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CJ 296, Sector II, Salt Lake City
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Ph: 09433014193;
Email: sbhakta57@gmail.com
E mail: iapwb@rediffmail.com

## *Editorial*

**Fight Pneumonia, save a child : Wednesday, November 12, 2014 is 6th World Pneumonia Day.**

Globally, pneumonia remains the most deadly disease for children younger than five. Yet with a combination of vaccination efforts and treatment with antibiotics, the Global Alliance for Vaccines and Immunisation (GAVI) calls pneumonia "one of the most solvable problems in global health." Every 15 minutes, a child dies due to pneumonia.

Pneumonia is a preventable and treatable disease that affects 155 million children under 5 and kills 1.6 million each year. This makes pneumonia the number one killer disease of children under 5, claiming more young lives than AIDS, malaria, and measles combined. Every one out of five global child death is due to pneumonia.

More than 99 percent of deaths from pneumonia occur in the developing world, where access to health care facilities and treatment is out of reach for most children. In spite of the massive death toll of this disease, affordable treatment and prevention options exist. There are effective vaccines against the two most common causes of deadly pneumonia, *Haemophilus influenzae* type B and *Streptococcus pneumoniae*. A course of proper antibiotics can cure the disease completely if it is started early enough. The Global Action Plan for the Prevention and Control of Pneumonia (GAPP) released by WHO and UNICEF on World Pneumonia Day, 2009, finds that 1 million children's lives could be saved every year if prevention and treatment interventions for pneumonia were widely introduced in the world's poorest countries.

Investments in preventing, treating, and protecting children against the two leading killers of young children – pneumonia and diarrhea – have contributed to significant declines in child mortality over the last decade, but there is more to be done. Tackling these two diseases will make the greatest strides toward reducing child deaths and achieving Millennium Development Goal 4.

World Pneumonia Day is held annually on November 12 to raise awareness of Pneumonia, promote treatment, prevention and generate action to fight against pneumonia. The United Nation first observed the day on November 12, 2009.

Let's observe sixth World Pneumonia Day on 12th November, 2014, Wednesday, to fight against pneumonia.

**Dr Santanu Bhakta**, *Editor in Chief*

*Original Article*

# Constipation Therapy : Recent Advances

**Dinesh S. Pashankar**
*Division of Pediatric Gastroenterology*
*Department of Pediatrics,*
*Yale University School of Medicine, New Haven, CT, USA*

## Introduction

Constipation with or without encopresis is a common problem in children. The prevalence of constipation is reported to be 0.7 to 29% in children worldwide[1]. The exact prevalence in India is not known, but appears to be rising due to changes in lifestyle and dietary choices[2]. Constipation is often a chronic problem in children, lasting for many years. Chronic constipation can lead to problems such as abdominal pain, encopresis, urinary tract infections and psychosocial issues.

Approximately 85 % of childhood constipation is functional in nature without any obvious organic identifiable cause[3]. Rare organic conditions presenting with constipation include Hirschsprung's disease, neurological disorders and celiac disease. These disorders need specific treatment for underlying causes[4]. The aim of this article is review therapy of functional constipation and recent advances including role of a new laxative polyethylene glycol 3350.

## Treatment of Functional Constipation

The systematic approach to childhood constipation involves stepwise approach that includes education, disimpaction, maintenance therapy including dietary intervention, laxative therapy and behavioral modification[5]. Recently, evidence-based clinical practice guidelines were published by the European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition in 2014[6].

## Education

Education of the family and the child involves unhurried explanation of the physiology of normal defecation and the pathogenesis of constipation and encopresis, preferably with the help of a diagram of the anorectum. It is important to explain to parents the vicious cycle of hard stools, painful defecation and withholding that is seen in many children. Action of laxatives and the treatment plan should be outlined. It should also be stressed that this is a chronic problem and may require a regular long-term treatment for many months.

## Disimpaction

Fecal impaction is usually diagnosed by physical examination or by the abdominal x-ray. Disimpaction can be performed by oral or rectal route using different medications. The approach for disimpaction depends on the urgency for disimpaction and physician's preference. The oral approach is noninvasive and takes longer time for disimpaction. The rectal approach is invasive and leads to faster disimpaction within hours.

Polyethylene glycol electrolyte lavage solutionis given as a large volume (up to 4 liters) lavage over a few hours for disimpaction. It is a very effective way of complete disimpaction within a day, but often requires nasogastric tube administration and hospitalization. It is also associated with adverse effects such as nausea,

vomiting, and abdominal distension[1]. Fecal disimpaction can also be achieved by using higher doses of laxatives such as mineral oil, magnesium hydroxide or lactulose for few days. However, poor palatability of these medications makes it difficult for children to take large doses. In the Western World, polyethylene glycol 3350 with and without electrolytes (PEG) has been successfully used for disimpaction in a dose of 1.5 g/kg/day for 3 days [7]. Disimpaction occurs slowly over 2-3 days. It is very effective and is well tolerated by children without any significant adverse effects. Therefore, it is recommended as a first line of therapy for disimpaction in the Europe and the Unites States[6].

The rectal approach by enemas and suppositories is invasive and not welcome by children. Glycerin suppositories can be used safely and effectively in infants. Phosphate enema administration is generally effective in children for fecal dispaction from the distal colon in a couple of hours. However, it is not effective for fecal impaction in the proximal colon. Phosphate can be absorbed in the systemic circulations, causing hyperphosphatemia. Severe hyperphosphatemia can lead to hypocalcemia, convulsions and coma. The risk of hyperphoshatemia is higher in children younger than 2 years of age and with repeated administration in a short time and therefore these practices should be avoided.

**Dietary Intervention**

Use of fiber has been shown to be beneficial in the treatment of constipation[8]. While fiber can be only therapy for mild constipation, laxatives are often necessary in addition to fiber for moderate and severe constipation. Also, compliance with fiber can be an issue for children due to poor palatability. Intake of vegetables and fruits with high sorbitol contents such as peaches and prunes should be encouraged. Excess intake of dairy products such as cheese may predispose children to constipation and should be discouraged.

**Laxative therapy**

Table 1 shows available laxatives with suggested recommended doses and possible adverse effects. Dose ranges are weight or age based and should be adjusted on an individual basis.

Osmotic laxatives absorb water in the gastrointestinal tract and soften stools. Lubricant laxatives lubricate and facilitate passage of stools from the colon. Both these types of laxatives are not habit-forming and can be used for long-term use. Stimulant laxatives cause the colonic contraction to expel stools. These are not recommended for long-term use due to adverse effect profile. In the past, milk of magnesia, lactulose and mineral oil were used to treat chronic constipation in children. These laxatives were effective in short term. However, poor palatability and adverse effects led to poor compliance, resulting in a low success rate.

Polyethylene glycol is an inert osmotic laxative that doesnot get absorbed in the gastrointestinal tract and therefore it has no systemic toxicity[1]. It is not fermented by colonic bacteria so it does not cause abdominal distension and flatulence as seen with lactulose. It can be mixed in a beverage of child's choice, so compliance over long-term is excellent. We reported short-term efficacy and optimal dose of PEG in the first pediatric study in 2001[9]. Subsequently, we studied a large number of children who were taking PEG for many months to assess long-term safety and efficacy. Clinical adverse effects were rare and included transient diarrhea (10%), bloating (6%) and abdominal pain (2%). There were no significant biochemical adverse effects associated with PEG therapy [10]. The success rate with PEG therapy was 93 % in children with constipation and 52 % in children with constipation and encopresis[11]. These rates are better than other laxatives for constipation and similar to other laxatives for therapy of constipation and encopresis[1]. While PEG is available without electrolytes in the USA, it is available as a formulation with electrolytes in Europe. Investigators from Europe have also reported excellent efficacy and safety of PEG with electrolytes over long-term in children[11]. Both these products have been used successfully for last few years in the Western world. PEG has also been used successfully and safely for children younger than 2 years of age for constipation[12]. In comparison trials, PEG was noted to

**Table 1.** Commonly used laxatives in children

| Medication | Dosage | Adverse effects |
|---|---|---|
| **Osmotic Laxatives** | | |
| Magnesium hydroxide (Milk of magnesia) | 0.4 to 4.8 g/day (Age-adjusted dose) | Hypermagnesemia, hypophosphatemia, and secondary hypocalcemia, use with caution in infancy and renal impairment |
| Lactulose | 1-3 g/kg/day | Flatulence, bloating, abdominal cramps, nausea |
| Polyethylene glycol 3350 (PEG) | 0.4 g/kg/day (Dilute in liquid) | Diarrhea, bloating |
| **Lubricant Laxatives** | | |
| Mineral oil | 1-3 ml/kg/day (Max 90 ml/day) | Nausea, vomiting, anal leakage, risk of lipoid pneumonia if aspirated, not recommended in infants and neurologi cally impaired children |
| **Stimulant Laxatives** | **(Short Term Use Only)** | |
| Seena | 2.5 to 20 mg/day | Abdominal pain, idiosyncratic hepatitis, melanosis coli, hyertrophic osteoarthr opathy |
| Bisacodyl | 5 to 10 mg/day | Abdominal pain, hypokalemia, renal mucosal abnormalities, urolithiasis |

be more effective than lactulose and milk of magnesia in various pediatric studies[6]. Therefore, it is recommended as a first line of therapy for childhood constipation by recent guidelines proposed by Pediatric Gastroenterology societies in the Europe and US[6].

PEG is now available in India with electrolytes and should be considered as a safe and effective therapy for constipation in children. The initial recommended dose is around 0.4 g/kg/day and it should be adjusted in an individual patient to achieve painless soft stools. It is important to remember that childhood constipation is chronic in many children and may require laxative therapy for many months. We recommend initial therapy for 2 months and then to reassess children to see whether long-term therapy is required.

### Behavioral Modification

Behavioral modification is an important component of therapy, particularly for children with constipation and encopresis. It involves regular toilet sitting for up to 5 minutes, three to four times a day after meals to establish normal bowel habits. This is combined with a reward system and positive reinforcement from parents.

### Summary

Constipation is a common and chronic problem in children. A therapeutic approach involving education, disimpaction, dietary advice, maintenance therapy with laxatives and behavior modification is recommended. Recent guidelines recommend polyethylene glycol with electrolytes as a laxative of choice.

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## East Zone PEDICON 2013, Tezpur, Guwahati

*Review Article*

# Acute on Chronic Liver Failure

**Sutapa Ganguly**

*Principal and Professor of Pediatrics, CSS College of Obs.,Gyne. and Child Health*

Acute-on-Chronic Liver Failure (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with Chronic Liver Disease (CLD) either secondary to superimposed liver injury or due to extra hepatic precipitating factors such as infection, variceal bleeding, trauma or surgery[1].

Liver failure can develop as Acute Liver Failure (ALF) in the absence of pre-existing liver disease; Acute-on-Chronic Liver Failure (ACLF) where there is an acute deterioration of known or unknown chronic liver disease; or a chronic decompensation of end stage liver disease.

There is limited data on the entity of ACLF and there were no consensus guidelines on definition, diagnosis and management. The working party of Asian Pacific Association for the Study of Liver organized a 2-day meeting on 22nd and 23rd January, 2008 to finalize recommendation and guidelines on the definition, diagnosis and management.

**Definition of ACLF**

Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease[1].

