# ANNALS OF
# THE INSTITUTE OF CHILD HEALTH CALCUTTA

(Affiliated to West Bengal University of Health Sciences)





***Published by***
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# ANNALS OF THE INSTITUTE OF CHILD HEALTH CALCUTTA

ISSN - 0300 - 533X ● VOLUME 14 ● NUMBER 1 ● JANUARY – JUNE 2014




## CONTENTS

Clinically, a case of Acute Encephalitis Syndrome (AES) is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, come, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness.

Acute Encephalitis Syndrome (AES) including Japanese B encephalitis (JE) is a group of clinically similar neurologic manifestation caused by several different viruses, bacteria, fungus, parasites, spirochetes, chemical/ toxins etc. A period of up to 14 days is considered to define 'acute'. In an epidemic situation fever with altered sensorium persisting for more than two hours with a focal seizure or paralysis of any part of body, is encephalitis. Presence of rash on body excludes Japanese Encephalitis. AES with symmetrical signs and fever is likely to be cerebral malaria. The outbreak of JE usually coincides with the monsoon and post monsoon period when the density of mosquitos' increases while encephalitis due to other viruses especially entero-viruses occurs throughout the year as it is water borne disease.

Most of the encephalitic illnesses are sporadic. But it is only JE which spreads in epidemic proportions though sporadic cases are also reported. When the inflammatory and immune reactions of viral encephalitis subside, the lesions heal with glial scar formation. The neurons lost usually do not regenerate. So in the aftermath, patients are often left with severe permanent neurological deficits.

A case of viral encephalitis including JE presents with a prodrome of fever, headache, nausea, diarrhea, vomiting, and myalgia lasting for 1-5 days. It is followed by irritability, altered behaviour, convulsions and coma. The progression of disease is rapid. Features of raised intra cranial tension are commonly present in acute stage of illness. The patient may develop difficulty of speech and other neurological deficits like ocular palsies, hemiplegia, quadriplegia and may have extrapyramidal signs in the form of dystonia, choreoathetosis and coarse tremors.

A suspected case that meets the clinical case definition for AES may be classified in one of the following four ways.

(i) Laboratory-confirmed JE: A suspected case that has been laboratory-confirmed as JE.

(ii) Probable JE: A suspected case that occurs in close geographic and temporal relationship to laboratory-confirmed case of JE, in the context of an outbreak.

(iii) Acute encephalitis syndrome (Due to agent other than JE): A suspected case in which diagnostic testing is performed and an etiological agent other than JE virus is identified.

(iv) Acute encephalitis syndrome (Due to unknown agent ): A suspected case in which no diagnostic testing is performed or in which testing was performed but no etiological agent was identified or in which the test results were indeterminate.

All the cases of Acute Encephalitis Syndrome (AES) should be reported as they have similar clinical manifestations. Their case management usually follows a common protocol along with situation specific treatment.

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**Dr Maya Mukhopadhyay**
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Editor

# Japanese Encephalitis – When to Suspect and What to Do ?

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## Introduction

Japanese encephalitis (JE) emerged in Japan in the year 1870 thereafter spreading across East and South-East Asia and has became the most important cause of epidemic encephalitis and a serious public health problem with significant mortality and morbidity[1]. Annual estimated cases are 30,000–50,000 with 10,000–15,000 deaths[2]. Fortunately most JE have either mild features or are asymptomatic.The ratio of manifested to inapparent infection varies from 1:25 to 1:1000.the disease mainly affects the children between age group of 3-14 years. Currently, there is no cure for the disease as no antiviral is available against JE.

## Epidemiology

First case of JE in India was from Vellore, Tamil Nadu in the year 1955.Subsequently West Bengal reported first major outbreak in Bankura and Burdwan in 1973 with repeat outbreak in Burdwan in 1976.Wide spread outbreaks were reported from Andhra Pradesh, Assam, Karnataka, Tamil Nadu, Uttar Pradesh and West Benga[l3]. JE has remained a tropical disease uncommon in the West. With rapid globalization, unplanned urbanisation, deforestation and climatic shift, JE has started to emerge in areas where the threat was previously unknown and may soon become a global pathogen and cause of worldwide pandemics[4].

## Agent

JE is a neurotropic RNA arbovirus (arthropod-transmitted virus) belonging to the family Flaviviridae and genus Flavivirus, which is antigenically closely linked to other flaviviruses like Dengue and Yellow Fever[5]. In phylogenetic analysis Japanese Encephalitis Virus (JEV) has only single serotype, but geographic strains differ by RNA sequencing[6].

## Ecology

JEV exists in a zoonotic transmission cycle between pigs, birds and mosquito (fig1). Unlike many other mosquito-borne diseases, an amplifying host ,pig is important in the epidemiology of human JE.Water birds (herons,egrets and ducks) are the main reservoir for disseminating the virus.Pigs allow multifold virus multiplication without suffering from disease and thus continues prolonged

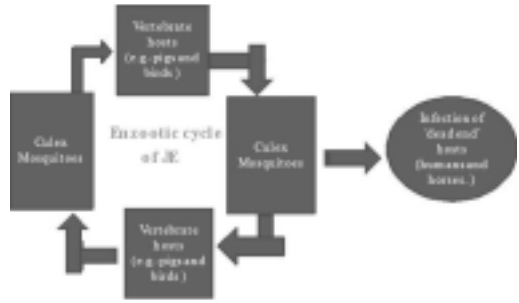


**Fig 1. Transmission cycle of JE**

viraemia allowing transmission to man via mosquitoes. Infection in human appears to be correlated with living in close proximity with animal reservoirs, especially pigs. Humans and other large vertebrates such as horses are not efficient amplifying hosts, and because of low and transient viremia they are 'dead-end' hosts for the JEV. It does not spread from human to human.Patients are not infectious but should avoid further mosquito bites.

Culex mosquito is the principal vector of JE in India.Host-feeding patterns of these mosquitoes are highly zoophilic i.e. feed on animals and mostly set away from human habitations.There resting habit is mainly exophilic i.e. rest outdoor.. A marked increase in the proportion of human feedings during the hot season, because of increased availability of humans sleeping outdoors[7]. Transmission of JE virus to man is incidental and accidental and causes termination of transmission.

Vertical transmission of JEV in mosquitoes probably explains the "overwintering" of virus between epidemics.

There are two epidemiological patterns of transmission :

Endemic pattern – Southern tropical areas with viral circulation in most months of the year, with a broad seasonal peak, probably resulting from irrigation practices.

Epidemic pattern is more in northern temperate areas with clear summer seasonality[3].

**Vector**

The major mosquito vectors of JEV vary in different geographic regions(Culex tritaeniorhynchus,C. vishnui, C. pseudo-vishnui and tolal 11 species along with some species of Aedes and Anopheles mosquitoes). Culex vishnui group of mosquitoes are most important vector species in India. Culex mosquitoes generally breed in water bodies like irrigated rice fields, shallow ditches and pools,wet pit latrines, septic tanks, barrow pits, cess pools, drains, unused wells , marshes and standing water around planted fields .It can fly up to 5 kms and has nocturnal biting habit[7]. Epidemics usually coincide with monsoons and post-monsoon period when the vector density is particularly high. Female mosquitoes get infected after feeding on a viraemic host (usually pigs) and transmit the virus to other hosts after an extrensic incubation period of 9 to 12 days. The mosquitoes remain infected for life. The average life span of a mosquito is about 21 days. Rural setting offers the amplifier hosts in abundance along with mosquito favouring conditions so JE prevalent in rural area.Infection with JEV confers lifelong immunity,if infected person survives.

**Pathology and Pathogenesis**

Grossly oedematous brain with changes seen mainly involving grey matter.The commonly affected parts are the thalamus, substantia nigra, ,cerebral cortex,cerebellum and anterior horns of the spinal cord[8]. Lesions include meningeal inflammation, perivascular lymphocytic cuffing, neuronal degeneration and neuronophagia and microglial proliferation forming glial nodules.

Pathological changes seen in extraneural tissues are hyperplasia of germinal centres of lymph nodes,enlargement of malpighian bodies in spleen, interstitial myocarditis,swelling and hyaline changes in hepatic Kuffer's

cells,pulmonary interalveolitis and focal haemorrhages in kidney.

Following an infected mosquito bite it takes about 5-15 days for the disease to develope. After transmission JEV multiplies locally and in regional nodes. After a phase of transient viraemia, central nervous system (CNS) is invaded. JEV is thought to invade brain via vascular endothelial cells by endocytosis.Experimental study in mammalian host has shown JEV tropism to neurone on CNS.

JEV causes neuronal cell death in two ways:

Direct neuronal killing - viral multiplication within neuronal cells leads to cell death.

Indirect mode of killing - massive inflammatory response causes an up-regulation of reactive oxygen species and cytokines such as (TNF$\alpha$), which, in turn, causes neuronal death. The key factor is the uncontrolled overactivation of microglia cells[3].

JE is a part of acute encephalitis syndrome (AES) which is a group of clinically similar neurologic manifestation caused by a wide range of infections and other causes.

AES is defined by WHO as a person of any age, at any time of year, with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures). Other early clinical findings can include an increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness.

AES cases are mainly reported from Assam, Bihar, Karnataka, Tamil Nadu and Uttar Pradesh which contributes approximately 80% of cases and deaths respectively with a case fatality rate ranging from 20 to 25%[5].

**Case classification**

Suspected case: A case that meets the clinical case definition for AES. Suspected cases should be classified in one of the following four ways.

Laboratory-confirmed JE: A suspected case that has been laboratory-confirmed as JE.

Probable JE: A suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak.

Acute encephalitis syndrome – other agent: A suspected case in which diagnostic testing is done and an etiological agent other than JE virus is identified.

Acute encephalitis syndrome – unknown: A suspected case in which no diagnostic testing is done, or in which testing identified no etiological agent, or in which the test results were indeterminate.

Differential diagnosis of AES given in table 1.

**Clinical Manifestation of JE**

JE can be divided into 4 stages as shown in box 1

**Box 1: Stages of JE**

| |
|---|
| Prodromal stage – 2-3 days. |
| Acute stage – 3-4 days |
| Sub acute stage – 7-10 days |
| Convalescence – 4-7 weeks |

**Table 1:** Differential diagnosis of AES

| | |
|---|---|
| **Endemic/Epidemic Encephalitis** - | Japanese B Encephalitis |
| **Sporadic Encephalitis** - | Herpes Simplex Virus(HSV) |
| | Entero Virus-polio and non polio (coxsackie A&B,echo and others) |
| | Dengue,Varicella,Measles,Mumps and Rubella Viruses. |

**Others**

***Infective Causes:***

Parasitic-malarial,toxoplasmal
Spirocheatal-syphilis
Potozoal-amoebic
Bacterial - Acute TBM,Pyogenic brain abscess
Fungal-cryptococcal
Rocky Mountain spotted fever

***Non Infective Causes:***

Acute Disseminated Encephalomyelitis (ADEM)
CNS lupus erythematosus
Nonmetastatic CNS tumors
Cerebrovascular diseases
Metabolic Diseases

***Prodromal stage :***

For those small number of patients who manifest the disease , it starts suddenly in form of non specific febrile illness with headache,vomiting and myalgia followed by acute stage.

***Acute stage:***

It shows features of brain damage - irritability,altered behaviour and seizures are common along with abnormal movement including tremor or rigidity.Focal neurodeficit like asymmetric spontaneous eye movement,absent pupillary and corneal reflex and muscle weakness are also seen. A proportion of patients may have an acute flaccid paralysis that may be mistaken as poliomyelitis[9].

Neuropsychiatric manifestation are also seen in older children which may be erroneously diagnosed as mental disease.Those with brain stem involvement manifested with abnormal posturing,ocular abnormality and absent brainstem reflex which may detoriate rapidly without prompt intervention.

***Subacute stage:***

In this phase the severity of neurological manifestation lessens.Other complication like orthostatic pneumonia,urinary tract infection and bed sore may set in unless properly managed.A child in deep coma may regain consciousness but manifest bizarre posturing and rigidity.

