaccination?

- Vaccination is for protection against disease with demonstrated and documented field safety, and globally out of 120 million annual birth cohort only 8-10 million babies receive aP vaccines (while 70-80 million babies receive wP vaccines).
- Of these 8-10 million babies in the developed countries, 50-60% birth cohort is facing resurgence or adolescent pertussis (along with non-booster response); and currently, there is no solution in sight.
- Hence for the pediatricians, protection against the disease should be the priority, than slightly higher reactogenicity due to wP vaccine as compared to the aP vaccines.

8) What should be done, in case parents demand for 'painless vaccine' in the primary series?

- It was reinforced that it is absolutely essential to

dispel the myth about 'painless vaccine', as all vaccines have some degree of associated local and systemic reactogenicity.

- Hence, the parents must be explained about the superiority of the wP vaccines in the primary series, as compared to aP vaccines.

9) Are all wP pentavalent vaccines are same?

- WHO recommends EBA for evaluating the quality of available evidence, based on Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology (GRADE) methodology ranks the high quality evidence as grade 4 evidence, as generated in Randomized Controlled Clinical Trials (RCCTS).
- When choosing which DTwP pentavalent vaccine from the available vaccines, following criteria need to be considered; as, vaccine efficacy, high immunogenicity, large safety database, Post Marketing Surveillance (PMS) data, published clinical trial database, sustained WHO prequalification and global usage.

10) Are all wPpentavalent vaccines same on reactogenicity scale?

- As mentioned in the latest IAP publication in October, 2014; currently available all DTwP vaccines are not same and they differ in their reactogenicity profile.

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East Zone PEDICON 7-9 November 2014, Tripura