**Acute Events in ACLF**

***Infectious etiology:***

(i) Hepatotropic and nonhepatotropic viruses

(ii) Reactivation of Hepatitis B or Hepatitis C[2,3]

(iii) Superinfection with Hepatitis E virus and Hepatitis A are important etiology in Indian subcontinent[4,5].

(iv) Other infectious agents afflicting liver[6].

***Noninfectious etiology:***

(i) Hepatotoxic drugs

(ii) Flare of autoimmune hepatitis or Wilson disease

(iii) Variceal bleed

(iv) Surgical intervention

(v) Alcohol in adolescents and young adults

Hepatitis E and Hepatitis A were responsible for acute insults for precipitating ACLF in 75% and 28% cases respectively in a study in children at SGPGI in 2012[7] (J Pediatr Gastroenterol Nutr 2012).

***Underlying chronic liver disease:***

1. Compensated cirrhosis of any etiology
2. Chronic hepatitis
3. Cholestatic liver disease
4. Autoimmune liver disease
5. Metabolic liver disease
6. Non alcoholic steato hepatitis

Wilson disease and autoimmune hepatitis were important causes of underlying liver disease in children in the study from SGPGI[7] and PGIMER[8] defining the liver failure in

ACLF.

Patients in ACLF manifest in varied forms owing to heterogeneity in the patient population. In published reports, patients included had severe jaundice associated with organ failure manifested as hepatic encephalopathy or hepatorenal syndrome.

Jaundice is considered an essential criterion for diagnosis of ACLF. A cutoff level of >5 mg/dl is considered to enroll a larger group of patients. Coagulopathy is mandatory for defining ACLF and INR >1.5 is an essential criteria. Development of clinical ascites and/or encephalopathy was taken as a marker of decompensation.

**Pathophysiology**

Systemic Inflammatory Response, characterized by a predominantly proinflammatory cytokine profile causes transition from stable cirrhosis to ACLF. Preinflammatory cytokines are believed to mediate hepatic inflammation, apoptosis, and necrosis of liver cells; cholestasis and fibrosis[9,10].

ACLF patients have immunologic defects compatible with sepsis. The clinical picture of both ACLF and septic shock is strikingly similar characterized by progressive vasodilatory shock and multiorgan failure.

ACLF is a state of severe functional failure of neutrophils and this defect is associated with increased risk of infection, organ failure and mortality[11].

Liver plays a prominent role in the metabolism of asymmetric dimethyl-L-arginine (ADMA) an endogenous inhibitor of NO production. Hepatocellular damage is the main determinant of elevated ADMA[11].

**Role of Sepsis and Cytokines in ACLF**

It is likely that cytokines influence the development and course of ACLF. Inhibition of the inflammatory cytokine responses might offer a novel approach for reducing morbidity and mortality in patients with ACLF[12]. Circulating toxins in the setting of ACLF cause secondary liver damage and liver regeneration is impaired despite circulating growth factors.

Recent studies suggest that the transition from stable cirrhotic condition to the burst of are acute decompensation leading to ALF is based on an acute systemic inflammatory response, mainly mediated by cytokines[13].

TNF-$\alpha$ and IL-6 probably have dual action, induce hepatocyte death in one hand and promote hepatocyte proliferation on the other through differential interactions with Kupffer cells and hepatocytes.

***Liver histology in ACLF:***

Since it is not easy and practical to obtain a liver biopsy in patients with ACLF who are relatively sick, the need for liver biopsy should be individualized in patients with ACLF, considering the clinical condition of the patient. Transjugular liver biopsy is relatively safe.

Two distinct histologic patterns are seen[14].

*Pattern I* – Hepatocyte ballooning, rosette formation, cellular cholestasis, variable interface activity and fibrosis.

*Pattern II* – Marked ductular proliferation, coarse, inspisated bile plugs and foci of confluent / bridging necrosis, eosinophilic degeneration of hepatocytes, higher stage of fibrosis. Pattern II was associated with a much worse prognosis.

***Prognostic scores in ACLF:***

ACLF constitutes an illness in which two simultaneous insults are operating – acute and chronic. The degree of each insult would differ quantitatively, nevertheless resulting in the same level of decompensation.

It is important to determine the prognosis in ACLF specially over short-term, with respect to the use of temporary liver support or even transplantation in these patients. There are limited data on the predictors of survival in children with ACLF.

Two categories of prognostic modes are used

*Category I*

Evaluating the severity of illness

(i) Acute Physiology and Chronic Health Evaluation (APACHE) II and III

(ii) Simplified Acute Physiology Score (SAPS)

(iii) Mortality Prediction Model II

*Category II*

(i) Quantifying organ dysfunction and failure

(ii) Multiple Organ Dysfunction Score

(iii) Organ System Failure (OSF)

(iv) Sequential Organ Failure Assessment (SOFA)

(v) Mayo-end-stage liver disease score (MELD)

In a study from PGI, Chandigarh by Dr. Thapa, *et al* for grading of organ dysfunction the SOF; score was calculated. It constitutes the parameters of respiration, coagulation, cardiovascular system, central nervous system, and renal and liver functions. Multivariate analysis revealed SOFA and INR are good predictors of survival[8].

**Management**

***Antiviral Treatment in ACLF :***

(i) Antiviral therapy should be initiated in patients with ACLF due to hepatitis B

(ii) Lamivudine may be used for a short-term period, but other potent drugs like entecavir in children above 12 years may be preferred in view of long term and for viral suppression with low frequency of resistance

(iii) Vaccination of patients with non-viral CLD e.g., Wilson disease, autoimmune hepatitis with Hepatits B and A vaccines recommended.

***Use of liver support devices in ACLF:***

(i) MARS an important option to give additional time for recovery or to serve as a "bridge" to transplantation[12].

(ii) Removes toxins generated during liver failure and lowers TNF-a, IL-10 and IL-6 that may perpetuate liver damage

(iii) However, in a meta-analysis, MARS did not reduce mortality significantly compared with standard medical treatment (RR, 0.56; 98% CI; p=0.11)[15].

(iv) MARS may improve hepatic encephalopathy in patients with ACLF.

(v) Plasma exchange needs further validation for the treatment of ACLF

***Liver transplant in ACLF :***

(i) Orthotopic liver transplant remains only definitive therapy for patients who do not improve with supportive measures to sustain life.

(ii) Post transplant survival rates for ALF have been reported to be as high as 80-90% but accurate long term data for ACLF is not available yet[16].

(iii) Developing effective methods of liver support or other alternatives for transplantation and better prognostic scoring systems remains key goals to further improve overall survival rates for the condition.

(iv) King's College Hospital criteria needs further validation for patients with ACLF.

(v) Earlier intervention required if HRS develops.

(vi) Liver transplantation should not be done when there is HRS with anuria.

***Criteria when not to transplant :***

(i) Hemodynamic instability and high dose inotrope dependence (Sepsis, bleeding).

(ii) All patients with liver failure are at risk of acquisition of severe bacterial or fungal infection which preclude or complicate transplantation[17,18].

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## An Appeal

Shubho Vijaya and Happy Diwali to you all.

This is second 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 2014, 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.

*Fact Sheet*

# Skin Prick Test and Its Clinical Utility in Allergic Diseases

**Major K. Nagaraju**
*Pediatric Allergist & Immunotherapist*
*VN Allergy & Asthma Research Center*
*Director, Saveetha Medical College, Chennai*
*President, Pediatric Allergy Association of India*

## Introduction

Incidences of atopic diseases like allergic rhinitis, allergic conjunctitivits, allergic asthma, atopic eczema and food allergies are increasing all over the World, and India is no exception. Allergic disease is one of the three most common reasons why patients attend their family physician. Respiratory diseases represent about 25 percent of all visits to general practitioners and about 80 percent of patients with recurrent presentations are found to be allergic. Allergic conditions have a significant impact on health and economy of the country.

Although the reasons for increase of allergic diseases are not well known, allergen exposure is recognized as an important environmental risk factor in genetically predisposed individuals. The diagnosis of allergic disease requires a detailed history, physical examination, and allergy testing, i.e., skin testing or the in vitro determination of allergen-specific immunoglobulin E (IgE). Best method to do allergy skin testing is by prick test and it is the gold standard for the diagnosis of IgE mediated allergic diseases.

## Diagnosis of Atopic Diseases

Diagnosis of atopy is by demonstration of elevated specific IgE by either one of the following tests – Skin prick tests or by serum specific IgE. Out of the two tests, skin prick testing is given more importance as the results include a combination of two tests when compared to serology. To be clinically important it is not only important to have specific IgE, but there is a need for these IgE to be present on the mast cells and basophils in the right conformation as two neighboring IgE's to bind with the epitopes in a single allergen molecule. Only then will there be degranulation of the mast cells and the basophils.

The skin prick tests not only demonstrate that there is specific IgE, but also confirm that these are located appropriately on the mast cells and basophils so as to elicit an allergic reaction. Whereas, the serology measures only the free IgE in the blood without any information on how they are placed on the effector cells related to allergy.

## Allergy Skin Tests

Allergy skin tests are performed by introducing a small quantity of allergen into the epidermis by pricking, puncturing or scratching the skin or by intra dermal injection. The introduced allergen reacts with mast cell bound IgE antibodies causing the release of chemical mediators, leading to wheal and flare, which can be measured. History, clinical examination and aerobiology of the locality will guide the physician, how many allergens to be tested in a particular patient.

### *Skin prick test :*

This is the best test to identify type 1 hypersensitivity reaction. Since the invention of prick test by Lewis and Grant in 1920, this test is very popular and replaced the scratch and intradermal technique. Due to high false

positive results intradermal test is out dated and this technique is reserved for those patients with a history typical of allergy but prick test negative.

*Indications for skin prick test in respiratory allergic diseases* –

1. Specific allergen avoidance measures and the disease monitoring.
2. Specific allergy treatment : pharmacotherapy.
3. Plan specific immunotherapy.
4. Early identification of infants at increased risk for later development of allergic diseases.

*Contra Indications for skin prick test* –

1. Recent anaphylaxis, because test results become unreliable. Testing usually is postponed for 4- 6 weeks after an acute episode.
2. Severe eczema
3. Dermographism, because of difficulty in interpreting the results.
4. Unstable asthma.
5. Patients on beta-adrenergic blocking agents – a relative contraindication.

*Method* – This test demonstrates tissue bound IgE and identifies the atopic state. The test is performed after cleaning the skin and a lancet / 25 or 26 gauge needle piercing through a drop of allergen extract placed over the skin. The skin is pierced at an angle of 45 degree into the epidermis up to a depth of 0.5 mm and slightly bevelled upwards producing a pricking sensation, so as to allow an adequate entry of the antigen beneath the stratum corneum.

*The site of prick* – It may be on the volar aspect of the forearm or back. The site is observed after 15 -20min for wheal and flare. Generally, a wheal of 3 mm diameter can be regarded as positive. The concentration of glycerinated allergen extract used for testing is 1: 10 Glycerinated buffered saline and histamine (Concentration of 1mg/ml) is used as negative and positive control respectively. The panel of antigens are to be tested according to the geographic area in addition to common indoor allergens. Depending upon the wheal and flare and presence or absence of pseudopodia, skin test results should be graded 0 to 4+, and the grade of reaction is clearly stated along with the skin test results. Qualitative scoring (0 to 4) is no longer used by many clinicians because of inter physician variability in this method of scoring and interpretation. Positive allergy tests demonstrate sensitization but do not always indicate clinical reactivity.