***Convalescence:***(fig 2, 3)

Parkinsonian like state may be seen as the child recovers.Rigidity,tremor and bradykinesia may develop. Both long tract and extrapyramydal signs tend to improve gradually.Those with severe involvement shows little recovery with persistent weakness and marked wasting of involved limbs.Some may develop speech and swallowing difficulty..JE not only have high case fatality ( 0.3% to 60%)and about 50% percentage of the survivors are left with permanent neuropsychiatric sequelae .30% of


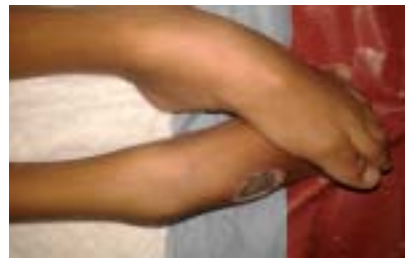

**Fig 2 and 3 : JE Case with Sequele**

survivors have persistent motor deficits and 20% have severe cognitive and language impairment[10].

Unfavorable signs at beginning which predicts poor outcome are shown in box 2.

**Box 2: Poor prognostic indicator of JE**

| |
|---|
| Open eyelids |
| Absent dolls eye movement |
| Non reacting pupil |
| Hanging jaw |
| Rapid breathing |
| Excessive secretions |
| Persistence of fever |
| Absence of response to pain |
| Decorticate posture |
| Decerebrate posture |
| Refractory seizure |

Clinically it is difficult to differentiate between JE and other viral encephalitis.Presence of rash excludes Japanese Encephalitis.AES with symmetrical neurological signs of upper motor neuron lesion and fever is likely to be cerebral malaria.

**Laboratory Criteria For Diagnosis:**

Clinically its difficult to distinguish JE from other causes of AES.Like other viral encephalitis JE also shows lymphocytic pleocytosis with normal CSF glucose and elevated protein.Serologic cross-reactivity among other viruses, specifically dengue and west nile virus, may lead to confusion in the diagnostic evaluation of Japanese encephalitis (especially in India).

***Laboratory confirmation of a JE virus infection includes:***

1. Presence of IgM antibodies specific to JE virus in a single sample of cerebrospinal fluid (CSF) or serum, as detected by an IgM-capture ELISA specifically for JE virus.
2. Detection of JE-virus antigens in tissues by immunohistochemistry;
3. Detection of JE-virus genome in serum, plasma, blood, CSF or tissue by reverse transcriptase polymerase chain reaction (PCR) or an equally sensitive and specific nucleic acid amplification test.
4. Isolation of JE virus in serum, plasma, blood, CSF or other tissue;
5. Four fold rise in lgG antibody titre specific to JE measured by haemagglutination inhibition (HI) in paired sera during the acute and convalescent phase of illness. The two specimens for IgG should be collected at least 10-14 days apart[11].

In MRI studies bilateral thalamic lesions,specially haemorrhagic is highly suggestive of JE[12]. The lesions are hypointense or hyperintense in T1 and T2 weighted images respectively (see fig.4).

**Management:**

The treatment is entirely supportive as there is no current effective antiviral therapy. There is a direct relationship between the time lag in onset of symptoms and initiation of supportive therapy. Immediate management of cases reduces fatality considerably. Since the disease is predominantly rural , the main cause of high mortality is transporting patient over long distances to the tertiary care hospital without proper medical care during this transport which causes irreversible brain damage. Infrastructure of clinical management with standard operating procedure or guidelines for management of cases should be available at base level of health care[9].

As a part of general management adequate airway should be ensured and gentle suction used to clear the throat and oxygen administered.Proper fluid along with ionotropic support to maintain adequate cerebral perfusion as autoregulation in brain fails.Hypoglycemia should be avoided. If required glucose infusion started.Convulsion should be managed with anticonvulsant but phenobarbitone should be avoided as it further depress the patient.Normal temparature should be maintained as hyperthermia increases intracrenial pressure(ICP). Raised ICP managed by proper positioning of the patient (head end elevated) and judicious use of osmotic diuretics lile mannitol,3%Nacl followed by glycerol.In cases of respiratory failure ventilatory support may be needed. Catheterisation in comatose patient reduce bladder distention. Scrupulous nursing is needed to prevent bed sores and aspiration pneumonia.Aadequate nutrition is maintained by ryles tube. Disability limitation and rehabilitation may require; physiotherapy, speech therapy and special support as per the deficit.

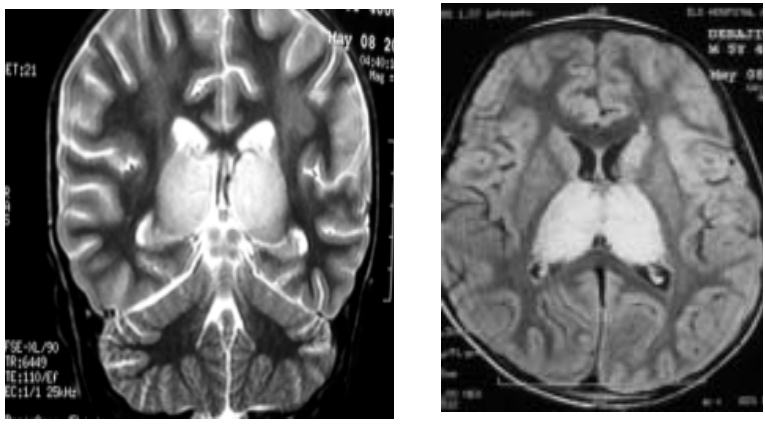

**Fig 4 : MRI Showing Abnormal Intensity in Bilateral Thalamic Region**

A significant research on minocycline as an anti-JEV drug , showed reduction of neuronal apoptosis, microglial activation, active caspase activity, proinflammatory mediators, and viral titer markedly . Another compound that has shown inhibition of JEV replication completely in vitro is an N-methyl isatin-b thiosemicarbazone derivative[8].

Study on effect of high-dose dexamethasone on the outcome of acute encephalitis due to JEV to reduce cerebral oedema revealed no statistically significant benefit.

National Vector borne Disease Control Programme (NVBDCP) developed surveillance guidelines and issued the same to all JE endemic states with the advice that JE be commonly reported under Acute Encephalitis Syndrome

It is very important to report all the suspected cases of AES or JE to the appropriate health authorities to prevent further spread of disease and if an outbreak of JE is suspected it must be reported immediately to the district health office.

**Control and Prevention of JE**

Control programs for JE have focused on three major areas

1. Mosquito control- Residual insecticidal spraying has been suggested in all animal dwellings with appropriate insecticide before the onset of transmission season[13]
2. Amplifying host (Pig) control

   As a part of interruption of transmission both the control has failed.
3. Vaccination

With the availability of safe, effective and affordable vaccines, JE control is now possible and should be extended to all areas where JE is a public health problem.

Currently three vaccines are available in India[14].

1. Live attenuated, cell culture-derived SA-14-14-2 vaccine developed in China.This vaccine is used in some parts of India from Government sector since 2006 in between the age group of 1-15 years as a single dose. Unfortunately the protective efficacy was found to be only 35% hence a second dose was recommended. However this vaccine is not available in private market.
2. An Inactivated Vero Cell Culture-derived SA 14-14-2 was launched in India.This vaccine is recommended as a 2-dose vaccine 28 days apart. 0.25 ml is administered IM in children between 1-3 years and 0.5 ml for children above 3 years
3. A second Vero Cell Culture-derived Kolar strain vaccine was introduced for children above 1 year.2 doses each of 0.5 ml given at 4 weeks apart.

Immunization strategy in endemic area is to give one time mass immunization to susceptible age group followed by routine immunization in the population. Age group of vaccine to be decided based on local epidemiology.

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## *Asthma Clinic*

This clinic provides comprehensive all round care for young asthmatics. Along with doctors, experienced asthma nurses and health workers train the patient and their parents to manage the disease better with medical devices and environmental control.

# Diabetes in Young: Beyond Type1

**Moutusi Raychaudhuri**
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## Introduction

Until recently, type 1 diabetes mellitus (T1DM) was not only the most common form of diabetes seen in youth, but also perhaps the only form of diabetes seen in children and adolescents. However, this trend has started changing. Type 2 diabetes mellitus (T2DM), earlier considered a disorder of the middle aged or elderly is increasingly being reported among young adults and now also in adolescence and childhood, probably due to the burgeoning epidemic of childhood obesity. Indeed, the epidemic of T2DM is now spreading so rapidly, that already in some countries like Japan, T2DM is more common than T1DM in children.

In India, apart from T1DM and T2DM, there are other forms of diabetes in the young including maturity-onset diabetes of the young (MODY), fibrocalculous pancreatic diabetes (FCPD), endocrine diabetes and the rare genetic causes of diabetes.

## Classification of Diabetes in Young

(a) T1DM ( immune mediated/idiopathic)

(b) T2DM ( typical/atypical )

(c) Genetic defects of ß -cell function (eg. MODY)

(d) Drug- or chemical-induced (eg. glucocorticoids)

(e) Diseases of the exocrine pancreas (eg. FCPD, cystic fibrosis)

(f) Endocrinopathies (eg. Cushing's syndrome)

(g) Genetic syndromes associated with diabetes (eg. PWS)

(h) Gestational diabetes mellitus (GDM)

**Classical Features of T1DM and T2DM:** (Refer to Table1)

### *Atypical presentations in T1DM:*

In some cases distinguishing T1DM from T2DM may be difficult at presentation. T1DM may be detected before progression to DKA and so all cases of T1DM may not necessarily present with DKA. The child may be overweight to begin with especially with prevalence of childhood obesity on the rise and this goes against the popular concept of the lean T1DM. Family history of DM may be present as because the prevalence of T2DM is increasing in epidemic proportions. Moreover Indian children are often antibody negative at diagnosis1. GADAb is present in 42%, IA-2Ab is found in only 33%, both antibodies are absent in 45. There may be apparent response to oral agents as the honeymoon phase sets in

### *MODY :*

The inheritance pattern is autosomal dominant

**Table1.**Classical Features of T1DM and T2DM

| | Type 1 diabetes | Type 2 diabetes |
|---|---|---|
| Onset | Acute—symptomatic | Slow—often asymptomatic |
| Clinical picture | • Weight loss<br>• Polyuria<br>• Polydipsia | • Obese<br>• Strong family history type 2 diabetes<br>• Ethnicity—high-prevalence populations<br>• Acanthosis nigricans<br>• PCOS |
| Ketosis | Almost always present | Usually absent |
| Insulin | • C-peptide negative | • C-peptide positive |
| Antibodies | • ICA positive<br>• Anti-GAD positive<br>• ICA 512 positive | • ICA negative<br>• Anti-GAD negative<br>• ICA 512 negative |
| Therapy | Insulin invariably | Oral hypoglycemic agents |
| Associated autoimmune diseases | Yes | No |

and often three consecutive generations are affected. Onset of the disease usually occurs before age of 25 to 30 years. Obesity is generally absent. The disease is characterized by mild to moderate hyperglycemia. MODY is classically not associated with autoimmunity or insulin resistance. There is evidence of impaired (not absent) insulin secretion and significant C-peptide levels are present. Insulin may be ultimately needed in low doses to achieve adequate glycemic control. Genetic testing is mandatory to diagnose and classify MODY.