*How many allergens to be tested?*

The number of the allergens selected for skin testing should be determined based on the patient's age, history, environment and living conditions, local aerobiological data and cross reactivity of allergens. Routine use of large numbers of skin tests without a definite clinical indication not warranted. The number of allergens to be tested for allergy diagnosis reflects the clinician's scientific knowledge and clinical experience.

*Medications to be avoided before the skin prick test* – First generation antihistamines (for few days), second generation antihistamines (for one to two weeks) and tricyclic anti depressants are to be avoided before allergy skin tests, as they interfere with the test reaction. Short course of systemic steroids and inhalation drugs do not interfere with allergy skin tests and they can be continued if required.

*Adverse reactions to skin prick test* – Life threatening generalised systemic reactions is very rare. Physicians must be aware of vasovagal attacks which are common in adolescents and those afraid of needle. Therefore physician who is doing allergy skin prick tests must explain to the patient about the procedure and alleviate the fear about the needle pricks.

*Causes of false-positive skin prick test* –

1. Irritant reaction
2. Nonspecific enhancement through axon reflex from nearby strong reaction. To prevent this place the antigens > 2mm apart.

*False negative causes of skin prick test* –

1. Extract of diminished potency.

2. Medications modulating allergic reaction
3. Diseases attenuating the skin response, e.g. eczema
4. Decreased reactivity of the skin in infants and elderly patients
5. Too soon after systemic anaphylactic reaction

**Skin prick test versus RAST**

***Skin prick test :***

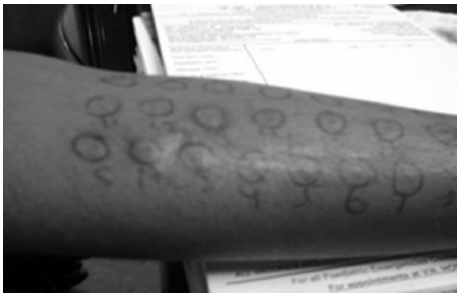
1. High sensitivity
2. Result available in minutes
3. Greater selection of antigens
4. Cheaper
5. Minimal equipment
6. Semi quantitative
7. Results evident to patient

***Allergen specific serum IgE test (RAST):***

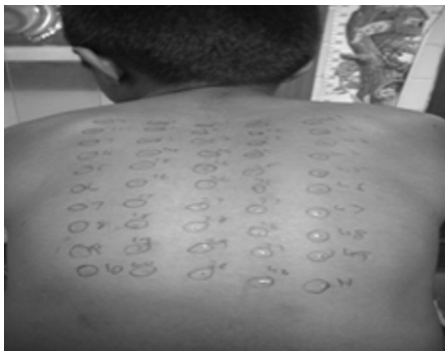
1. No risk of anaphylaxis,
2. Medications do not affect results.
3. Not dependent on skin condition.
4. Convenient for patients
5. No fear of needle prick.
6. Perceived by patients as more scientific.

**Points to remember.**

1. Skin Prick test is the gold standard for the diagnosis of IgE mediated diseases.
2. Allergy skin prick test is cheaper & highly sensitive than RAST.
3. > 3mm of induration of allergen is indicative of positivity.
4. Positive skin prick test indicates sensitivity to particular allergen only.
5. Positive skin prick test coupled with history and physical examination will give a clue for diagnosis of respiratory allergies.



Skin Prick test reaction in the forearm



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# Antimicrobial Use in Office Practice – Avoid Antibiotic Abuse

**Jaydeep Choudhury**
*Associate Professor, Department of Pediatrics, Institute of Child Health, Kolkata*

There are three indications of antimicrobial use – for treating infections, for prophylaxis and empirical use. In ideal situation, antimicrobials should be used only in case of proven infections. Hence proper diagnosis is the first step towards rational antimicrobial use. Prophylactic use is indicated only in certain selective situations where standard protocols have to be followed. Empirical use is by and large subjective, where it is used mainly by personal experience and intuition. Though this is not the ideal way to use an antibiotic but it is the most common mode of antibiotic use. It is imperative that antimicrobial resistance is a direct consequence of antimicrobial use. The consequence of a single case of antimicrobial resistance is far reaching as microbes are not limited by any boundary. Although awareness of the consequences of antibiotic misuse is increasing, overprescribing remains widespread. It is much easier to prevent antimicrobial resistance than to treat even a single case. This article will discuss antimicrobial use in common infections encountered in office practice.

**Typhoid**

Over the years *Salmonella typhi* has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin)[1]. By definition this is known as Multi Drug Resistant Typhoid Fever (MDRTF). Fluoroquinolones are widely regarded as the most effective drug for the treatment of typhoid fever[2]. Ciprofloxacin and ofloxacin are common fluoroquinolones that has been proved to be affective in children and there is no evidence of superiority of either. Fluoroquinolones like ofloxacin or ciprofloxacin are used in a dose of 15mg/kg/day to a maximum of 20mg/kg/day.

There is considerable evidence from the long term use of fluoroquinolones in children that neither they cause bone or joint toxicity nor impairment of growth[2]. Fluoroquinolones have the advantage of lower rates of stool carriage than the first line drugs. However, fluoroquinolones are not approved by Drug Controller General of India to be used under 18 years of age unless the child is resistant to all other recommended antibiotics and is suffering from life threatening infection.

Rarely some strains of *S. typhi* have shown reduced susceptibility to fluoroquinolones. Resistance to nalidixic acid is a surrogate marker which predicts fluoroquinolones failure and can be used to guide antibiotic therapy[2]. The resistance to fluoroquinolones may be total or partial. The nalidixic acid resistant *S typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones.

Third generation cephalosporins are used in the treatment of enteric fever[1,2]. Of the third generation cephalosporins, oral cefixime has been widely used in children. Amongst the third generation injectable cephalosporins ceftriaxone, cefotaxime and

cefoperazone are used of which ceftriaxone is most convenient. Oral cefixime is used in a dose of 15-20 mg/kg/day in two divided doses. Parenteral third generation cephalosporins include ceftriaxone 50-75mg/kg/day in one or two doses, cefotaxime 100 – 150 mg/kg/day in two or three doses and cefoperazone 50-100 mg/kg/per day in two doses.

Recently azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever. Azithromycin is used in a dose of 20 mg/kg given once daily. Aztreonam and imipenem are also potential third line drugs[2].

In case of uncomplicated typhoid oral third generation cephalosporine eg, cefixime should be the drug of choice as empiric therapy[2]. If by 5 days there is no clinical improvement and the culture report is inconclusive add a second line drug e.g. azithromycin or any other drug effective against *S typhi* depending on the sensitivity pattern of the area. For complicated typhoid the choice of drug is parenteral third generation cephalosporin eg, ceftriaxone[2]. In severe life threatening infection fluoroquinolones may be used as a last resort. Aztreonam and imepenem may also be used. Combination therapy though practiced all over needs substantiation with adequate data from studies[3,4].

Relapses involving acute illness occur in 5-10% of typhoid fever cases that have been apparently treated successfully[5-7]. Cultures should be obtained and standard treatment should be administered[8]. They are sensitive to same antibiotics which were given for the first episode and should be given for a period of 5-7days.

Tables 1and 2 depict antibiotics in the management of both complicated and uncomplicated typhoid[2].

**UTI**

Children older than 3 months of age with uncomplicated UTI are treated with oral antibiotics for 7 to 10 days[9,10]. Amoxicillin, co-amoxiclav or an oral cephalosporin is preferred for initial treatment. Following availability of sensitivity reports, treatment may be modified accordingly. Fluoroquinolones should be avoided as first line medication. Their use should be guided by results of urine culture and sensitivity. Nalidixic acid and nitrofurantoin should not be used to treat UTI since they do not achieve therapeutic concentrations in the renal parenchyma and blood streams[9].

With adequate and effective therapy, clinical improvement like resolution of toxemia and fever occurs by 48-72 hours. Urine culture is sterile after 48 hours of effective antimicrobials. USG abdomen and repeat urine culture should be performed, if there is no clinical improvement after 72 hours of antimicrobial therapy. Maintenance of hydration, antipyretic and supportive therapy should be managed properly during an episode of an acute UTI.

Following the treatment of UTI, prophylactic antibiotic therapy is initiated in children below 2 years of age, until appropriate imaging of the urinary tract is completed.

Although the evidence of benefit of long-term low-dose antibiotic prophylaxis for prevention of UTI is not strong, it is the most widely used strategy to prevent UTI in clinical practice[11]. Antibiotic prophylaxis is recommended in the following[12,13]:

(i) Infants with UTI pending completion of evaluation,

(ii) Children with VUR and

(iii) Those with recurrent febrile UTI even if the urinary tract is normal.

Medications used for prophylaxis are usually given as single bedtime dose (Table: 3).

The following drugs are recommended for treatment of UTI in children as shown in Table:4.

**Acute Respiratory Infections (ARI)**

Acute respiratory Infections (ARI) in children less than 5 years old are the leading cause of childhood morbidity and mortality in the world.

***Acute Pharyngo-tonsillitis***

Pharyngotonsillitis is one of the commonest clinical situations that we come across in day to day practice. It comprises of 40% cases of URI and nearly 80% of them are viral[14]. It is one of the most common situations for antibiotic misuse. Group A beta hemolytic streptococcus infections are self limiting and signs and symptoms subside

**Table 1** : Treatment of Uncomplicated Typhoid

| Susceptibility | First Line Oral Drug | | | Second Line Oral Drug | | |
|---|---|---|---|---|---|---|
| | Antibiotic | Daily Dose (mg/kg) | Days | Antibiotic | Daily Dose (mg/kg) | Days |
| Fully sensitive | 3rd Gen. Cephalosporine eg. Cefixime | 15-20 | 14 | Chloramphenicol<br>Amoxicillin<br>TMP-SMX | 50- 75<br>75-100<br>8 TMP<br>40 SMX | 14-21<br>14<br>14 |
| Multidrug resistant | 3rd Gen. Cephalosporine eg. Cefixime | 15-20 | 14 | Azithromycin | 10-20 | 14 |

**Table 2** : Treatment of Severe Typhoid

| Susceptibility | First Line Parenteral Drug | | | Second Line Parenteral Drug | | |
|---|---|---|---|---|---|---|
| | Antibiotic | Daily Dose (mg/kg) | Days | Antibiotic | Daily Dose (mg/kg) | Days |
| Fully sensitive | Ceftriaxone<br>or<br>Cefotaxime | 50-75<br><br>100-150 | 14 | Chloramphemicol<br><br>Ampicillin<br>TMP-SMX | 100<br><br>100<br>8 TMP<br>40 SMX | 14-21<br><br>14<br><br>14 |
| Multidrug resistant | Ceftriaxone<br>or<br>Cefotaxime | 50-75<br><br>100-150 | 14 | Aztreonam | 50-100 | 14 |

**Table 3**. Antibiotics for Prophylaxis[9,10]

| Drug | Dosage (mg/kg/day) | Remarks |
|---|---|---|
| Cotrimoxazole | 1-2 of trimethoprim | Avoid below 6 weeks age, G6PD deficiency |
| Nitrofurantoin (NFT) | 1-2 | Gastrointestinal upset; avoid below 3 months and with impaired renal functions |
| Cephalexin | 10-12 | Use in infants where NFT and cotrimoxazole is contraindicated |

**Table 4.** Drugs in the Treatment of Urinary Tract Infections (9, 10)

| Drug | Dosage (mg/kg/day) | Remarks |
|---|---|---|
| **Oral** | | |
| Amoxicillin, co-amoxiclav | 20-40 in 2-3 div. doses | Rapid bacterial resistance |
| Cefadroxil | 30 in 2 div. doses | Ineffective against Proteus spp |
| Cefaclor | 40 in 3 div. doses | |
| Cephalexin | 50-70 in 3 div. doses | |
| Cefixime | 8 in 2 div. doses | Broad spectrum |
| Ciprofloxacin | 10-20 in 2 div. doses | Not first line drugs |
| Ofloxacin | 10 in 2 div. doses | |
| **Parenteral** | | |
| Gentamicin | 5-7.5 | Monitor for renal toxicity |
| Amikacin | 15-20 | May be given as once daily dose |
| Cefotaxime | 100-150 in 3 div. doses | Safe and effective as a single agent |
| Ceftriaxone | 75-100 in 1-2 div. doses | |

in 4 to 5 days. However antibiotics are needed for prevention of non-suppurative complications of rheumatic fever. The drugs recommended are Penicillin V 250 mg twice daily in children and thrice or four times daily in adolescents or amoxycillin 40-50mg/kg/day 10 days or Benzathine penicillin 6 lakh/12 lakh units, depending upon weight of the child, deep IM after negative test dose[15]. If the patient is allergic to penicillin, erythromycin ethylsuccinate 40-50mg/kg tid or azithromycin 10mg/kg od 5 days or cefaclor 30mg/kg 10 days.

***Acute Otitis Media***

Middle ear disease is obviously a major health problem for children. The most common cause of otitis media is *Streptococcus pneumoniae*, followed by non-typable *Hemophilus influenza, Moraxella catarrhails* and occasionally *Streptococcus pyogenesis*[15]. The choice of antibiotics is shown in table 5.

Severe disease is defined as explosive onset severe otalgia, toxicity and high fever (>102°F).

Alternate antibiotics are the following.

In non-severe cases :

(i) Type 1 penicillin allergy : Azithromycin, Clarithromycin

(ii) Non-type 1 allergy: Cefdinir, Cefpodoxime

**Table 5.** Antibiotic selection in acute otitis media[16]

| Severity | Initial management with antibacterial agents | Treatment failure at 48-72 hours after initial observation alone | Treatment failure at 48-72 hours after initial management with antibacterial agents |
|---|---|---|---|
| Non severe | Amoxycillin | Amoxycillin | Amoxycillin- clavulnate |
| Severe* | Amoxycillin-clavulante | Amoxycillin-clavulante | Ceftriaxone for 3 days |

In severe cases :

Ceftriaxone for 3 days for initial management. For initial antibiotic failure, tympanocentesis plus clindamycin is recommended.

***Acute Sinusitis***

The bacteriology of acute sinusitis is virtually identical with organisms recovered from children with acute otitis media. *Streptococcus pneumoniae*, nontypable *Haemophilus influenza* and *Moraxella catarrhalis* predominate[14]. Though self-limited in most children amoxicillin is the drug of choice for effectiveness, cost and safety. Second-line antibiotics are the same as for the treatment of middle-ear disease: amoxicillin-clavulanate, azithromycin, cefaclor and cefuroxime axetil. Therapy should be continued for a minimum of 14 days.

***Community Acquired Pneumonia***

Community acquired pneumonia is an acute infection of the pulmonary parenchyma in a previously healthy child, acquired outside of a hospital setting. The patient should not have been hospitalized within 14 days prior to the onset of symptoms or has been hospitalized less than 4 days prior to onset of symptoms.

The following table 6 gives the probable agents at various age groups in order of common prevalence[14].

Empiric therapy should be based on knowing the most likely pathogen in each community. *S. pneumoniae* is an important causative agent for community acquired pneumonia at all ages. Because it is difficult to distinguish between bacterial, viral, and mixed infections, most children with community acquired pneumonia are treated with antibiotics. Selection of antibiotic is dictated by the age of the child and epidemiological factors and sometimes the results of the chest radiography as shown in table 7. The antibiotics should be given for 5-7 days[17].

**Pyogenic Meningitis**

Acute bacterial meningitis is a medical emergency and appropriate antibiotic is the main stay of treatment. Child with suspected meningitis should receive antibiotics ideally after performing LP. In cases where LP is contraindicated antibiotics should be given immediately.

**Table 6.** Agents at various age groups in order of common

| Age | Microbial agent |
|---|---|
| 0-3 months of age | Gram Negative organisms<br>Group B Streptococcus<br>*Streptococcus pyogenes*<br>*Chlamydia*<br>Viruses |
| 3 months-5 yrs of age | Strep pneumoniae<br>*H. influenzae*<br>Viruses<br>*Staphylococcus*<br>*Strep. pyogenes*<br>*Mycoplasma pneumoniae* |
| >5 yrs of age | *Strep pneumoniae*<br>*Chlamydia pneumoniae*<br>Viruses<br>*Staphylococcus*<br>*Strep. pyogenes*<br>*H. influenzae*<br>*Mycoplasma pneumoniae* |

The choice of antibiotics depends upon the causative organism in that particular age group. Most common organisms include pneumococcus, meningococcus, and *H. influenze* type b[18]. In children more than one month of age 3rd generation cephalosporin, ceftriaxone or cefotaxime are recommended for initial therapy[18]. Cefotaxime 200mg/kg/24hr, given every 6 hour or ceftriaxone 100mg/kg/24hr given either every 12 hour or as a single dose. As India has started showing intermediate resistant pneumococci, penicillin is no longer recommended. Vancomycin has role in therapy of penicillin or cephalosporin resistant meningitis in combination with cephalosporin. Monotherpay with vancomycin is not recommended. Vancomycin is used in the dose of 60mg/kg/24 hr, given every 6 hours. In patients who are immunocompromised and where Gram negative bacterial meningitis is suspected empiric therapy may start with ceftazidime and aminoglycosides. In patient with CSF shunt empirical therapy can be done with vancomycin and meropenem. Combination of third

**Table 7.** Antibiotic therapy in domiciliary patients

| Age | First Line | Second Line | Suspected Staphylococcal ds |
|---|---|---|---|
| Upto 3mo | Usually Severe, treated as inpatients | | |
| 3mo- 5yrs | Amoxycillin | Co-amoxy clavulinic acid<br>or<br>Chloremphenicol<br>or<br>Cefuroxime | Amoxycillin+Cloxacillin<br>or<br>Cefuroxime<br>or<br>Co-amoxy clavulinic acid |
| >5 yrs | Amoxycillin | Macrolide<br>or<br>Co-amoxy-clavulinic acid<br>or<br>Chloremphenicol | Amoxycillin+Cloxacillin<br>or<br>Cefuroxime<br>or<br>Co-amoxy clavulinic acid |

generation cephalosporin plus beta lactamase inhibitor has no role in the treatment of pyogenic meningitis.

Pneumococcus or meningococcus which are susceptible to penicillin or ampicillin (MIC$\leq$ 0.6$\mu$g/ml) should be treated with penicillin G or ampicillin. If they are not susceptible to penicillin but susceptible to cephalosporin, 3rd generation cephalosporin like ceftriaxone or cefotaxim must be used. Isolates that are not susceptible to penicillin and have a MIC of $\geq$1$\mu$g/ml to 3rd generation cephalosporin should be treated with vancomycin plus cefotaxime or ceftriaxone. For *S pneumone* with intermediate resistance to penicillin cefipime and meropenum may be considered as alternative therapy.However trails with cefipime are not adequate but may be tried in patients who fail with other antibiotic courses. The other organism which might be responsible for bacterial meningitis in children should be treated with antibiotics as summarized (Table 8, 9).

With adequate antibiotic CSF usually becomes sterile within 24 to 36 hours after initiation of therapy. Repeat lumber puncture after 48-72 hours of treatment is indicated if there is no clinical improvement or when meningitis caused by resistant pneumococcus or Gram negative enteric bacilli.

*Duration of therapy* – Duration of therapy depends upon the causative pathogen and clinical course. For complicated cases longer course may be needed. For pneumococcus 10-14 days therapy is required, where as meningococcus and *H influenze* type b meningitis should be treated for 5-7 days and 7-10 days respectively[18]. If the CSF reports are suggestive of acute bacterial meningitis without any identifiable pathogen patients should continue to receive therapy for 7-10 days. Gram negative bacillary meningitis should be treated for 3 weeks or at least 2 weeks after CSF sterilization. In case of 7 days non responders try to determine the cause by clinical examination, CSF and imaging studies modify duration of treatment accordingly[19].

Avoid antibiotic abuse. It is important to use antibiotics judiciously right from the first contact with a physician. Though empiric antibiotic use is inevitable, but it should be bacteriologically logical. Good antibiotic stewardship involves selecting an opportunity drug and optimizing its dose and duration to cure an infective while minimizing toxicity and conditions of selection of resistant bacterial strains.

**Table 8** : Summary of Treatment with Antibiotics in Bacterial Meningitis in Children (18)

| Bacteria | Antibiotic of choice |
|---|---|
| Listeria | Ampicilin ± Gentamicin |
| *Esch coli* | Ceftriaxone or cefotaxime ± aminoglycoside |
| Pseudomonas aerogenosa | Ceftazidime or Cefipime + aminoglycoside |
| *Staphylococcus aureus* | |
| Methicillin sensitive(MSSA) | Cloxacilin |
| Methicillin resistant(MRSA) | Vancomycin ± Rifampicin |
| *Streptococcus agalactie* | Penicillin G or Ampicillin ± Gentamicin |
| Enterococcus | |
| Ampicillin sensitive | Ampicillin + Gentamicin |
| Ampicillin resistant | Vancomycin + Gentamicin |

**Table 9** : Dosages of Commonly Administered Antibiotics for Bacterial Meningitis in Infants and Children

| Antibiotic | Total daily dose | (Dosing interval in hours) |
|---|---|---|
| 1. Ampicillin | 200 - 300 mg/kg | (6) |
| 2. Cefipime | 150 mg/kg | (8) |
| 3. Cefotaxime | 200-300 mg/kg | (6-8) |
| 4. Ceftazidime | 150 mg/kg | (8) |
| 5. Ceftriaxone | 100 mg/kg | (12- 24) |
| 6. Gentamicin | 7.5 mg/kg | (8) |
| 7. Meropenem | 120 mg/kg | (8) |
| 8. Penicillin G | 450,000 units/kg | (4-6) |
| 9. Rifampicin | 10-20 mg/kg | (12-24) |
| 10. Linezolid | 10mg/kg | (12) |

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## East Zone Academy of Pediatrics
## (EQ Workshop & Midterm EB Meeting)

# Tuberculosis – Newer Diagnostic Tools

***Devdeep Mukherjee, **Ritabrata Kundu**
** RMO, **Professor, Department of Pediatrics, Institute of Child Health, Kolkata*

## Introduction

Over the years, research has primarily been in formulating newer drugs for treating Tuberculosis (TB). However, only 30% of the population, infected with TB is correctly diagnosed and an even lower number of cases are diagnosed in high-TB-burden, resource poor settings.

We are yet to have a gold standard diagnostic tool for diagnosing latent TB. The commonly used TB diagnostic tools are still suboptimal in their performance for childhood TB, smear-negative TB, extrapulmonary TB, HIV-TB and drug-resistant TB. Besides these, in recent years, new ways of performing some "old" tests (e.g. sputum smear microscopy) and few innovative tools (e.g. new technologies for molecular diagnosis) are under investigation or have already been endorsed by WHO.