***FCPD:***

High prevalence in seen in certain parts of India especially in the South. Common age of presentation is 10 – 30 yrs though it may occur earlier also. Four cardinal diagnostic features are abdominal pain, pancreatic calculi, steatorrhoea & diabetes. Patients are usually lean but may be normal weight. USG abdomen clinches the diagnosis. FCPD usually requires insulin for control. However no ketosis occurs on withdrawal of insulin. Finally a high index of suspicion is needed for diagnosing FCPD

***Uncertainties in classification:***

There is considerable overlap in C-peptide levels between T1DM, T2DM and MODY at onset and therefore C-peptide has greater diagnostic value in established diabetes. 15 - 25% of newly diagnosed T1DM and MODY may be obese[2]. In Asian Indian urban children, half of those with T2DM have normal weight[3] and a significant number of T2DM present with DKA at diagnosis. 15 - 40% of clinically diagnosed T2DM have auto antibodies[4]

**The Present Scenario in India**

(a) Among 2,630 Indian subjects with diabetes in the young, 48% had T2DM, 43.2% had T1DM, 4.5% had GDM and 4.4% had other forms of diabetes[5]

(b) Clinic-based data suggest that T2DM is increasing in the young, although this could be due to increased awareness and/ or referral bias

(c) In most government hospitals T1DM is more common perhaps reflecting a socioeconomic bias due to free supply of insulin at these hospitals and the fact that T2DM in the young is mostly associated with overweight and obesity which are currently more common among the more affluent classes of society

**Risk Factors for T2DM in Children**

(a) Obesity

(b) Physical inactivity

(c) Predisposed race/ethnicity (includes Asians)

(d) At least one parent with T2DM

(e) T2DM in 1°/ 2° degree relatives

(f) Birth Weight <2.5kg or > 4.0kg

(g) Mother with GDM

(h) Evidence of insulin resistance (acanthosis nigricans, PCOD)

**Screening for T2DM in Children**

Overweight plus any two of the following

(a) Family history of T2DM

(b) Specific race/ethnicity

(c) Signs of or conditions associated with insulin resistance

(d) Maternal history of DM or GDM

Age of initiation: 10 years or onset of puberty

Frequency: Every two years

Diagnostic approach to diabetes in young is shown in fig 1 and treatment algorithm for T2DM in young is shown in fig 2.

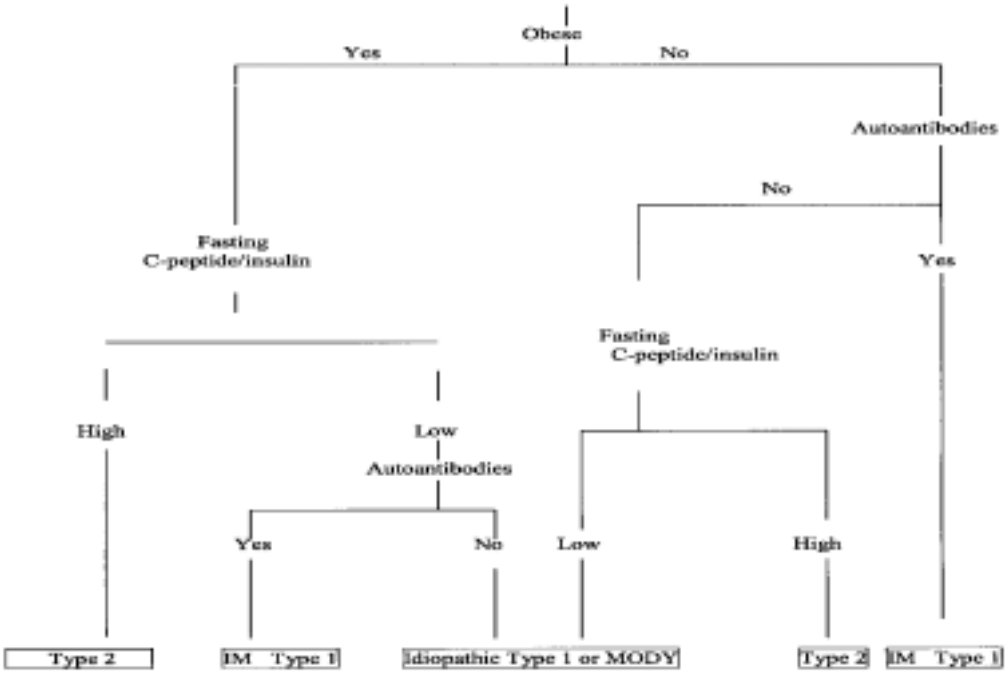


**Fig 1. Diagnostic Approach to Diabetes in Young**

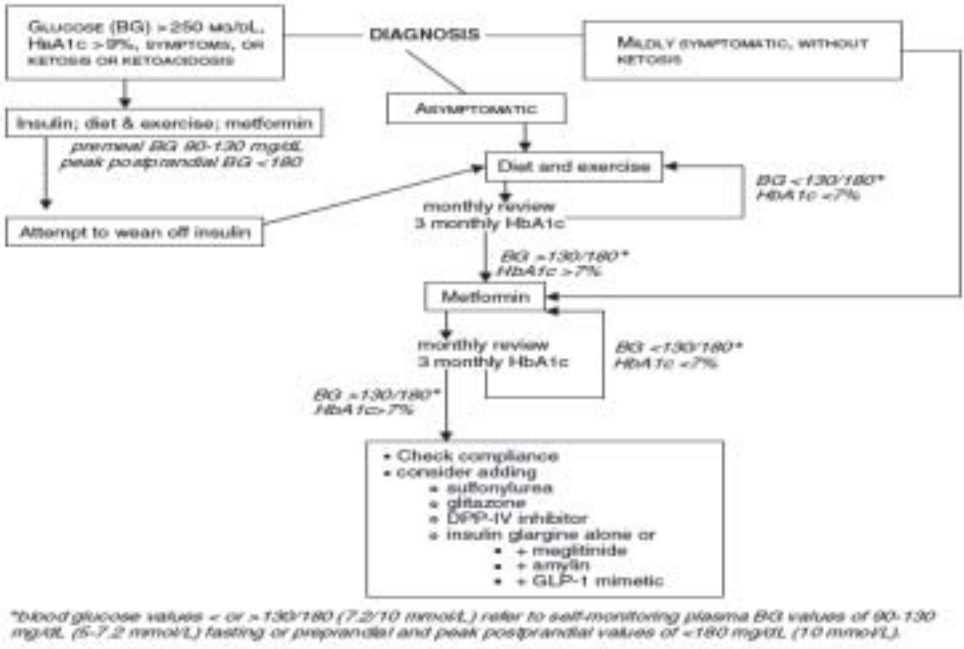


**Fig 2. Treatment Algorithm for T2DM in Young[4]**

## Comorbidities and Complications in Children with T2DM

Complications may be present at the time of diagnosis Significantly high rates of microvascular and macrovascular complications are seen and are directly linked with duration of diabetes.T2DM may be associated with other cardiovascular risk factors like obesity, hypertension and dyslipidemia. Polycystic ovary disease and nonalcoholic fatty liver disease should be excluded

The TODAY Cohort at Baseline showed that 26.3% had a blood pressure at the 90th percentile or greater, 13.6% had a blood pressure at the 95th percentile or greater, 13.0% had microalbuminuria, 79.8% had a low high-density lipoprotein level and 10.2% had high triglycerides[6]

## Treatment Outcome in TODAY Study Group[7]

(a) 699 patients aged between 10-17 years with a mean duration of T2DM of 7.8 months

(b) Started on metformin 1gm BD
   (i) Continued on metformin alone with failure rate of 51.7%
   (ii) Rosiglitazone 4mg BD added to metformin with failure rate of 38.6%
   (iii) Lifestyle added to metformin with failure rate of 46.6%
   (iv) Monotherapy with metformin associated with durable glycemic control in approximately half of children and adolescents with type 2

diabetes.

(v) Outcome in adolescents was much poorer than in adults

**Conclusion**

(a) All children and adolescents with diabetes need not have T1DM

(b) Accurate clinical history, detailed pedigree chart, few biochemical tests and simple physical signs can help to classify the diabetes in the young

(c) We should screen the young with obesity, family history of diabetes and with signs of insulin resistance for T2DM

(d) The cornerstone of management is lifestyle modification. This means more physical activity, healthy eating habits and preventing obesity. Oral agents may have to be added if indicated

(e) Awareness, education and intensive counseling among community and families will go a long way in prevention of T2DM in the young

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# *Immunization Clinic*

Immunisation Clinic of the Institute of Child Health offers service of not only EPI Vaccine, but also of all newer vaccines in reasonable cost.

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# Constipation in Children

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## Constipation in Children - Overview

Constipation occurs commonly in children, affecting up to 10% at any given time. Still, only 3% of parents actually seek advice from the doctor for this condition. Constipation describes the infrequent passage of stools (bowel movements) or the passage of hard stools. Any definition of constipation depends upon comparison with how often the child normally passes stools and with the usual consistency of his or her stools.

## Causes of Constipation

In majority of children, there is no identifiable reason for constipation in children. However, some of the causes may include:

***Diet :***

(a) Eating too much of food that is high in fat and low in fiber (such as fast food, "junk" food, and soft drinks) .

[In children, however, high-fiber diets have not been proven to improve constipation. Infants and children who eat well-balanced meals typically are not constipated].

(b) Eating a lot of sugar /desserts

(c) Not drinking enough water and liquids

***Lack of Exercise :***

Children who stay indoors, watching TV and playing video games, do not get enough exercise. Exercise helps move digested food through the intestines.

***Emotional Issues :***

(a) Pre-school and school-aged children are sometimes embarrassed to use public bathrooms and hold in their bowel movements, causing constipation.

(b) Toddlers can be overwhelmed by toilet training, especially when a parent is more anxious for the child to be out of diapers than the child is.

(c) Some children who experience stress at school, with their friends, or in the family, may have constipation.

***Busy Children :***

Too busy playing - Some children ignore signals their intestines give them to have a bowel movement. This can happen when children are too busy playing and forget to go to the bathroom.

Once a child becomes constipated, a vicious cycle can develop. Hard, dry stools can be painful to push out, and the child can avoid using the bathroom to avoid the discomfort. Eventually, the intestine will not be able to sense the presence of stool.

***Organic causes :***

(a) Abnormalities of the intestinal tract, rectum, or anus.

e.g : Anal stenosis, ano-vestibular fistula/ vestibular anus.

Hirschsprung's disease.

(b) Problems of the nervous system, such as cerebral palsy

(c) Endocrine problems, such as hypothyroidism, Gut hormones like Neuro-enolase deficiency .

(d) Hypercalcaemia

(e) Pre-sacral teratoma/ dermoid

(f) Certain medications (i.e., iron preparations and narcotics such as codeine)

1. Diabetes is common medical problem associated with constipation.
2. Although other symptoms of lead poisoning should be more obvious, children with chronic lead exposure may have constipation.
3. Cystic fibrosis causes constipation in children by many mechanisms.
4. Sexual abuse

**Symptoms**

Generally, if a child has fewer than three bowel movements per week, and the stools are hard or painful to pass, he or she may have constipation.

(a) Infants having painful bowel movements may extend their legs and squeeze their anal and buttock muscles to prevent passage of stool.

(b) Toddlers often rise up on their toes, rock back and forth, and hold their legs and buttocks stiffly.

*Other signs that children are constipated*

(a) Vague abdominal pain around the umbilicus or even severe attacks of abdominal pain

(b) Decreased appetite, nausea, or vomiting

(c) Urinary incontinence, frequent urination, or bedwetting

(d) Diarrhoea , which in cases of constipation is encopresis

(e) Repeated UTI

**History**

(a) What is meant when parents use the term constipation and how long has the condition been present?

(b) When did the child pass first stool after birth ?

(c) What is the size and consistency of the stools?

(d) How frequent are the bowel movements?

(e) Is pain present while the child passes stool and is there blood present?

(f) Is abdominal pain a problem?

(g) Are episodes of fecal soiling present?

(h) Does the child use the bathroom at school? His social habits and whether diapers are being / were used even when the child is/was 3 years old ?

(i) What over-the-counter, herbal, or prescription medications are being taken?

(j) What type of diet is the child on? Many a times the mother would say that she cooks everything in a pressure cooker and strains to get the liquid ,to feed the child.

(k) Any history of operation for Ano rectal malformation ?

**Examination**

General examination of the child and parent – one may find attention deficit . Parental attitude is very important as to whether they are over indulgent or very strict .

(a) Abdominal examination : look for distension , faecal masses - faecal masses can always be pitted with the fingers , thus differentiating them from other abdominal masses.

(b) Perineal examination : look for position and size of the anus, fissure(s) in ano (usually anterior &/posterior). Sentinel pile; peri-anal soiling or excoriation .

Note : Sentinel pile ( a small skin tag partially covering the fissure , is a natural phenomenon secondary to the fissure in ano and needs no treatment . Parents should be assured that it may persist lifelong without causing any problem )

(c) Digital examination : Assess the anal tone ( very high in fissure-in-ano ), rectal ballooning if any , hard stools , retro / peri-rectal mass.