## Advances in Diagnostics

### *1. Sputum handling :*

Improved sputum processing involves using bleach, NaOH or other substances to chemically digest or liquefy the sputum, which eliminates cellular residues, and makes the smear clearer to read — potentially increasing sensitivity by 10-15% according to one study.

### *2. Microscopy:*

Conventional microscopy with Ziehl – Neelson (ZN) staining has very poor sensitivity, more so in pediatric TB, extrapulmonary TB and in HIV patients infected with TB.

Fluoroscence microscopy although 10% more sensitive than ZN stain, its use has been curtailed because of the high costs. It also requires considerable technical expertise. The WHO recommends its use at intermediate laboratory level where more than 100 smears are examined per day[1-4].

Light emitting diode (LED) fluorescence microscopy – A recent WHO survey found that the diagnostic accuracy of LED microscopy was comparable to that of conventional fluorescence microscopy and superior to that of conventional ZN microscopy. It also has qualitative, operational, time (needs lesser time compared to ZN stain) and cost benefits over other microscopy. Shenai, et al have demonstrated LED microscopy to have a sensitivity of 78.3% and specificity of 92% for pulmonary samples and sensitivity and specificity of 34 % and 88.8% for extrapulmonary specimens respectively[1-4].

### *3. Culture methods (Box 1) :*

(a) *Bactec 460 TB system* – it is a radiometric culture technique where the growth medium for culturing Mycobacteria is supplemented with a substrate labeled with radioactive carbon (14c).

| Bactec 460 TB system (radiometric) | Bactec MGIT 960 (fluorescent) |
|---|---|
| Longer duration ( 24 -28 days) for demonstration of Mycobacterium | Shorter duration ( around 10 days) for demonstration |
| Drug susceptibility takes longer to be | Drug susceptibility is established quickly established |
| Low cost | High cost |
| Easy availability | Poor availability |

**Box 1 : Culture methods**

(b) *Bactec MGIT 960 system* – It is a fully automated system that uses the fluorescence of an oxygen sensor to detect growth of mycobacteria in culture.

Advantages: Isolation of *M. tuberculosis* provides a confirmatory diagnosis of TB. It enables early detection of cases and increases the yield of cases diagnosed (often by 30–50%).

Disadvantages: It is an expensive, elaborate procedure and requires skilled manpower. Contamination of specimen with other microorganisms also limits the diagnosis[4,5].

Solid and liquid culture systems are available. Whereas the solid culture media is less costly, the liquid helps in quicker diagnosis. However it is more prone to contamination than the solid culture media. Positive cultures must be classified into mycobacterial or non mycobacterial TB as HIV patients are more prone to develop the latter[4,6,7].

***4. Drug susceptibility testing (DST):***

It is used to make a definite diagnosis for drug resistant TB. It can be done phenotypically or genotypically.

(a) Phenotypic methods involve culturing *M. tuberculosis* in the presence of anti-TB drugs to detect growth (indicating drug resistance) or inhibition of growth (indicating drug susceptibility). It involves tests on solid or liquid media.

*Direct testing* – Here a set of drug-containing and drug-free media are inoculated directly with a concentrated specimen.

*Indirect testing* – Drug-containing media is inoculated with a pure culture grown from the original specimen. These remain the gold standard methods of DST.

(b) Genotypic methods target specific molecular mutations associated with resistance against individual drugs.

*Drawbacks* – These can only be performed in central research laboratories because of the high expenditure. The accuracy of the test varies depending on the drug being tested.

(a) *First line DST* – This accurately diagnoses rifampicin and isoniazid resistance and is less reliable for ethambutol, pyrazinamide and streptomycin.

(b) *Second line DST* – Aminoglycosides, polypeptides and fluoroquinolones have good reliability and reproducibility, allowing a diagnosis of XDR-TB. Reliability and reproducibility for other second-line drugs (ethionamide, prothionamide, cycloserine, terizidone, paminosalicylic acid, clofazimine, amoxicillin–clavulanate, clarithromycin, linezolid) is not recommended[4,8].

**Noncommercial Methods**

They are cheaper but have high possibility for errors due to lack of standardization. Performance is also highly operator-dependent.

The methods include MODS, colorimetric redox indicator (CRI) methods (based on the reduction of a coloured

indicator) and the NRA (based on the ability of *M.tuberculosis* to reduce nitrate).

***Recommendations for their respective use are:***

*MODS (microscopic observation drug susceptibility assay)* – It helps in rapid screening of patients with TB, especially MDR-TB. It also fascilitates drug susceptibility testing[4,9,10].

***Molecular testing :***

*Line probe assays (LPA)* – They have been endorsed by WHO in 2008 for rapid first-step identification of MDR TB only. It also helps in rapid detection of resistance to rifampicin (alone or in combination with isoniazid). It has a turnaround time of 1-2 days.

*Disadvantages* – It can be performed at the national level laboratories. LPAs do not eliminate the need for conventional culture and DST capability. Currently available LPAs are registered for use only on smear-positive sputum specimens of *M. tuberculosis*. For smear-negative specimens, conventional culture (solid or liquid) needs to be performed before LPA testing[11].

*Nucleic acid amplification tests (NAAT)* – It is utilized for rapid diagnosis and drug susceptibility testing for TB. However, it can only be done as a follow up investigation on smear positive sputum samples and on patients with pulmonary TB. The sensitivity however decreases in smear negative cases and also in extra pulmonary TB.

***Xpert MTB/RIF:***

This is a fully automated molecular test utilizing real time PCR (amplifying MTB specific sequence of rpoB gene) for detection of MTB and drug resistance to rifampicin. Results are obtained within 90 minutes. This test has a sensitivity of 99.1% and specificity of 100 % for detecting resistance to rifampicin. The sensitivity for smear positive cases was 99.6% and for smear negative cases was 81%. This test performed well for all specimens (sensitivity 63 – 100 %), except for cerebrospinal fluid (sensitivity 29%). The Xpert test has also shown good results for diagnosing pulmonary and extrapulmonary TB and therefore is suitable for use in countries where TB is an endemic disease[4,12,13].

*Drawbacks* – High running costs have limited the use of this test on a large scale.

***In house PCR:***

Several methods of in house PCR techniques have been experimented with. These are also beneficial in detecting non tuberculous mycobacteria. The sensitivity can vary from 45 – 95%. Nucleic acid targets employed for this has been 16S rRNA, Antigen b, 23S rRNA, IS6110. Further research is needed for this to be employed in resource poor settings[4].

*Advantages* – Species identification and early detection.

*Drawbacks* – Inconsistent results compared to NAAT.

***Antigen detection methods:***

Lipoarabinomannan is the most commonly targeted antigen. Sensitivity in pulmonary TB varies from 2 – 100% and specificity from 33 – 100 %. Even for extrapulmonary TB, this remains the same. However further research is necessary for large scale use of this method[4,14].

***Other diagnostics tools:***

(a) Urease breath test for rapid diagnosis of TB

(b) Loop mediated isothermal amplification (LAMP) of DNA

WHO recommends liquid culture and rapid species identification to address the needs for culture and drug susceptibility testing in a country specific comprehensive plan for lab strengthening.

The diagnosis approach to a patient for tuberculosis is shown in figure 1.

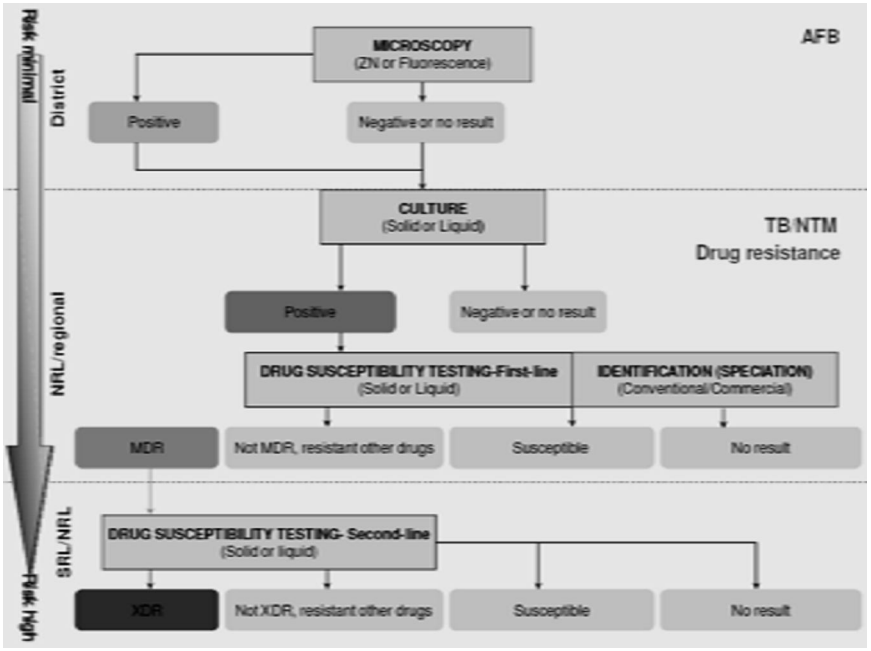


Fig 1. Diagnostic approach to a patient of Tuberculosis

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## Approach

# Neonatal Sepsis

**Kheya Ghosh Uttam**
*Assistant Professor, NICU In-Charge, Institute of Child Health, Kolkata*

Infections during the neonatal period is the commonest cause of neonatal mortality. It causes about 30-50% of total neonatal deaths in developing countries[1,2]. It is estimated that upto 20% of neonates develop sepsis and approximately 1% die of sepsis related causes[2]. The incidence and mortality is even higher in VLBW babies. Even though neonatal care has dramatically improved over the last decade, gestation specific mortality due to sepsis has not changed much. The incidence of neonatal sepsis in India according to the data from National Neonatal Perinatal Database (NNPD, 2002-2003) is 30 per 1000 live births[3].

### Definition

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia / fungemia in the first month of life. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelits, and urinary tract infections. Superficial infections like conjunctivitis and oral thrush are not usually included under neonatal sepsis.

### Classification (Table 1)

Neonatal sepsis can be classified into two major categories depending upon the onset of symptoms. Early onset sepsis (EOS) and late onset sepsis (LOS)[4].

### Etiology

Etiology varies in different parts of the world and often changes over the years. The clinical presentation and the risk factors of EOS and LOS are different but the organism causing the EOS and LOS in India are similar and so are their antibiograms. In Indian studies gram negative organisms have been more frequently responsible for sepsis (65-85%) as compared to gram positive organisms[3].

***Common organisms :***

Klebsiella, *E. coli*, pseudomonas, *Staphylococcus aureus*, *Candida* spp.

***Less common organisms :***

Enterobacter, citrobacter, salmonella and streoptococcus groups B and D.

***Uncommon organisms :***

Group B Streptococcus.

### Clinical Features

Mostly nonspecific and subtle, some are organ specific. A high index of suspicion is needed for early diagnosis.

(a) Hypo/hyperthermia

(b) Lethergy, poor cry, apnea, hypotonia, decreased movements.

(c) Refusal to suck, vomiting

(d) Poor perfusion, mottled skin, brady/tachycardia, failure to thrive.