**Investigations**

Usually, in majority of children with constipation no elaborate investigations are necessary apart from getting a detailed history and physical examination . However if any organic cause is suspected then few investigations are ordered for .

*Biochemical* : Thyroid hormone assay, Blood sugar , electrolytes including calcium .

*Radiology* : Thin paste barium enema in an unprepared bowel to see the retro-rectal space, collapsed segment, coning and transition zone. One should never order for this examination immediately after a bowel wash /enema. 24 hours film is mandatory.

*Anorectal manometry* : To assess the pressure reflex, which is a reliable test to differentiate between acquired constipation and aganglionosis (Hirschsprung's disease).

*Rectal biopsy*

**Treatment**

The main aim in treating a child with idiopathic constipation is to break the cycle of painful defecation and withholding the act .

In cases of chronic constipation with impacted stool may need disimpaction ( at times under general anaesthesia )

***Diet :***

Give the child plenty of fluids and juices, such as prune or apple juice.

A well-balanced meal consisting of whole bran cereals, fruits, and vegetables (with less candy and dessert) also helps. In adults, high-fiber diets have been shown to improve bowel function. In children, however, high-fiber diets have not been proven to improve constipation. Infants and children who eat well-balanced meals typically are not constipated.

***Toilet training*** : This is to enhance the reflex. At times it is a good idea to take advantage of the gastro-colic reflex and make the child go to the toilet about ten minutes after meal , and make him sit for 10- 15 minutes.

***Position*** : It is important to make the child sit straight so that the anal canal position is right for evacuation . It is worth noting that "Indian style" toilets are more physiological as it keeps the position of anal canal and also

adds the abdominal pressure to enhance the act .

***Stool softeners*** : Laxatives are used to keep the stool soft – it must be used in high doses

***Local anaesthetic jelly*** : 2% Lignocaine jelly to be applied 10-15 minutes before the child is made to sit in the toilet . This relieves the feeling of pain during defecation .

***Ointment to heal the fissure***

Rarely surgical intervention in the form of lateral sphincterotomy is required in older children.

**Follow up**

After initial treatment, maintenance treatment may be needed for several months to ensure regular bowel habits are achieved and maintained. This may take upto a year or at times more.

The parents must be advised not to stop the laxatives without consulting the doctor , because it must be continued for few months after the child has a toilet training

**Prevention**

To prevent constipation from returning, the child should make changes in behaviour, diet and fluid intake.

(a) Long-term use of laxatives may be indicated for several months or up to a full year.

(b) Regular toilet habits need to be encouraged in the mornings or after meals to take advantage of the body's normal urge to empty the bowel.

(c) Continued use of positive reinforcement with verbal or other rewards or both often contributes to long-term bowel success

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# Implementing Lean Six Sigma in Clinical Laboratories

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When Ben Franklin coined the adage "Waste not, want not," he may have unwittingly inspired Henry Ford to envision the lean production principles that Toyota fine-tuned more than half a century later to catapult the motor company to world-class status. And Toyota probably never foresaw that the Lean Management system, as it's come to be known, would one day make its way into clinical labs.

In laboratories, waste takes many forms: transportation, overproduction, defective products, human potential, and information. "But the king of all waste is the waste of time"

The principles of lean manufacturing have been slow to migrate to laboratories because they are quite different from manufacturing environments. While most of the key principles of traditional Lean still apply, there are many unique challenges involved in effectively implementing them in laboratories. Compared to manufacturing environments most analytical and microbiological laboratories have a relatively low volume of samples but a high degree of variability and complexity. Many standard lean tools are not a good fit, however Lean can be applied to labs.A generic approach is not suitable for laboratories but careful adaptation of the techniques based on a thorough understanding of Lab operations will deliver significant benefits in terms of cost or speed or both.

**Conventional laboratories**

It is a common occurrence for testing laboratories to suffer from long and variable lead times. Some of the problems or issues which can be attributed to conventional or "non lean" laboratories are:

**Lack of focus**

Analysts and Microbiologists are typically focused on test accuracy and individual test run efficiency. Very often, personnel are dedicated to specific tests and there is little or no control of the progress of individual samples through a sometimes highly variable test routing that can be dependent on product type and/or the intended market.

**Long and variable lead times**

In many test laboratories, it is normal to find queues in front of each test where individual samples wait until enough similar samples arrive to constitute an 'efficient test run'. This approach causes long and variable lead times and, contrary to popular belief, does not result in higher productivity.

**Ineffective 'fast track' systems**

To deal with the long lead times, 'Fast Track' systems are often developed in an effort to deal with urgent samples but these often become unworkable. Frequently, the proportion of samples designated as priority becomes so large that 'fast tracking' quickly

becomes ineffective.

**High levels of WIP**

Laboratories often maintain high levels of work in process (WIP) which inevitably results in lots of (non value adding) effort being expended in controlling, tracking and prioritizing samples and in planning analyst work. Companies often respond to this situation by investing in a "Laboratory Information Management System" (LIMS) or some other IT system. However these systems do not in themselves improve performance. The underlying process by which work is organized and moves through the lab must first be re-engineered based on lean principles.

**Volatile incoming workload**

For many testing laboratories the incoming workload is inherently volatile with significant peaks and dips. This causes low productivity (during dips) and/or poor lead time performance (during peaks). Very often the capacity of the lab is not well understood and there is no mechanism to level or smooth the workload.

**Why Lean Six Sigma in Labs?**

The combined Lean Six Sigma toolbox shares a patient-centric, value-based philosophy with rapid-fire deployment methodologies designed to rapidly transform clinical and administrative processes and improved responsiveness to deliver real, bottom-line results. The pace of change in labs today requires new thinking to solve common challenges such as:

(a) Increased sample volume and complexity

(b) Insufficient skilled staff available (e.g. only 2 incoming microbiology technicians for every 7 retiring)

(c) More complex regulatory environment

(d) Increased demand for faster results

Lean Six Sigma addresses these challenges and helps labs rapidly identify efficiency and effectiveness improvements with significant, sustainable results.

**Labs that have implemented Lean Six Sigma have achieved the following results:**

(a) A medical reference laboratory improved turnaround time by 54% and cut costs by $250,000 per year

(b) A clinical lab achieved a TAT target goal of 95% achieved from 85% a year earlier

(c) A hospital lab improved patient satisfaction percentile rank from 15 to >60 within six months

(d) A reference lab achieved:

  (i) Productivity improvement >30%

  (ii) Space savings of >450 sq ft

  (iii) Standardized work practices

  (iv) Reduction in errors and error potential

  (v) Test turnaround time (CT) reduced by 50%

(e) A hospital reduced the footprint for a new lab from 60,000 sq ft to 40,000 sq ft (cost avoidance of $800,000)

(f) A blood bank installed a new lab without adding space (cost avoidance of $400,000)

**Implementing lean in the lab**

To address the above problems and issues a

Lean Laboratory uses Lean principles to eliminate waste. There are a number of principles that can be used but the goal is always primarily focused on improving measurable performance and/or reducing costs. The following key principles always apply:

**Specify value**

The first step in designing any Lean laboratory is to specify value. Every activity in the laboratory is identified and categorizing as 'value add', 'non value add' (from the customers perspective) and 'incidental'. Incidental work is non value add in itself but essential to enable 'value add' tasks to be carried out. A significant focus of any Lean Lab initiative will be to eliminate or reduce the non value add activities.

**Identify the value stream**

Another key Lean step is to develop value stream maps of the overall release process. This should avoid the error of working on point solutions that only end up moving a bottleneck to another process and therefore do not deliver overall improvements. For example, there is no real value in reducing analytical laboratory lead times below the time of a release constraint test in the Microbiology lab. You can however use increased velocity to help 'level the load' or to maximize individual test run efficiency.

**Make value flow and create pull**

A Lean laboratory will normally have a defined sequence of tests and associated analyst roles that make good use of people and equipment. A key principle is to flow work through the laboratory so that once testing begins on a sample, it is kept moving and not allowed to queue between tests. This creates a focus and drive to reduce 'through-put' time which can be converted into a lead-time reduction or used to allow samples to wait in an incoming queue to facilitate level loading and /or grouping for efficiency.

'Pull' is interpreted as testing according to customer priority. If this is not inherent in the order in which samples arrive, then the samples are taken from an incoming queue according to customer demand and thereafter processed in FIFO order with no overtaking.

**Level the load and the mix**

At its simplest, leveling the load (overall workload) and the mix (the mix of sample types) is about putting the same amount of work into the lab on a daily basis. This is probably the most critical step and potentially the most beneficial for the majority of testing Laboratories. Successfully leveling a volatile load and mix will significantly improve productivity and/or lead time. The productivity improvement can be used to provide additional capacity or converted into a cost reduction.

**Eliminate waste**

Lean laboratories continuously look to develop solutions and re-engineer processes to eliminate or reduce the non value add and incidental tasks identified when 'specifying value'.

**Manage performance**

An essential part of Lean in the Laboratory is to manage and review labs performance daily, ensuring that Key Performance Indicators (KPI's) are good and that the overall

laboratory process is 'in control'.

**Improving Lab Performance with Six Sigma**

Laboratories can be a taxing environment in which to implement Lean and Six Sigma is always challenging. Labs are not the same as manufacturing units – where Lean and Six Sigma got their start – because they typically have more variability in workload, less operational focus, less process reliability and longer task cycle times. However, through creative adaptation of the techniques it is possible for practitioners to deliver significant improvements in cost or speed.

**Define**

Defining the goals of a Lean laboratory project may seem like a simple task, but that's not always the case. The project goals can be the deciding factor in garnering support for the project from top management and from other employees. So the goals of the project should be chosen to mirror those of the business. The laboratory in any case study had goals of reducing the end-to-end cycle time of their products while keeping the cost per unit as low as possible.

Tools such as Pareto charts and value stream maps are useful in deciding where the focus of a Lean laboratory project should be. A Pareto analysis of the incoming laboratory workload revealed that the majority of the workload (85 to 95 percent) was driven by three products: Products A, B and C (Figure 1).

Product A and C were from the same product family, received mostly the same tests and could be tested together at the same time.

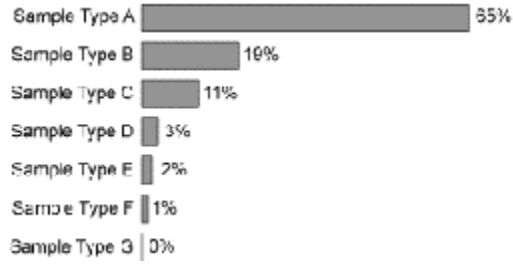


**Figure 1: Volume of Incoming Laboratory Workload by Product Type**

While Product B accounted for 19 percent of the sample volume, it did not account for 19 percent of the lab's workload as it only required two very simple tests; in comparison, Products A and C received nine different tests. The project team decided to focus exclusively on A and C as they accounted for 80 to 90 percent of the lab's workload and were the main priorities of the site.

The as-is process map revealed that a significant portion of the testing cycle time was spent on approval and release activities carried out after the batches were fully tested. As a result, the project team decided that approval activities would also be within the scope of the project.

**Measure**

During the Measure phase of the project, the team set out to establish valid reliable metrics to monitor progress toward the chosen goals. The lab already had in place metrics on cycle time. A look at the breakdown of cycle times for Product A showed a spread of times centred around 11 to 15 days, which corresponded to the lab's target cycle time of 15 days. Sixty-six percent of samples either met the 15-day target time or were completed early, while 33 percent of samples were late.

The average cycle time was 14.8 days (Figure 2).

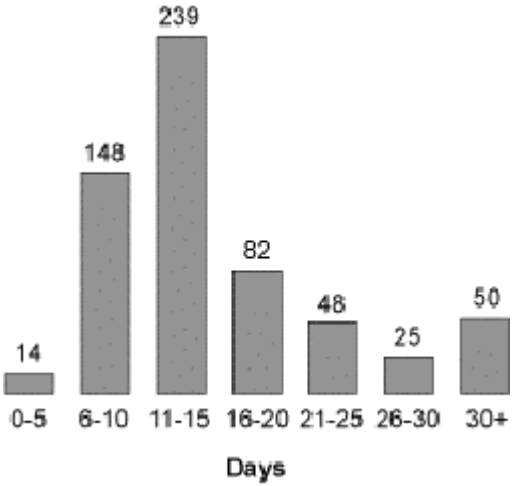


**Figure 2: Product A Cycle Times (January to April)**

Next, the project team considered how resources were used in the lab. It was immediately striking that the bulk of the resources in the lab were occupied by one test: Test x. Every one of sample type A and sample type C required this test and it was not possible to batch samples together; they had to be run individually. Also, the results of this test were required by a separate department in order for that department to proceed with their process. As a result, the laboratory heavily resourced this test with the aim of trying to test every sample every day. This was an inefficient tactic, as it resulted in variable numbers of samples being tested each day. For instance, five analysts might test 12 samples on one day and only test 4 the following day – representing a 67 percent drop in productivity from one day to the next. A strategy was required that would be consistently productive without adversely affecting cycle times. To do this, it would be necessary to control the number of samples tested each day.

**Analyze**

The Analyze phase of the project looked at all the available data to determine the best way to move toward the desired goals of the project. The project team found that:

(i) Each day the lab received between 1 and 17 samples, resulting in an average of 7 per day.

(ii) Weekly the lab received between 25 and 45 samples, resulting in an average of 36 per week.

(iii) The weekly incoming workload was much less volatile than the daily pattern (coefficient of variance 0.2 versus 0.6).

Therefore, although it was impossible to predict how many samples would arrive on a given day, it was possible to say with reasonable certainty that over the week the lab would receive approximately 36 samples. It was clear that it would be possible to have some level of control over the number of samples tested if a weekly testing pattern was developed due to the smaller weekly variation. Next, the team determined the time needed to complete each test (or takt rate). The number of samples for each test would be different as Product C received some tests that product A did not (for example, Ccntent uniformity) and vice versa. .

Having analyzed and reviewed all of the data, the team decided on a clear strategy. The lab would run:

(i) A fixed, weekly repeating pattern of tests

(known as a rhythm wheel).

(ii) Tests at the weekly average (i.e., the weekly takt rate).

(iii) Every test every week.

(iv) Tests of samples in first-in/first-out (FIFO) order.

In reality, the team had to pick a figure slightly above the average test number in order to cope with the expected weekly volatility, deliver acceptable lead times and account for failures/repeat testing. It was obvious that to follow this strategy some tests would have to be run more often. To ensure that productivity would not suffer, the team decided to reduce capacity for some tests (e.g. Test x) in order to reallocate those resources to increase capacity for other tests. Because a batch is only as fast as its slowest test, the end result would be to create more uniform overall cycle times for each of the tests.

**Improve**

To improve productivity and ensure consistent results, the team developed standard work for each of the testing roles. The team set about identifying:

(i) The optimum number of samples for one analyst to test in one shift.

(ii) The best order in which to perform test activities.

(iii) Any improvements that could be made to the process.

(iv) Long periods of inactive time that could be used to run other short tests.

(v) How many times to run the test each week.

Because the new pattern – the rhythm wheel – controls what tests occur each day, it removes much of the unpredictability and volatility that individual analysts experience in day-to-day testing. This provides consistent results, thus ensuring both productivity and shorter lead times.

There was, however, concern over what effect the rhythm wheel would have on lead times for Test x. The team agreed that they would model the outcome for this test before any changes were made. Using data from the previous six months of testing, the model showed that 49 percent of samples would have been tested the day they arrived, 31 percent the next day and the remainder after two days. This was deemed acceptable by all affected process owners.

**Advantages of a rhythm wheel:**

(i) It was more productive than the old system, requiring only 40 full-time equivalent (FTE) shifts versus 54 FTE – a 26 percent improvement.

(ii) It removed the uncertainty around the equipment capacity and avoided equipment conflicts.

(iii) It removed a lot of the stress and scrambling from the daily testing routine for the analysts.

(iv) Every test was run every week to ensure consistent and short lead times.

To address the issue of the long approval and release activity wait times, as identified in Define, the process was reengineered to remove this delay by operating to the laboratory's testing takt rate and reviewing

every batch every day.

Once all the changes were implemented, average cycle times fell from 15 to 8 days. The overall laboratory headcount was reduced from 20 testing analysts to 15, a 25 percent productivity improvement.

**Control**

The Control phase was initiated to ensure that the lead time and productivity gains established from the project would not be lost or eroded over time. To ensure that analysts knew exactly what was expected of them, the team designed set roles which clearly showed:

(i) The activities required for the test role.

(ii) The best order in which to complete them.

(iii) Clear break targets.

The set roles were successful at sustaining the productivity within the laboratory.

The key performance indicators for the process were printed and posted weekly to show exactly how the lab's cycle time was performing. There was a definite morale boost to the lab to see the lab performance consistently ahead of its targets. Before the project, 66 percent of samples were tested inside the 15-day target time. After the project was completed, the target was changed to 10 days, and all samples were consistently tested within the target time, with an average lead time of 8 days. This translated to an annualized 3.9-fold return on investment for the project.

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# Changing Concepts in the Management of Acute Pancreatitis in Children

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**Is it a common diseased of childhood?**

Acute pancreatitis occurs in all age groups, even in infants. Currently, the best estimates suggest that there are 1.6 to 1.2 pediatric cases per 100,000 individuals per year, an incidence that approaches the incidence of disease in adults.

**What are the common causes?**

***Biliary Disease*** – Gallstone pancreatitis is a more common cause of acute pancreatitis in children than previously believed. Gallstone pancreatitis or other biliary disease should be suspected if the patient has elevations in transaminase levels and/or hyperbilirubinemia.

***Systemic Illness*** – In recent studies, acute pancreatitis associated with systemic illnesses accounted for more than 20% of reported cases. Typically, these children were in an intensive care unit. Pertinent associations include sepsis, shock (alone or with sepsis), hemolytic uremic syndrome, and systemic lupus erythematosus. Of these diseases, hemolytic uremic syndrome has had the highest prevalence[1,2].

***Trauma*** – Although the prevalence of pancreatitis associated with trauma is probably not as high as previously thought, trauma remains an important cause of pancreatitis. Most often, unintentional blunt trauma causes damage to the pancreas, but child abuse can result in traumatic pancreatitis as well[3].

***Idiopathic*** – Despite improvements in diagnostic testing, the rate of idiopathic pancreatitis continues to be significant and unchanged[1,2].

***Metabolic*** – Although metabolic diseases are uncommon causes of acute pancreatitis, it is important to recognize them because treatment can prevent recurrent episodes. Disorders that cause hypercalcemia, hypertriglyceridemia, and inborn errors of metabolism have all been associated with acute pancreatitis

***Autoimmune Pancreatitis*** – Autoimmune pancreatitis has become increasingly recognized in childhood.

Autoimmune pancreatitis occurs in two forms (types 1 and 2). Type 2 seems to be more common in children and has an association with inflammatory bowel disease and other autoimmune diseases. In adults, the diagnosis of type 1 autoimmune pancreatitis relies on elevated levels of immunoglobulin G4 (IgG4), diffuse or segmental enlargement of the pancreas, strictures of the pancreatic duct, and histologic features. In children, IgG4 elevation may not be present, even with typical histology. In general,and regardless of serum IgG4 status, pediatric (and adult) patients with type 1 or type 2 autoimmune pancreatitis

respond to corticosteroid therapy[4].

***Anatomic Pancreatobiliary Abnormalities –*** Pancreaticobiliary abnormalities such as pancreas divisum, abnormal junction of the common bile duct and main pancreatic duct (common channel syndrome), choledochal cysts, and annular pancreas increase the risk for acute pancreatitis. Pancreas divisum is present in up to 15% of the population. Recent studies suggest that the presence of a SPINK-1 (serine protease inhibitor Kazal type 1) or CFTR (cystic fibrosis transmembrane conductance receptor) mutation along with pancreas divisum increases the risk of acute pancreatitis and accounts for the observation that only a fraction of people who have pancreas divisum develop acute pancreatitis[5].

**Diagnosis**

Acute pancreatitis can occur in mild and severe forms. In general, mild pancreatitis is limited to the pancreas and the peripancreatic fat, whereas severe disease includes pancreatic necrosis, involvement of other organs, cardiovascular collapse, infection, or fluid collections.Most children (>=90%) have mild disease[3].

At least two of three criteria: (1) abdominal pain suggestive of or compatible with acute pancreatitis (ie, abdominal pain of acute onset, especially in the epigastric region); (2) serum amylase or lipase activity at least three times greater than the upper limit of normal; and (3) imaging findings compatible with acute pancreatitis

**Any specific pattern of pain?**

Specifically, pancreatitis has been shown to present with epigastric pain in 62% to 89% of patients and diffusely in 12% to 20% of patients. Assessing pain in children who are nonverbal, have static encephalopathy, or are developmentally delayed can be challenging. Parental report of irritability is a common presenting sign in nonverbal children.In infants and toddlers, abdominal distension, vomiting, andfever were common presenting complaints[6].

**Serum Amylase or Lipase Activity At Least Three Times Greater Than The Upper Limit of Normal.**

Amylase and lipase values rise 2 to 12 hours and 4 to 8 hours, respectively, after the onset of pancreatic inflammation. At present, both amylase and lipase should be measured because only one or the other may be elevated in individual patients.

**Imaging rationale of acute pancreatitis**

The frequency of gallstone pancreatitis in children provides the most compelling argument for early imaging. Endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) identify cholelithiasis best. Because fluid in the pancreaticobiliary ducts appears bright, they can be visualized easily. Although MRCP is expensive and requires general anesthesia in younger children, it has largely supplanted endoscopic retrograde cholangiopancreatography (ERCP) as the preferred diagnostic study for biliary and pancreatic ductal disease because it is less invasive and does not cause pancreatitis, which can occur after ERCP. EUS is not widely available in pediatric centers. Transabdominal ultrasonography represents a reasonable compromise for evaluating patients

who have suspected gallstone disease. Ultrasonography also may provide corroboration of acute pancreatitis and assist in identifying causes. Findings can include pancreatic edema, dilated main pancreatic duct, pancreatic calcifications, and fluid collections. Contrast-enhanced computed tomography (CT) of the abdomen is a second option for imaging the pancreas. A CT scan can show the same findings as ultrasonography and also may provide information about the presence or absence of pancreatic necrosis. In general, CT scans are most useful several days into the course of acute pancreatitis if the patient fails to improve or if the pancreas is inadequately visualized on ultrasonography.

Is there any scale to assess the severity of pancreatitis?

The Midwest Multicenter Pancreatic Study Group analyzed the criteria of the Ranson and Glasgow scores, plus additional criteria and developed a scoring system for children[1]. The eight severity factors included age (<7 years), weight(<2 kg), admission WBC (>18,500), admission LDH (>2,000), trough calcium (<8. mg/dL) and trough albumin (<2.6 mg/dL) in the fi rst 48 hours, 48-hour fl uid sequestration (>75 mL/ kg/48 h) and 48-hour rise in urea (>5 mg/dL).If each criteria is assigned a value of one point, then the outcome of patients with 0 to 2 points was 8.6% severe, 1.4% death; 2 to 4 points 8.5% severe, 5.8% death; and 5 to 8 points 80% severe, 10% death. The accuracy of this system was validated in three centers. Of note, young age and low weight are major risk factors, often associated with severe systemic diseases a pattern also noted by others[2].

**Changing patterns of treatment**

Limited adult data suggest that aggressive hydration in the first 24 hours decreases the risk of multiorgan system failure[9]. Thus, intravenous fluid boluses to rehydrate the patient and subsequent fluid administration at 1.5 times maintenance rates are recommended.

Despite the long-time teaching that morphine should be avoided because it may cause paradoxical contraction of the sphincter of Oddi, this effect has not been demonstrated in clinical practice, and morphine can be used safely in patients who have acute pancreatitis[10].