(e) Feed intolerance, abdominal distension, diarrhoea,

**Table 1.** Classification of neonatal sepsis

| Early onset sepsis[4,5] | Late onset sepsis [5,6] |
|---|---|
| Presents within first 72 hrs. of life.<br>Source : Maternal genital tract.<br>Clinical presentation :<br>Respiratory distress, and pneumonia common | Presents after 72 hrs. of life.<br>Source : nosocomial, community acquired.<br><br>Septicemia, pneumonia, meningities. |
| Predisposing / Risk factors :<br>● Low birth weight (LBW)/ Prematurity<br>● Febrile illness in mother with evidence of bacterial infection within 2 weeks prior to delivery.<br>● Foul smelling and/or neoconium stained liquor .<br>● Rupture of membrane >24 hrs.<br>● Single unclean/ more than three sterile vaginal examination(s) during labour.<br>● Prolonged labour(sum of 1st and 2nd stage of labour > 24 hrs.)<br>● Perinatal asphyxia (Apgar seore <4 at 1 min). | LBW<br>Prematurity<br>Hospital acquired infection<br>● Admission in NICU<br>● Use of Mechanical Ventilation<br>● Invasive procedures.<br>● Administration of parentral fluid<br><br>Community acquired sepsis :<br>● Poor hygiene<br>● Poor cord care<br>● Bottle-feeding<br><br>● Prelacteal feeds. |

NEC.

(f) Tachypnea, severe chest indrawing, nasal flaring, grunting.

(g) Convulsions, bulging AF, irritability, stupor/coma.

(h) Multiple boils, umbilical redness and discharge.

(i) Sclerema, shock, DIC, Pulmonary hemorrhage.

**Diagnosis and Management**

Proper interpretation of sepsis screen, CFS findings, blood cultures, chest x-ray are important for diagnosing neonatal sepsis. It is also important to follow proper procedure for collection of culture samples. Blood culture is the gold standard for diagnosing septicemia and should be performed in all cases of suspected sepsis before starting antibiotic. All blood cultures hould be observed for at least 72 hours before they are reported to be sterile. Presently Bactec blood culture system can detect bacterial growth within 12-24 hours. This method can also isolate bacteria at a very low concentration of 1-2 colony- forming unit per mL.

**Approach to a neonate with suspected EOS**

(a) Role of sepsis screen in EOS : There is no rationale for performing a sepsis screen in suspected EOS. (Procalcitonin and IL-6 are more promising than the standard screen for the diagnosis of EOS but they are not routinely available)[7].

(b) Symptomatic neonates : Neonates who turn symptomatic within 72 hours must be clinically assessed for probability of sepsis. 20% of symptomatic neonates in India suspected to have EOS are blood culture positive[8].

(i) Antibiotics should be started (after drawing a blood culture) in symptomatic neonates with any of the risk factors for EOS or when chest X-ray is suggestive of pneumonia or the symptoms cannot be explained by other illness.

(ii) On the other hand, symptomatic neonates without above supportive features need not be started on antibiotics immediately but should be continuously monitored.

(iii) Lumbar puncture for CSF examination must be done in all symptomatic neonates (with the exception of preterm neonates with respiratory distress at birth with no risk factors for sepsis)[9,10]. The decision for performing LP should not be based on sepsis screen or blood culture results.

(c) Asymptomatic neonates with the presence of risk factors for sepsis : May be evaluated using risk factor scoring system to take a decision regarding starting antibiotics.

**Approach to a neonate with suspected LOS**

(a) All neonates who become symptomatic after 72 hours of life must be evaluated for sepsis. Evaluation involves categorization of these neonates into those with low probability or high probability of sepsis.

(b) A sepsis screen (TLC <5000/cumm, ANC – low counts, as per Manroe[11] chart for term and Mouzinho's[12] chart for pretern, I/T Ratio >0.2, Micro-ESR >15mm in 1st hr. CRP > 1 mg/dl) is performed in neonates with a low probability of sepsis. If all the parameters are negative, antibiotics may not be started and the neonate must be monitored clinically. However the sepsis screen must be repeated after 12-24 hrs. A negative repeat screen strongly indicates against starting antibiotics whereas a positive repeat screen with persistence of symptoms may warrant antibiotics.

(c) A sepsis screen is not warranted in neonates with a high probability for sepsis. Instead these neonates should be directly started on antibiotics pending blood culture.

(d) A CSF examination must be performed in all neonates with a high probability of sepsis as well as in those neonates with a low probability of sepsis with a positive sepsis screen.

(e) UTI should be suspected and investigated appropriately (specially with known urinary anomalies, bladder catheterizations turbid urine etc.) Routine urine culture in all neonates with non-specific symptoms is not recommended.

**Antibiotic therapy**

There is generally no distinction in the choice of empirical antibiotics in suspected EOS or LOS as the bacterial and sensitivity profile in India seem to be similar in both situations[3,7].

**Policy for community acquired sepsis[13]**

(a) Ampicillin + gentamicin / Amikacin

(b) If evidence of staphylococous : Cloxacillin + gentamicin / Amikacin.

(c) If evidence of meningitis : Add cefotaxime.

***Policy for nosocomial sepsis :***

Every newborn unit should have their own antibiotic policy based on local sensitivity patterns and the profile of pathogens. Preferably use penicillins plus an aminoglycoside combination.

**Upgradation of empirical antibiotics**

(a) Failure to improve / appearance of new sign in 48-72 hours.

(b) If neonate is very sick or deteriorating very quickly consider bypassing the first line of antibiotics and start with second line antibiotics.

***Antibiotic therapy once culture report is available:***
It must first be assessed whether the growth is a contaminant. If the growth is non-contaminant, the antibiotic sensitivity must be assessed to decide whether antibiotics need to be changed or not.

***Guidelines :***

(a) Change to narrower spectrum and lower cost sensitive antibiotic even if baby is improving and/or empiric antibiotics are reported sensitive.

(b) Use single sensitive antibiotic expect for pseudomonas where two sensitive antibiotics are recommended.

(c) If baby worsens despite use of sensitive empiric antibiotics (in vivo resistance), change to an alternate sensitive antibiotic with narrowest spectrum and lowest price.

(d) If empiric antibiotics are reported resistant but baby is improving clinically, it may or may not be a case of in-vivo sensitivity and one may or may not continue same antibiotics.

However change to sensitive antibiotics in case of pseudomonas, klebsiella and MRSA and in case of CNS infections and deep-seated infections.

If no antibiotic has been reported sensitive or only moderate sensitivity is reported to some antibiotics use combination in highest permissible dose.

***Duration of antibiotics :***

Culture positive sepsis : Give sensitive antibiotic for a total duration of 10 – 14 days. Use of quantitative CRP assay is not recommended to decide on stoppage of antibiotics[14].

***Culture negative sepsis :***

(a) Asymptomatic at risk of EOS : Stop antibiotics.

(b) Suspected EOS or LOS and the neonates completely asymptomatic over time : Stop antibiotics.

(c) Suspected EOS/LOS and the neonates improves but not become asymptomatic – Repeat a CRP assy[15].

If CRP positive – Continue Antibiotic

IF CRP negative – Stop antibiotics.

(d) Suspected EOS / LOS and the neonate has not improved or worsened – Upgrade antibiotics.

Clinically proven meningitis : Give total of 21 days course of parenteral antibiotics that cross uniflamed meninges.

UTI : May be treated for 7 – 14 days.

Proven bone or joint infections : Must be treated for at least 6 wks. of this, at least 4 wks of parenteral antibiotics

General Supportive Care – Neonates should be nursed in a thermo-neutral environment taking care of cardio-respiratory and nutritional support and maintaining sugar, calcium electrolytes, hematological profile etc.

***Adjunctive therapy :***

(a) IVIG – Currently available evidence does not support the use of IVIG[16].

(b) Colony stimulating factors – No evidence to support the use of CFS either as a treatment modality or as a prophylaxis therapy[17].

(c) Blood exchange transfusion – BET may be performed in a case of deteriorating sepsis with sclerema provided the general condition of the baby allows the procedure[18].

Prevention is the best way to manage sepsis. EOS can be prevented by appropriate obstetric care and LOS can be prevented by promoting breast feeding, maintaining proper hygiene and asepsis and decreasing invasive interventions.

***Nosocomial infections (NI) in neonates:***

Term healthy babies may suffer from nosocomial staphylococcal skin infections, mastitis and omphalitis. Premature and low birth weight babies, on the other hand, are highly susceptible to NI due to gram negative bacteremia, coagulase negative staphylococcus and candida. Additionally nursery outbreaks due to RSV, enteroviruses, CMv are well recognized. Early recognition and rapid initiation of treatment is important to save the neonates.

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## Answer of Photo Quiz : Purpura Fulminans

Now that you have recognized it, can you answer the following?

(1) It is also known as ?
(2) Name the various forms of the defects of Protein C anticoagulant pathway.
(3) Disease Mechanism (aetiopathogenesis) ?
(4) Laboratory findings ?
(5) When to suspect ?
(6) Management?

*Find answer in Page No.36*

*Case Report*

# Tongue Burn in a Newborn

**S Dutta, P Choudhury, K Kafeel**
*Department of Pediatrics, Central Referral Hospital, Gangtok*

**Introduction**

This is a case report of a rare incidence of burn injury in a new born over the tongue and lower lip from charcoal.

**Case summary:**

A new born female admitted for feeding care on day 23 of life with burn injury over the tongue and lower lip following exposure to charcoal (traditional way of keeping the child warm in winters) associated with minor burns over lower limbs and poor feeding.

Baby delivered by institutional vaginal delivery to a primigavida mother at 40 weeks of gestation on 08.10.2012 with good APGAR at 1 and 5 min. Birth weight was 4.0 kgs .Post-natal period was uneventful. GRBS maintained. Baby immunized (BCG, OPV) and discharged at 40 hrs of life.

On examination: Child alert but irritable, pink and euthermic.

(i) Pulse rate: 136/min; Respiratory rate: 50/min

(ii) Good peripheral pulsations, CFT<3 secs

(iii) SPO2: 97% in room air; weight = 4.2 kgs

(iv) No pallor/cyanosis/icterus

(v) Well-defined ulcer over anterior 2/3rd of the tongue (2cm x 3cm) with slough formation (Fig 1 and 2)

(vi) Blister over lower lip in midline

(vii) Systemic examination: No abnormality detected

The baby was started on intravenous fluids at full maintenance for first 24 hours of admission. Dermatology and surgery consultations were sought and the child was started on oral Ampiciilin-Cloxacillin combination and

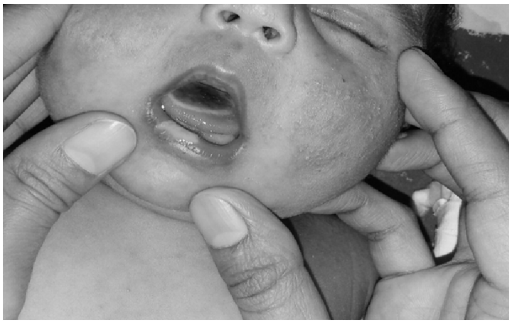

Fig 1

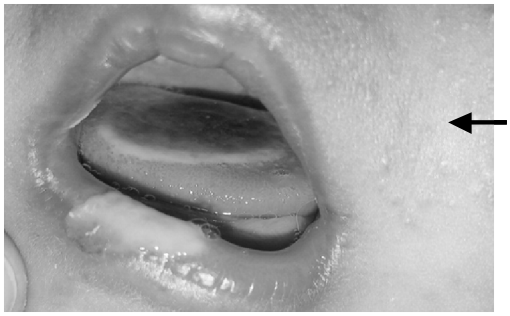

Fig 2

oral analgesics (suspension and gel for topical application). Palladai feeds were started after 24 hours and child was put to the breast by 48 hours. I/v fluid was tapered and stopped.