Perhaps the greatest change in the management of acute pancreatitis is the early institution of nutrition. In patients who have mild acute pancreatitis, oral feedings can be started within 24 to 48 hours after admission. In the past, clear liquids were started, but recent studies in adults show that regular meals can be given[1]. Limited data suggest that the practice of prescribing a low-fat diet is not necessary. About 10% of patients will have abdominal pain after starting oral intake. Usually, feedings can be resumed in the patients in another 24 hours[3,12,13]. An increase in serum levels of pancreatic enzymes is not an indication to stop feedings. Patients who have severe pancreatitis also can be successfully fed early in the treatment course. Typically, these patients are fed through enteral tubes or by using total parenteral nutrition (TPN). Enteral feeding is preferred over TPN because of the complications associated with the intravenous catheter and the expense of TPN. The only clear indications for TPN include inability to tolerate enteral nutrition due to

prolonged ileus, pancreatic fistulae, or complicating abdominal compartment syndrome. The choice of enteral route, gastric or jejunal (which bypasses the ampulla of Vater), is controversial and generally depends on the custom at individual institutions.

Acute pancreatitis should be conducted . The routine use of antibiotics is not recommended; they should be reserved for patients who have evidence of infected necrosis.


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# Epistaxis in Children

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Epistaxis is derived from a Greek word epistazo which means bleeding from nose. It is a common paediatric complaint which is usually benign and self-limiting[1]. Epistaxis usually occurs in children aged two to ten years, with a peak between three and eight years. Boys are more commonly affected than girls.It is uncommon in infancy and after puberty unless associated with coagulopathy ,neoplasia or choana atresia.The true incidence of epistaxis in children is difficult to assess as only a small number seek medical attention.

Most of cases (80%–90%) are idiopathic. Nose has got prominent vascularity and dual blood supply and blood vessels within the nasal mucosa run superficially and are therefore comparatively unprotected. Nose can bleed if they're disturbed by a minor injury, such as picking or blowing nose. It can also occur if the mucous membrane inside the nose dries out and becomes crusty. This can be caused by an infection, cold weather or the drying effect of central heating. Montaque L et al[2] postulated that chronic recurrent mild grade infection causes neovascularisation of nasal mucosa which is responsible for recurrent epistaxis.

**Etiology**

(a) The primary cause of epistaxis in children is minor trauma, such as nose picking of dry nasal mucosa.There is an increased incidence of epistaxis observed during winter months[3].

(b) Nasal foreign bodies that cause local trauma can also be responsible for epistaxis.

(c) Children with deviated nasal septum are more prone to have nasal bleeding.

(d) Children with migraines have a higher incidence of recurrent epistaxis than children without migraines. The Kiesselbach plexus, which is part of the trigeminovascular system, has been implicated in the pathogenesis of migraine[4].

(e) Children with gastroesophageal reflux into the nose may have epistaxis secondary to mucosal inflammation.

(f) Different medicines such as aspirin, antiplatelates can cause bleeding. Long term corticosteroid nasal spray also causes epistaxis.

(g) Less common causes of epistaxis include vitamin K deficiency, malabsorption,liver disease which can lead to clotting factor deficiencies and uraemia.

Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is an autosomal dominant disease. It causes capillary fragility of the skin, mucous membranes and viscera.Epistaxis is very common in these

patients.

Wegener's granulomatosis is an acquired vascular disease which causes bleeding from nose.

(a) Juvenile nasal angiofibroma in adolescent males may cause severe nasal bleeding .Patient usually present with torrential bleeding with a history of unilateral nasal blockage.

(b) Nasal bleeding is more frequent in hypertensive children.

**Management**

A nosebleed usually stops by pinching nostrils for ten minutes. Leaning forward and breathing through mouth will drain blood down the nose instead of down the back of the throat. After having a nosebleed, a clot might form inside the nose. It should not be removed it as it is part of the healing process and helps prevent further nosebleeds. It is better to avoid contacts with persons having cough and cold.

Prevention of epistaxis is difficult. Moistening the air especially during the winter months and drinking lots water can help. Children should be taught to sneeze with their mouths open to avoid building high pressure into the nostril. Their fingernails should be trimmed regularly. Petrolium jelly can be used to soften the nasal musosa .Some other measures are to avoid blowing of nose and nose picking, to avoid contact sports and irrational use of blood thinning agent and nasal decongestant.

Childhood nosebleeds are rarely severe and seldom require hospital admission[5]. Still rapid assessment of general appearance, vital signs, airway stability and mental status are needed in every child. If possible a general examination should be done to exclude hepatosplenomegaly, petechial rash or any other abnormal signs. Once the child is settled, the nasal cavity can be examined with a light. Most children older than six years can tolerate a flexible fibre-optic examination. If the source of bleeding is clearly visible, chemical cautery with silver nitrate can be done under local anaesthesia .Care should be taken to avoid excessive cautery or cauterising both sides of the septum to avoid septal perforation.

If cauterising doesn't work or bleeding persists nasal pack insertion or even endoscopic artery ligation might be needed in few cases.

Management of children with recurrent epistaxis is same, but there are different opinion regarding prevention .Five randomised controlled trials (RCT) are done till date[6]. The RCTs compared 0.5% neomycin + 0.1% chlorhexidine cream with no treatment, petroleum jelly with no treatment, 75% with 95% silver nitrate nasal cautery, and silver nitrate cautery combined with 0.5% neomycin + 0.1% chlorhexidine cream against 0.5% neomycin + 0.1% chlorhexidine cream alone; 0.5% neomycin + 0.1% chlorhexidine cream with silver nitrate cautery. No statistically significant difference found between the compared treatments .They only concluded that 75% silver nitrate was more effective than 95% silver nitrate at two weeks following application. Apart from pain due to silver nitrate cautery, no serious adverse effects were reported from any interventions.

In a study done by Bjelakovic B et al[7] showed

that overall effectiveness of propranolol was noted in some children with nasal bleeding when given a dose of 1.5-2 mg/kg/day (divided into three doses) as a second line therapy for terminating epistaxis. They concluded that propranolol could be a favorable treatment option for patients with primary epistaxis.

**When to refer**

Bleeding uncontrolled by direct pressure even after twenty minutes, significant bleeding or presence of anaemia should warrant urgent referral to hospital.

Epistaxis might be the initial sign of serious systemic illness. Children with recurrent epistaxis despite medical therapy are at higher risk of having a bleeding disorder.(8 )Screening coagulation studies revealed only 20% of patients with a bleeding disorder, but a subsequent comprehensive hematology evaluation revealed the diagnosis in the majority of patients.

Children with lesions not in the Kiesselbach area should be considered for referral to otolaryngology for evaluation with rhinoscopy and nasopharyngoscopy to search for the source of bleeding. This is particularly important when epistaxis is combined with nasal airway obstruction, especially when unilateral obstruction is present.

**Conclusion**

(a) Childhood epistaxis is very common and frightening, but rarely requires hospitalisation.

(b) There are different views in management of recurrent epistaxis, but no statistically significant difference is found between the compared treatments.

(c) We must be careful about the management of epistaxis in children as in some cases it is the presenting feature of some serious systemic disease.

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# Interference on Immunogenicity of Vaccines by Immune Globulins

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There is always a potential risk on development of adequate immunogenicity of certain vaccines after administration of immune globulin containing Preparations.

Passive immunity is induced in the recipient by transfer of preformed antibodies against infective agent This passively acquired antibodies will confer temporary immunity to the recipient. It gives ready made immunoglobulin which help to fight infection immediately. However as it is for a temporary period this passive immunity wanes after a few weeks to a few months .But it is very useful when instant immunity is required[1].

The most common form of passive immunity is the natural transplacental passive transfer of the immunoglobulins from mother to newborn. This protects the child for first few months till the time that infant develops its own immunity after repeated exposure to various antigens. The other examples of the passive immunity are infusing immunoglobulins in the person to protect him for a specific disease[2].

Passively acquired antibodies can interfere with the immune response to certain vaccines, both live and inactivated and to toxoids which may result in poor immune response to recipient. Either Intramuscular or Intravenous administration of immune globulin containing preparations will transfer preformed antibodies to the recipient which will adversely affect the immune response to live virus vaccines[2].

**Immune globulin containing preparations include[3]**

(1) Intra muscular and intra venous immune globulin

(2) Packed red cells

(3) Whole Blood

(4) Plasma

(5) Platelet Products

(6) Specific Hyper immune globulins against Tetanus, Hepatitis B, Hepatitis A,, Rabies, Measles, Varicella Zoster.

**Guidelines for Administering Antibody Containing Products and Vaccines[3]**

***(A) For inactivated and subunit vaccines:***

Mechanism by which passively acquired antibodies interfere with the immunologic response to inactivated and subunit vaccines and toxoids is not clear. Such Interference is less marked than with live vaccines and requires exposure to large doses of passively acquired antibodies. Moderate doses of parenterally administered immune globulins have not inhibited development of a protective immune response to DTP, Tetanus -Toxoid, Hepatitis-B, Hib-conjugate vaccine.

Inactivated and Subunit vaccines may be

administered simultaneously or at any time before or after receipt of an immune globulin preparations. For example, concurrent administration of recommended doses of Hepatitis-B Immune Globulin, Tetanus Immune Globulin, or Rabies Immunoglobulin and the corresponding inactivated vaccine or toxoid will produce an adequate immunity. In other words in such circumstances of combined active-passive immune-prophylaxis, only standard doses of the corresponding vaccines are recommended. Neither supplemental doses nor increase in vaccine dose-volume are recommended. But the vaccine and immunoglobulin should be administered at two different sites. Administration of Hepatitis-A vaccine together with IG has been recommended for situations in which immediate and prolonged proection against HAV infection is desired. Although this combined active-passive immunization has been demonstrated to result in siginificantely reduced serum antibody concentration than those induced by vaccine administration only, but this concentrations are still many times higher than those considered protective and sero-conversion rates are not affected. These reduced immunogenicity, therefore, is to be considered clinically insignificant.

***(B) For live virus vaccines:***

The live vaccine multiplies inside the body after administration and stimulates the immune system to induce an adequate immune response. Administration of antibody containing products ,simultaneously with live vaccines, will inhibit the viral replication and insuffient antigenic mass.

The degree and duration of interference will depend on:

(i) Evidence of interference between immune globulin and the vaccine.

(ii) Half life of specific antibody.

(iii) The dose of immunoglobulin

Human blood and immune globulin preparations contain measles, mumps. rubella and varicella antibodies. To reduce the possibility of interference ,postponement of administration of these vaccines are suggested as depicted in Table 1.

**Table 1**: Suggested intervals between administration of Antibody-containing products and Measles, MMR, Varicella Vaccine[3]

| | | |
|---|---|---|
| Kaswasaki disease | 2gm/Kg/IV | 11 Months |
| ITP* | 400mgm/kg/IV | 8 months |
| Plasma/Platelet Products | 10mL/kg(160mg IgG/kg)IV | 7 months |
| Whole Blood | 10mL/kg(80-100mg IgG/kg)IV | 6 months |
| Packed RBCs | 10mL/kg(60mg IgG/kg)IV | 6 months |
| Tetanus IG | 250units (10mg IgG/kg)IM | 3 months |
| Hepatitis-B IG | 0.06mL/ kg (10mg IgG/kg)IM | 3 months |
| Hepatitis A IG** | 0.02mL/ kg (3.3mg IgG/kg)IM | 3 months |

*Immune Thrombocytopenic purpura **contact prophylaxis

N.B. Washed RBCs if administered in a dose of 10mL/kg having negligible IgG will not have any interference with the live vaccines.

Immune globulin preparations administered too soon (less than 2 weeks) after vaccination with MMR or Varicella vaccines can interfere with the immune response and in such circumstances readministration of the vaccine is recommended after the appropriate interval listed in Table 1. For example if whole blood is administered less than 14 days after receipt of Varicella vaccine ,the vaccine should be readministered at least 6 months after the receipt of whole blood unless serologic testing indicates an adequate immune response to the initial dose.

RESPONSE TO OPV, yellow fever vaccine and live oral typhoid(Ty21a) is not affected by the administration of antibody containing products. Therefore these vaccines may be given simultaneously with blood products. Live attenuated influenza vaccine can be administered at any time before or after receipt of antibody containing blood products[3].

Although there is no available data on the effect of rotavirus vaccine, the ACIP recommends that live Pentavalent rotavirus vaccine be deferred for 6 weeks after receipt of the antibody containing blood products, provided the maximum upper age limit of initiation of the vaccine is not crossed[3].