Baby shifted to mother's side at 72 hours of admission and discharged at 96 hours on antibiotics for 3 more days. Weight at discharge: 4.37kgs

She was reviewed after 3 days (on completion of antibiotics). The ulcer showed signs of healing and the baby was comfortable on breast feeding. Multivitamin drops and analgesic gel were continued. A second review done when she came for her one and half months vaccination showed near complete resolution of lesion.

**Discussion**

Burn injury over the tongue may be seen in children less than 3 years of age either from feeding of hot liquids or due to electrical injury from biting cables. The occurrence, however, is extremely rare in new-borns especially now with aggressive exclusive breast feeding for 6 months campaign in developing countries. This article also highlights the use of harmful traditional methods still practised despite improved literacy and public health care.

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## *Obituary*

**Dr. Shanti Ghosh**

Dr. Shanti Ghosh, Past President of IAP passed away to her heavenly abode on Saturday morning, August 16, 2014.

For many years Dr. Shanti Ghosh headed the pediatric department at Safdarjung Hospital, one of the largest tertiary level multi-disciplinary healthcare institutions in Asia. Dr. Ghosh had authored several books on health, nutrition and child care and published over 150 articles in national and international journals. Her numerous accolades include the Dr. Kamala Menon Award and Dr. M.K. Seshadri Award from the Indian Council of Medical Research, Outstanding Asian Pediatrician Award of the Association of Pediatric Societies of South Asia and International Pioneer of Newborn Medicine by the American Academy of Pediatrics. As her contributions in maternal and child health have led to major policy reforms, she is fondly referred to as the "the mother of neonatal care in India".

Dr. Ghosh had been advising the Delhi Ministry of Health for several years. As a chairperson of the Child Survival Group and member of the Safe Motherhood Group, she was involved in the planning of India's progress in maternal and child health for decades. Internationally, Dr. Ghosh had served as advisor for the WHO regional office, Food and Agriculture Organization, World Food Program, SIDA and other international agencies Bangladesh and Bhutan. From 1978 to 1983, she served as WHO's advisor for family health in Afghanistan.

Dr. Ghosh worked with Mahatma Gandhi during India's freedom struggle, and her late husband Sudhir Ghosh served as Gandhi's official emissary on several missions.

Dr Shanti Ghosh was felicitated by "Lifetime achievement award" by Indian Academy of Pediatrics during Golden Jubilee Pedicon in Kolkata on 17 January 2013.

*Case Report*

# *Salmonella typhi* Septic Arthritis of the Hip - A Case Report

***Biplab Maji, **Nupur Ganguly, ***Apurba Ghosh**
**RMO, **Associate Professor, ***Professor, Institute of Child Health, Kolkata*

*ABSTRACT: Salmonella infection can present as enteric fever, gastroenteritis, septicemia with or without local suppurative lesions, and as carrier state. The local suppurative lesions are most commonly associated with immunosuppression or underlying chronic debilitating diseases and may involve any site in the body including the osteoarticular tissue. Here we describe a case of Salmonella typhi arthritis of hip joint in an immunocompetent child who responded to a 6 week course of antibiotic based on the culture and sensitivity report. The case is presented for its rarity and to highlight the atypical manifestations of Salmonella typhi in endemic regions.*

## Introduction

Before the developement of conjugate vaccine, *Haemophilus influenza* type b , *Staphylococcus aureus* and streptococci were the major causes of septic arthritis in pediatric patients[1]. The knee joint is most commonly affected followed by hip and shoulder joints. Gram-negative bacillary arthritis is rarely encountered in young and healthy host, and is more commonly associated with immunosuppression and underlying chronic debilitating diseases[2]. Here we describe a case of septic arthritis in a immunocompetent child caused by *Salmonella typhi.*

## Case Report

A five year old male child was admitted with complaints of high grade fever for last one week, acute pain in left hip for last 3 days with acute urinary retention. There was also marked restriction in movements of left hip with abduction and external rotation of the hip joint . The presenting features appeared about ten days after the child was pushed down while playing and had injury in the left hip joint. Laboratory findings included a hemoglobin level of 10.1 g/dl, total leukocyte count of 9580/$mm^3$ (78% polymorphonuclear cells, 14% lymphocytes), platelet count 2.4 lakhs / $mm^3$ and AST 20U/L. Creatine kinase was 384 U/L, erythrocyte sedimentation rate (ESR) was 86 mm/h with a high C-reactive protein, measuring 117 mg/dl (range, 0-6 mg/dl). Empirical therapy with ceftriaxone and cloxacillin was started. X-ray hip joint revealed increase in the joint space and soft tissue swelling. MRI of left hip joint showed (Fig 1& 2) joint effusion with marrow oedema in the left femoral neck region with edema of the adjacent muscles. A diagnosis of septic arthritis was made and a needle aspirated sample was sent for pathology. The pus sample did not yield any growth but the blood culture revealed heavy growth of *Salmonella typhi*. The Widal test was positive with a titres of 1:320 for TO and TH for *S. typhi.* Urine analysis revealed no evidence of infection. Cloxacillin was changed to ofloxacin according to sensitivity report. The report was communicated to the surgeon and arthrotomy was planned, but parents refused for arthrotomy and drainage. Fever continued for 14 days and gradually came down to normal along with normal movement of the hip joint. HIV, Antinuclear antibody, Rheumatoid factor, and HLA-B27 were all negative. Serum C3, C4 and complement function were normal. Hemoglobin electrophoresis showed no abnormality thus excluding hemoglobinopathy. Serum

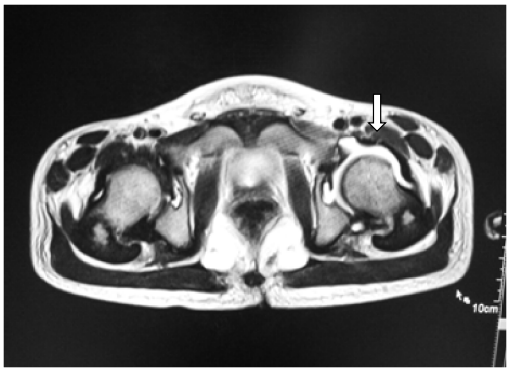

Fig 1: MRI of the hip joint shows collection around the head of the left femur

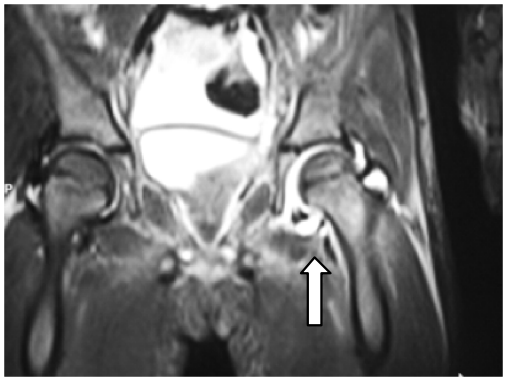

Fig 2: AP view shows joint effusion of the left hip with marrow oedema of the femoral neck

immunoglobulin concentrations were normal when measured during his convalescence, with a normal CD4, CD8 count, suggesting no immunodeficiency. After two weeks of treatment the child became afebrile and was able to walk around comfortably. But antibiotic was continued for a total duration of 6 weeks.

**Discussion**

Typhoid fever is caused by the bacterium Salmonella serovar typhi which spreads via feco-oral route. The incubation period is usually 8-14 days but depends on the infective dose and can vary from three days to one month. The pathophysiological mechanism involved in *Salmonella typhi* infection is by its fimbrial adherence to the Payer patches in distal ileum ,which is the main relay point for macrophages travelling from gut into lymphatic system. It has been hypothesized that typhoidal salmonellae expresses certain virulence mechanisms allowing them to down regulate a pathogen recognition receptor (PRR) mediated host response in intestinal mucosa. This results in the absence of neutrophilic infiltration[3]. Apart from gastroenteritis, enteric fever and carrier state[4], *Salmonella typhi* are known to metastasize to distant sites. They have a predilection for any skeletal sites causing either osteomyelitis or arthritis. The other presentations like neuropsychiatric, cardiovascular, hepatobiliary and genitourinary manifestations have also been seen. Occasionally, focal lesions such as brain abscess, spleen and liver abscess have been reported[5]. Salmonella arthritis is classified as septic arthritis and reactive arthritis, and septic arthritis is more likely if Salmonella is identified by culture of joint fluid. It is likely that there is a combination of other factors involved in addition to the presence of bacteria and it is also very likely that trauma is one of these factors. In most of the case report there was evidence of preceding trauma, as in our case and that could have acted as trigger for joint involvement. The exact infectious dose and time to reach the threshold for bacteremia for causing specific extra-intestinal infectious complications is unknown. It has been hypothesized by Perry[6] that capillary stasis reduces oxygen tension as a result of trauma and creates a nidus of infection locally that may develop into septic arthritis. In a study on rabbits by Onley, it was found that microtrauma in the presence of bacteremia renders joints susceptible for infection[7].

Culture should be done in all cases along with the Widal test even when patient presents late with prior use of antibiotic in the second week of infection in suspected case of Salmonella infection. Physicians should be aware of this rare manifestation of *S.typhi* infection. In all cases of pyrexia of unknown origin with bone involvement in an endemic area, one should consider *Salmoinella typhi* infection in the differential diagnosis. Early diagnosis, surgical intervention and administration of appropriate systemic antibiotics depending on the sensitivity report play a pivotal role in successful treatment. More than 100 cases of salmonella arthritis were reviewed, which revealed that the disease is primarily of children and young adults, with a favourable response. But septic arthritis affecting the hip is a known risk factor for poor outcome[8].

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**Answers :**

(1) Purpura Fulminans also known as purpura gangrenosa

(2) Defects in the protein C anticoagulant pathway may be Congenital (autosomal recessive) or acquired (caused by administration of vitamin k antagonists, severe liver failure or complications of prematurity).

(3) Regardless of the underlying cause of purpura fulminans, the mechanism of disease is similar with deficiency in protein C concentration or decrease in protein C activity which promotes blood clotting resulting from coagulation/ thrombosis in small blood vessels within the skin and rapidly leads to skin necrosis and disseminated intravascular coagulation.

(4) The cardinal features of purpura investigations are the same as those of disseminated intravascular coagulation: prolonged plasma clotting times, thrombocytopenia, reduced plasma fibrinogen concentration, increased plasma fibrin-degradation products and occasionally microangiopathic haemolysis.

(5) Early purpura fulminans lesions look similar to traumatic skin bleeds or purpuric rashes, such as immune thrombocytopenic purpura or thrombotic thrombocytopenic purpura; however, purpura fulminans will rapidly progress to necrosis whereas other purpuric rashes do not. In most cases, differential diagnoses may be distinguished from purpura fulminans by other clinical and laboratory findings.

(6) Early stage sepsis-associated purpura fulminans may be reversible with quick therapeutic intervention.[2][11] Treatment is mainly removing the underlying cause and degree of clotting abnormalities and with supportive treatment (antibiotics, volume expansion, tissue oxygenation, etc.). Thus, treatment includes aggressive management of the septic state. Purpura fulminans with disseminated intravascular coagulation should be urgently treated with fresh frozen plasma (10–20 mL/kg every 8–12 hours) and/or protein C concentrate to replace pro-coagulant and anticoagulant plasma proteins that have been depleted by the disseminated intravascular coagulation process. A multi-disciplinary care team is usually required for rehabilitation after purpura fulminans.