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# Triaging in Neonates

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## Introduction

Triage is the process of determining the priority of patients' treatments based on the severity of their condition. This helps in efficient patient treatment when resources are insufficient for all to be treated immediately. The term comes from the French verb trier, meaning to separate, sift or select.The term triage may have originated during the Napoleonic Wars from the work of Dominique Jean Larrey. The term was used further during World War I by French doctors treating the battlefield wounded at the aid stations behind the front.

Triage may be used in determining the order and priority of patients arriving at emergency, the order and priority of emergency transport, or the transport destination for the patient. Poor assessments, invalid categories, no objective methodology and tools for prioritizing patients and allocating resources, are clear obstacles for efficient triage system. Thus, appropriate categorization, resource rationing, effective response planning and training is essential for maximizing savings of lives. Inefficient triage also provides challenges in health care costs. Triage conventionally may be classified into simple, advanced, continuous integrated , reverse , over and under traige. With the advancement of medical technology modern approaches to triage are used which are increasingly based on scientific models and thus overcomes the limitations of triage.

As many neonatal deaths in hospitals occur within 24 hours of admission, triaging or rapid screening of these babies into emergency, priority and non- urgent group should be an essential part of management. This article deals with the concept of triage as it occurs in neonatal conditions. Triaging in neonate is essential for emergency management, for deciding the level of care required and for emergency transport. A sequential process for managing sick neonates as recommended by national neonatogy forum is described in this article.

## Triaging place

The place in the hospital where a neonate is first brought , usually the emergency or the reception area ,should be the triaging place. All the staff involved in the initial management of a child should be trained in assessing triage signs in neonates. Sick neonates are triaged and accordingly appropriate actions are taken (Table 1). The doctor trained in neonatal care should undertake the responsibility of emergency treatment and management of the neonate.

**Table 1.**Category and action required in neonatal triage

| Category | Action required |
|---|---|
| Emergency cases | Need emergency treatment |
| Priority cases | Need assessment and rapid action |
| Non-urgent cases | Need assessment and counselling |

### Emergency triage assessment

Every neonate should be assessed for emergency or priority signs and triage accordingly( table 2). Neonates with no emergency or priority signs are treated as non-urgent cases.

*Steps of management* – After a neonate is triaged and stabilised accordingly, the baby should then be managed further in necessary level of care. Detailed history should be taken and relevant examination and laboratory investigation should be performed. Once the diagnosis is reached specific treatment should be given along with supportive treatment. Response to treatment should be monitored and if there is inappropriate response, complications or wrong diagnosis should be thought of. After the recovery , the baby should be discharged with follow up advice and the mother should be taught when she should return to the health facility. (Fig 1)

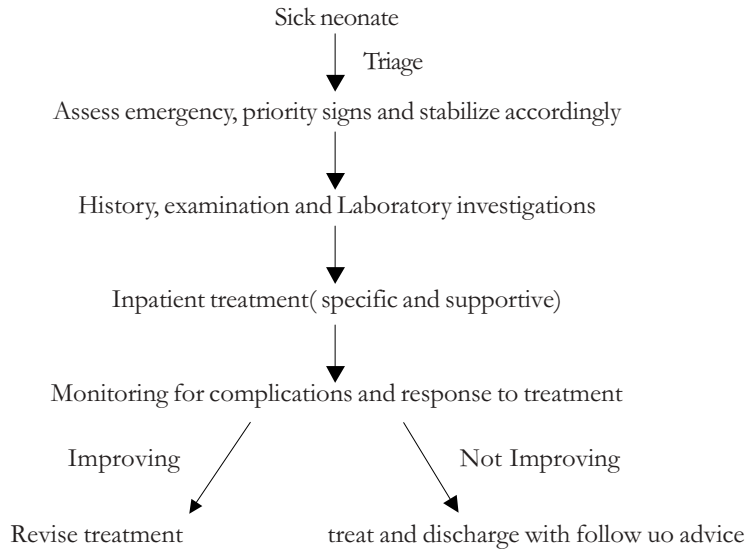
### Emergency treatment after triaging

Immediate treatment after triaging depends upon the clinical signs, keeping in mind TABCD step: Temperature, Airway, breathing, Circulation,Coma, Convulsion and Dehydration.

**Table 2.** Signs for triage:

| Emergency signs | Priority signs | Non urgent signs |
|---|---|---|
| Hypothermia (temp<35.5$^0$C) | Small neonate (<1800 gms) | Jaundice |
| Apnoea or gasping respiration | Cold stress (temp 36.4$^0$C 35.5$^0$C) | Transitional stools |
| Severe respiratory distress (rate>70/min, severe retractions, grunt) | Respiratory distresas (rate >60/min. no retractions) | Developmental peculiarities |
| Central cyanosis | Irritable/restless/jittery | Minor birth trauma |
| Shock (cold periphery, CFT>3 sec, weak & rapid pulse) | Refusal to feed | Possetting |
| Coma, convulsions or encephalopathy | Abdomiunal distension | Superficial infections |
| | Severe jaundice (Appears<24 hrs/ stains palms and soles/lasts >2weeks) | Minor malformations |
| | Severe pallor | All cases not categorized as Emergency/Priority |
| | Bleeding from any sites | |
| | Major congenital malformations (Tracheo Esophageal Fistula, meningomyelocele, Anorectal malformation) | |
| | Large baby>3.8 kg | |

**Fig 1.** Steps in the management of sick neonates admitted to hospital




***1 . Maintaining Temperature:***

Cold clothes should be immediately removed and replaced with warm clothes and warm linen.babies should be ideally warmed up in manually operated radiant warmer till normal temperature is reached. Monitoring should be done every 15 -30 minutes. Alternatively, warming could be done using room heater, 200 watt bulb. In case of hypothermia , blood sugar should be checked immediately and sepsis screen should be send to rule out sepsis.

***2. Maintaining Airway:***

Neonates should be placed in sniffing position by placing a shoulder role beneath the shoulder blades (scapula) . Suctioning of the mouth followed by suctioning of the nose should be done if there is secretions.

***3.Assisting Breathing:***

If the baby is gasping or apnoeic , positive pressure ventilation should be initiated following NRP guidelines. If the baby has respiratory distress start oxygen therapy so as to maintain a saturation of 90-94%. Oxygen therapy may be given with oxygen hood at the flow rate of 5-8lt/min or by nasal prongs at the flow rate of 1-2 lt/min.

***4. Supporting circulation:***

If the neonate is in shock , IV bolus of normal saline should be given at the rate of 10ml/kg over 30 minutes. If features of shock persists it should be repeated. If the features of poor perfusion persists despite two fluid boluses, vasopressor should be started. Dopamine is used as the first line vasopressor in most cases of neonatal shock. The starting dose is 5-10microgram/kg/min. Depending upon the response, the dose of dopamine is titrated to a maximum of 20 microgram/kg/min. If despite dopamine infusion of 20 microgram/

kg/min, the baby continues to be in shock, Dobutamine is the next vasopressor of choice. Hydrocortisone may be considered in neonates not responding to maximum doses of both dopamine and dobutamine.

***5. Maintaining Euglycemia:***

Blood glucose should be checked in all sick neonates. If there is hypoglycaemia ( glucose level< 45mg/dl), IV bolus of 10% dextrose should be given in a dose of 2ml/kg.

***6. Managing Coma and Convulsions:***

Assessment of neonatal consciousness is done by simple AVPU scale (Table 3).

**Table 3.**AVPU Scale

| |
|---|
| A. Alert |
| V. Responding to Sound/Voice |
| P. Responding to pain |
| U. Unresponsive |

A neonate who is not alert, but responds to sound , is lethargic. A neonate with a coma scale of P or U should receive emergency treatment for coma after ensuring TABC. It should be remembered an unconscious neonate may or may not respond to pain.

If there is convulsion, immediate IV access should be done. If hypoglycaemia, 10% dextrose should be given. Otherwise , 10% Calcium gluconate 2ml/kg over 10 minutes should be given with cardiac monitoring. IV phenobarbitone should be started , if seizure continues, at the rate of 20mg/kg and should be infused over 20 minutes. Phenobarbitone may be repeated 5mg/kg till a total of 40mg/kg is infused. If seizure continues phenytoin should be added at the dose of 20mg/kg over 20 minutes.

Once the baby is triaged and stabilised , the baby should be further managed in appropriate level care neonatal units.

# Non-transfusion Dependent Thalassaemia

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Non-transfusion Dependent Thalassemia (NTDT) are a group of thalassemia; where transfusion is not recommended routinely (No transfusion or occasional transfusion).

Non-transfusion dependent thalassemia can be broadly divided into 5 categories;

1) Beta-thalassemia Intermedia.

2) E- Beta thalassemia.
3) Hb H disease.
4) S (HbS)/ beta-thalassemia

5) C (HbC)/ beta-thalassemia

***Beta-thalassemia intermedia[1] :***

Result from inheritance of 1 or 2 mild beta-thalassemia alleles or co-inheritance of genetic modifiers that reduce the severity associated with inheritance of 2 severe beta-thalassemia alleles.

***E-Beta thalassemia :***

Results from co-inheritance of the structural variant known as HbE and many different known as HbE and many different Beta-thalassemia alleles.

***Hb-H disease :***

Severity is related to its underlying molecular pathology—those who inherited deletion forms of alpha+ and alpha 0 thalassemia generally exhibit a mild clinical course.

***Prevalence :***

Beta-thalassemia intermedia most commonly found in Africa, Mediterranean, India and East-Europe.

(i) Hb H most common in South-East Asia, Middle East and Mediterranean.

(ii) E-Beta thalassemia most common in East India, Bangladesh and South East Asia.

**Pathophysiology of NTDT**

The clinical sequels are due to three main persistent factors

1. Ineffective erythropoiesis – Which causes massive erythroid marrow hypertrophy.
2. Chronic anemia – Which causes increased gastrointestinal iron absorption.
3. Iron overload – Due to ineffective erythropoiesis, peripheral breakdown of red blood cells and increased gastrointestinal iron absorption.

**Clinical Manifestation of NTDT**

Silent cerebral ischemia, pulmonary hypertension, right sided heart failure, extramedullary hemopoietic pseudotumours, hepatic fibrosis, cirrhosis and cancer, gall stones, splenomegaly, osteoporosis, venous thrombosis and leg ulcers.

**Iron Overload[2]**

Major source of iron overload in NTDT is increased intestinal absorption. As NTDT pts are rarely transfused, blood transfusion is minor source of iron overload in NTDT pt.

**Treatment Options**

(i) Splenectomy – Indicated for increased transfusion demand, hypersplenism and splenomegaly.

(ii) Transfusion- Indicated for low Hb, growth failure, skeletal deformity, infection, pregnancy and other disease specific complication.

(iii) Hydroxyurea- Can increase Hb F and decrease transfusion requirement.

Which NTDT patient should receive iron chelation therapy?[3]

(i) Patient > 10 yrs of age (Increased iron related morbidity).

(ii) Pt with a LIC > 5 or serum ferritin > 800 unit (Increased morbidity risk beyond this threshold).

Which chelator should be used?

An ideal chelator should be

(i) Effective.

(ii) Fewer side effects.

(iii) Oral preparation.

(iv) Once daily dose

At present there are three chelators in the market. Deferriprone is in capsule form; difficult to be taken in very low age group, Desferrioxamine has a very low compliance for its injectable preparation. Deferasirox, a relatively new chelator is now very popular for its high efficacy, oral dispersible preparation, once daily dose and relatively few side-effects.

*Thalassa study* – Thalassa is the first multinational, randomized, double-blinded placebo controlled study evaluates iron chelation therapy in NTDT patient.

***Result shows :***

(i) High base line iron burden and increasing LIC and SF in placebo highlight the need for iron chelation therapy.

(ii) Deferasirox at starting doses 5—10 mg/kg/day with dose escalations up to 20 mg/kg/day in iron overload patient significantly reducing LIC & SF.

(iii) Based on benefit/risk profile of Deferasirox in NTDT patient., chelation therapy should be considered when LIC> 5 unit.

**Conclusion[4]**

NTDT cover a broad spectrum of different forms of Thalassaemia characterized by a limited or no requirement for regular transfusion. Early clinical recognition of there disorders is essential to prevent affected children from being mistakenly placed on life-long transfusion therapy. Many patients with NTDT grow and develop normally with relatively low Hb level. There is increasing evidence that NTDT may be associated with a variety of clinical complication later in life. Iron levels should be regularly assessed and iron chelation therapy initiated where appropriate.