*Case Report*

# Severe Dengue with Multiorgan Dysfunction Syndrome (MODS)

***Prabhas Prasun Giri, **Rashmita Das, ***Ritabrata Kundu**
**Assistant Professor and In Charge of PICU,**Post Graduate Trainee,***Professor*
*Institute of Child Health, Kolkata*

***Abstract** : Dengue is a mosquito born tropical disease and India remains an endemic zone for it for the last couple of years. Dengue fever usually does not cause much problem in its febrile phase, but frequently causes trouble in the form of dengue shock with or without hemorrahagic manifestations due to prolonged capillary leak when the fever subsides. Uncompensated dengue shock may manifest as multiorgan dysfunction and carries worse prognosis with very high mortality. Here we present a nine year old girl who was admitted with dengue fever with compensated shock and upper GI bleeding and ultimately developed multiorgan dysfunction but saved with intense pediatric intensive care support.*

***Key words** : Severe dengue, hemorrhage, Liver failure, kidney injury.*

## Introduction

There is as yet no precise definition of multiple organ dysfunction syndrome (MODS). Clinically MODS can be considered as a sequential or concomitant occurrence of a significant derangement of function in two or more organ systems of the body, against a background of a critical illness. Organ dysfunction may be mild, moderate or severe, and multiple organs may show varying degrees of dysfunction. There is no universally acceptable classification system which defines parameters of organ specific failure. An ACCP/SCCM Consensus Conference which was held in 1991, defined MODS as "the presence of altered function in an acutely ill patient such that homeostasis cannot be maintained without intervention"[1]. Unquestionably the commonest cause of MODS all over the world (including the tropics) is sepsis due to bacterial infection, chiefly caused by Gram-negative bacteria. Hemorrhagic dengue can cause death from uncontrollable bleeding or from multiorgan dysfunction caused by bleeds into various organs of the body. Here,our index case admitted with severe haemorraegic dengue and developed MODS in the form encephalopathy, pulmonary edema, hepatic failure, pancreatitis, acute kidney injury, severe coagulopathy and needed multiple blood products transfusion, management of hepatic failure and hemodialysis and ultimately saved.

## Case Report

A nine years old girl admitted in our institution with history of 4 days of fever associated with vomiting from day1 of fever. There was also history of pain abdomen and hematemesis and decreased urine output for last one day. There was no past h/o dengue fever. On admission patient was irritable and in compensated shock. On examination pulses were feeble with prolonged CRT; there was tender hepatomegally, her HR was 120/min and BP was 100/80mmHg.She was treated urgently with IVF Normal Saline boluses and was shifted to PICU. Her investigations revealed TLC-10,400/dl,Hb-16.6gm/dl, PCV 48.2,Platelets 1,02,000/dl,CRP10mg/l (normal<6),urea 28mg/dl, creatinine 0.61mg/dl,sodium

128mEq/dl, potassium 4.9mEq/dl,SGPT-178IU/dl. Dengue NS1 and IgM were reactive. She was initially treated with inj. Cefotaxime, inj. Pantoprazole and ondansetron, inj. Vit-k. Though initial platelet count was in lower normal range but overnight her platelet count dropped down to 36000/dl and she also started to bleed from venous puncture sites. So we decided to give FFP and platelet transfusion. For next two days patient's condition remained same and we tried to maintain hydration .But on day3 her condition worsened with development of tachypnea, pedal edema, jaundice, ascites and the girl also became disoriented; at that time her GCS was 8/15 and melena continued. On investigation her liver enzymes was high (SGPT 6825,SGOT-15660), RFT was deranged(Urea-94,Creatinine 2.72) and on CXR there was features of diffuse pulmonary edema with pleural effusion(right>left)(figure 1).PT and NR was 37 and 3.4 respectively and amylase, lipase were elevated and there was evidence of ascites, pleural effusion and features of pancreatitis in USG abdomen. Anti HAV, HCV and HEV antibody, HBsAg were non reactive, Leptospira serology was negative. After this deterioration and development of multiorgan dysfunction, organ specific intensive care management was started. So we changed antibiotic to inj. Piperacillin-tazobactum in view of possible secondary bacterial infection. Continuous N-acetyl cysteine(NAC) infusion to support the failing liver at the dose of 100mg/kg/day. FFP and platelets transfusions were given to combat the active bleeding due to coagulopathy and thrombocytopenia .The girl was also put on Non Invasive Ventilation(NIV) as a mode of respiratory support. The girl started improving gradually by next 3 to 4 days.Sensorium had been improving, taken off from NIV , bleeding stopped and liver parameters were also improved ,but her renal parameters went downhill and creatinine started increasing gradually (table 1). Pediatric Nephrology opinion was taken and the girl was started on hemodialysis. Seven cycles of hemodialysis was considered and after that her renal function became normalized and ultimately she was discharged with a stable condition after 21 days of hospital

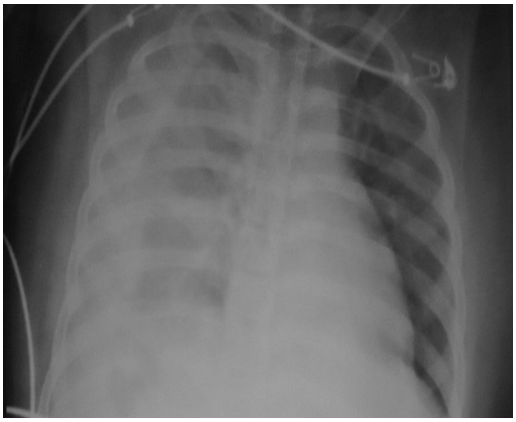

**Fig 1**. Pulmonary edema with pleural effusion

**Table 1**. Investigation report of Day 1 to Day 7

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| TLC | 10400 | | | | 15000 | | 19500 |
| DLC | N76L25 | | | | N67L28 | | |
| Hb | 16.6 | 14 | 13 | 13 | 10.4 | | 8.9 |
| PCV | 48.2 | 42 | 39 | 40 | 30 | | 25 |
| PLATELETS | 102000 | 36000 | 49000 | 26000 | 42000 | 87000 | 150000 |
| CRP | 10 | | | | 43 | | 25.7 |
| UREA | 28 | | | | 70 | 94 | 138 |
| CREATININE | 0.61 | | | | 1.93 | 2.72 | 4.9 |
| SODIUM | 128 | | | | 135 | 144 | 143 |
| POTTASIUM | 4.9 | | | | 4.3 | 4.7 | 4.5 |
| SGPT | 178 | | | | 6825 | | 2530 |
| SGOT | | | | | 15660 | | 2688 |
| PT/INR | | 16/1.4 | | | | 37/3.4 | 19.8/1.7 |

admission.

**Discussion**

Dengue is an acute infectious disease caused by an arbovirus of the flavivirus genus, and is transmitted by the female of the mosquitoes *Aedes aegypti, A. albopictus*, *A. scutellaris* and *A. polynesiensis*. The classical form of dengue is an acute and self-limited disease characterized by fever, prostration, headaches, retro-orbital pain, myalgia, nausea, vomiting, skin rash, leukopenia and thrombocytopenia[2-4].There are usually 3 phases of dengue, febrile, critical and recovery. Medical complications can be seen in all the phases of dengue. In febrile phase dehydration is the commonest complication though high fever may cause neurological disturbances and febrile seizures in young children. In critical phase shock from plasma leakage and severe hemorrhage may occur .Severe uncompensated shock with haemorrahage may lead to organ impairment like our index case. Complications can also occur in the recovery phase in the form of hypervolaemia usually due to overenthusiastic extra fluid administration and failure to identify the recovery phase. It may cause acute pulmonary edema and even frank heart failure. Presently the recent case definition defines dengue either as dengue without warning signs or dengue with warning signs or severe dengue. Severe dengue is the dengue that presents with shock with or without haemorrhaegic manifestations.

However, in recent times the reports of rare manifestations of dengue have become more common and may include central nervous system manifestations (encephalopathy.), liver and renal failure[5]. Liver enzyme elevations are common in dengue. Usually the SGOT levels are more than SGPT levels probably due to skeletal muscle injury. Occasionally jaundice is also seen[6].

Though hepatitis in patients of dengue is not uncommon, dengue is only rarely considered as a cause of acute liver failure[7]. The girl in our case had an acute fulminant hepatic failure as the Prothrombin time was deranged as well as the liver function. Although, severe hepatitis associated with dengue fever is a rare occurrence, it carries significant mortality and morbidity[8]. A cross-sectional study to investigate the clinical factors associated with mortality in patients with dengue viral infection was done at a tertiary care center in Karachi, Pakistan over a 3 year period. In this study they have concluded that severe hepatitis (SGPT>300), bleeding, altered mental status on admission and shock were clinical factors associated with high mortality in patient with dengue viral infection. Our proband has all of these risk factors and still managed to survive[9].

Now as the important differential diagnosis in a case presenting with fever with acute liver failure also includes complicated malaria, viral hepatitis A,E and B and leptospirosis we went for these tests and all of them came out to be negative. To date, only four cases of mixed infection with dengue and leptospirosis have been described; however, the concurrent rise of leptospirosis during a dengue outbreak has been reported. The possibility of co-infection with HEV should also be borne in mind, as water is the vehicle of transmission for both HEV and Leptospira[10-12]. Now treatment of dengue fever associated with acute liver failure includes mainly supportive therapy in the form of adequate fluid replacement, timely ventilator support, prophylactic antibiotic coverage to prevent secondary bacterial sepsis and continuous monitoring of neurological status[13]. Most of the cases recover with supportive therapy[14,15]. But now-a-days there is increasing evidence for use of NAC infusion in non-acetaminophen causes of ALF[16]. They recommended routine use of NAC in the dose of 100 mg/kg/day in all cases of ALF irrespective of the etiology. This was based on a retrospective single site review involving 170 children done by Kortsalioudaki, *et al*.[17]. In view of this, a retrospective analysis on NAC in dengue associated liver failure by Kumarasena *et al.* showed that NAC may have a role in dengue associated liver failure[18].We started NAC when found the girl in ALF and her liver function improved over next couple of days.

Pulmonary edema and ARDS are not uncommon in dengue. It may be due to fluid accumulation in lungs or solely may be due to widespread capillary leakage[5]. TV Devarajan, *et al* reported 2 cases of dengue in adults that developed ARDS[19]. Non invasive ventilation(NIV) is no becoming a popular mose of respiratory support among the intensivists. We used NIV in our case for 3 days.

Pancreatitis can be a manifestation of severe dengue infection[20]. It is manifested by pain abdomen with raised Amylase and Lipase enzymes along with ultrasonography features of pancreatitis.

Acute kidney injury is not a rare manifestation of severe dengue. It may be due to pre renal failure due to prolonged shock or may be due to acute tubular necrosis(ATN)[21]. If the deranged kidney function persists even after adequate fluid therapy, it is possibly due to ATN rather than pre renal AKI. AKI in dengue is associated with neurological involvement, prolongation of aPTT, greater length of hospital stay and increased mortality[22].Our patient has an AKI with possible ATN that needed 7 sessions of hemodialysis.

In conclusion, though severe dengue with MODS can be fatal, a multidisciplinary approach with level 3 intensive care can save life like our index case.

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