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# Allergic Bronchopulmonary Aspergillosis – A Few Points to Ponder

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**Introduction -**

Allergic Bronchopulmonary Aspergillosis (ABPA) is a TH2 lymphocyte hypersensitivity lung disorder in response to the fungus Aspergillus species mainly *A.fumigatus*, that affects patients with asthma and cystic fibrosis(CF)respectively[1]. ABPA is characterized by wheezing , pulmonary infiltrates which may lead to pulmonary fibrosis and or bronchiectasis.The inflamatory response to *Aspergillus fumigatus* is demonstrated by raised serum IgE, raised specific IgE to Aspergillus fumigatus, positive skin prick test (SPT)to Aspergillus and peripheral eosinophilia. ABPA, though not a very common condition, calls for prompt diagnosis and treatment as it is a potentially crippling disorder resulting in bronchiectasis and pulmonary fibrosis[3].

The diagnosis of ABPA is not straight forward as the the clinical and rediological features overlap with those of asthma and CF[1]. It is to be noted that the prevalence of ABPA is higher in patients with CF than in patient's asthma[4]. A recent Indian study shows that prevalence of ABPA in Indian children with CF is about 18%.

***Aspergillus fumigatus***

Before proceeding to discuss the pathophysiology of ABPA; it will not be out of context to recapitulate a few points regarding the fungus *A. fumigatus*.

As we all know microfungi(moulds)are microscopic plants which do not contain the pigment chlorophyl, hence are unable to synthesize carbohydrate from carbondioxide and water with the help of sunlight.Therefore they depend on plant and animal matter for their nutrition. A high relative humidity is essential for the growth of fungi(moulds).

Moulds produce small spores (2-5μgm) which become airborne and are responsible for causing diseases in the human beings. They produce disease either by causing infection or by causing allergies.

Aspergillus is one of the common moulds causing allergies in the human[6].

Most of the human lung diseases are caused by the species *A. fumigatus*. The spores of *A.fumigatus* grow at temperatures 15°C-53°C hence are termed thermotolerant. They grow on decomposing organic matter like compost pile, sewage treatment debris,damp walls and ceillings of buildings and bird excreta. Humid weather favours growth of fungi while sunny and windy weather favours spore release . The spore become airborn and are inhaled by human beings. In case of ABPA , after inhalation of spores from the environment, *A.fumigatus* hyphae (7-10 μg long)grow in the bronchial mucosa. The spores of *A.fumigatus* measures only 2-3.5 μm in diameter, so they easily pass the carina and enter the bronchi[4].

**Pathophysiolgy of ABPA**

*A. fumigatus* conidia (asexual spores)inhaled into the lungs binds to the surfactant molecules in the distal airway lumen,complement C3 and fibrinogen. They then germinate inside the airways to form hyphae. The hyphae release allergens ,proteases and virulence factors that contribute to[1] impaired mucocilliary clearence[2] inhibition of Macrophages and Neutrophils and[3] impaired action of fungicidal proteins and complements thus favouring further maturation and growth of the fungi.

It is important to note that just inhalation of *A.fumigatus* spores alone doesn't produce ABPA in sensitized individuals,though repeated inhalation causes triggering of fresh allergenic stimulus. Persistence of viable *A.fumigatus* in the airways seems to be the most important contributery factor for development of ABPA[7].

*A.fumigatus* antigens range from 10-100KD in weight, and there are 40 components that can bind to IgE antibodies[8]. There are 22 recombinant Aspergillus allergens designated Asp f1 to Asp f22[9].

A number of studies have demonstrated that 10 to 20 amino acid peptides from the recombinant allergens can stimulate T and B cells by binding to IgE or IgG antibodies[8,10]. Both IgE and IgG are essential for producing the unique inflamatory reaction of ABPA.

IgE antibodies through type1 hypersensitivity reaction worsen pre-existing asthma and peripheral eosinophilia. Precipitating IgG antibodies form immune complex with the *A.fumigatus* antigens which activate complement thereby causing inflamation and tissue destruction causing bronchiectisis. Primarily CD4+Th2 clones have been identified as causing intense immunological reaction by secreting IL-4,IL-5,IL-9,IL-10 and IL-13 and favouring IgE and IgG1 synthesis and survival of eosinophils and mast cell proliferation[11].

**Clinical Features**

Age Group-Adolscent ande young adults are mostly affected.

Patients with ABPA almost always are atopic,often have history of asthma or cystic fibrosis.

Occasionally patients with no history of asthma or cystic fibrosis present with lung infiltrates in chest x-ray and lobar collapse and are found to have ABPA[12]. Incidentally prevalence of ABPA is higher in patients with cystic fibrosis than those with asthma.Acute exacerbation of the disease is characterized by dyspnoea, wheezing,productive cough with expectoration of brownish mucus plugs. These episodes are often associated with fever.

**Critaria for diagnosis of ABPA[4,13,14,15]-**

A) ABPA in asthma
   - (i) Presence of Asthma
   - (ii) Positive Skin Prick Test to Asp.fumigatus or Aspergillus species.
   - (iii) Increased total serum IgE.
   - (iv) Elevated serum Asp.fumigatus Specific IgE Antibody or *A.fumigatus* Specific IgG Antibody.
   - (v) Chest roentgenographic infiltrates.

(B) ABPA in Cystic Fibroses

(i) Clinical detirioration – increased cough and expectoration, wheezing, exercise intolerance, detirioration of lung function parameters.

(ii) Positive SPT to *A.fumigatus* or presence of *A.fumigatus* specific serum IgE.

(iii) Precipitating antibodies to Asp.fumigatus or Asp.fumigatus specific serum IgG.

(iv) Chest roentgenographic infiltrates.

**Risk Factors**[1,5]

(i) Genetic- A number of genetic risk factors have been recently identified in the development of ABPA. These include HLA-DR and HLA DQ gene,IL4 receptor alpha chain (IL-4-RA)polymorphism, surfactant proteins A2(SPA2)polymorphism, Cystic Fibrosis Trans-membrane Regulator gene (CFTR)mutations.

(ii) Atopy

***In case of cystic Fibrosis :***

(i) Age more than 12 yrs.

(ii) Poor nutritional status

(iii) Pseudomonas infection

(iv) Medicines- Prolonged inhaled corticosteroids and or antibiotics, RhDNase therapy,Prolonged Azithromycine intake.

**Management**[16,17,2]

ABPA is a severe complication in patients suffering from bronchial asthma and cystic fibrosis as it causes long term damages like bronchiectases and pulmonary fibrosis. Therefore early detection and promt treatment of the condition is imperative.

In case of cystic fibrosis the diagnosis poses some problem because the clinical and radiological features of ABPA overlap with those of the former.

Development of new serological tests such as detection of specific IgE to recombinant Asp.fumigatus allergen,or Thymus and activation regulated chemokine(AARC/CCL17)promise to be of value in the accurate diagnosis of ABPA.

Anti inflamatory agents, notably systemic corticosteroids and bronchodilators remain the mainstay of treatment of ABPA.

Acute exacerbations are characterized by wheezing , increased total serum IgE and fall in Pulmonary Function Test (PFT)parameters.

Disease activity correlates with serum IgE titre.

Regular monitoring of serum IgE , PFT and chest x-ray is necessary for successful management of ABPA.

**Conclusion**

Allergic Bronchopulmonary Aspergillosis, ABPA usually affects patients with bronchial asthma or cystic fibrosis . Though not a very common disorder, it's importance lies in the fact that if left untreated it causes crippling complication like bronchiectasis and pulmonary fibrosis.ABPA is caused by hypersensitivity to the thermotolerant microfungi Aspergillus species , notably *A.fumigatus.*

ABPA is characterized by cough, wheezing, chest roentgenographic infiltrates and often

eripheral eosinophilia.

Diagnosis of ABPA is difficult because the clinical and radiological features overlap with those of asthma and cystic fibrosis.

Development of newer serological tests holds promise for more accurate diagnosis.

Early detection and prompt treatment of ABPA is essential to avert serious complications like bronchiectasis and or fibrosis.

Systemic corticosteroids and bronchodilators remain the mainstay of treatment.

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# Renal Biopsy in Pediatrics – An Overview

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## History

Before 1951, the only way of obtaining kidney tissue from a live person was through an open operation.

Three centuries after Malpighi first observed kidney tissue under the microscope, percutaneous renal biopsy was performed and published by Claus Burn and Paul Iversen of Copenhagen which has become the new standard of biopsy ever since[1]. Since then there has been significant development of techniques to safely obtain renal tissue from a patient by means of a percutaneous needle biopsy and to analyze the tissue not only by light microscopy(LM) but also by electron microscopy (EM) and immunofluorescence microscopy (IF). Thus the structural basis of almost every kind of renal disease that had been impossible to classify in an orderly fashion before have been revealed.

Robert M. Kark, met Iverson and together with Muehrcke and Franklin developed a technique of biopsy using the Vim Silverman needle in prone patients[2].

Immunofluorescence microscopy to detect tissue-bound immune deposits was developed by Coons and Kaplan in 1950[3]. But it was in 1955, that Mellors first applied the technique to renal tissue[4]. Antibody- and immune complex-mediated varieties of glomerulonephritis were categorised according to the visualised immune reactants that were contributing to their pathogenesis[5]. The 1961 CIBA Foundation Symposium on Renal Biopsy in London, was a landmark event in the maturation of the field of renal pathology. Between 1970 and 2010, etiology, pathogenesis, clinicopathological correlations, and classification were established for diverse renal diseases based on biopsy findings. Recent widespread availability of real-time imaging guidance using ultrasound or CT scanning have improved the perceived safety of the procedure.

Currently most nephrologists prefer to use the spring loaded, semi automatic or automatic biopsy guns rather than Vim Silvermann's needle.

## Indications of renal biopsy

A percutaneous renal biopsy is usually indicated to establish a diagnosis, help guide therapy, and ascertain the degree of active and chronic changes in the kidney. Kidney biopsy can also be performed to help assess genetic diseases.The routine evaluation of a percutaneous renal biopsy involves examination of the tissue under light, immunofluorescence, and electron microscopy[6].

Biopsy indications often vary according to the

region and population involved and mainly by presentation.In a 10 year review from Europe most frequent indications for renal biopsy were nephrotic syndrome (32.9%), asymptomatic hematuria (23.4%), urinary abnormalities in systemic diseases (15.8%) and proteinuria (11.4%). Primary glomerulonephritis (GN) was the most common finding (57.4%), followed by secondary GN (15.5%) and tubulointerstitial diseases (4.5%). According to histopathological diagnosis, the most common causes of primary GN were focal segmental glomerulosclerosis (20.9%), mesangioproliferative GN (14.6%), IgA nephropathy (8.9%) and minimal change disease (13%). Lupus nephritis (6%) and Henoch-Schönlein nephritis (4%) were the most common secondary glomerular diseases[7].

In an Indian series on 250 children the commonest indication for renal biopsy in nephrotic syndrome patients was SRNS(Steroid resistant Nephrotic Syndrome) (65.2%),followed by steroid dependency (SDNS) (17.6%) and frequent relapses (FRNS) (9.2%). In children with nephrotic syndrome, macroscopic hematuria presenting at the onset (0.8%) was one of the indications for renal biopsy[8].

**Contraindications**

Contraindications of renal biopsy can be absolute or relative.

Absolute contraindications to renal biopsy include the following:

(i) Uncorrectable bleeding diathesis

(ii) Uncontrollable severe hypertension

(iii) Active renal or perirenal infection

(iv) Skin infection at biopsy site

The following are relative contraindications to renal biopsy:

(i) Uncooperative patient

(ii) Anatomic abnormalities of the kidney which may increase risk

(iii) Small kidney

(iv) Solitary kidney

Recommended pre biopsy laboratory tests include a complete biochemical profile, complete blood count, platelet count, prothrombin time, partial thromboplastin time, and bleeding time.

**Techniques and procedures**

***Percutaneous renal biopsy techniques:***

Currently most percutaneous renal biopsies are obtained from the lower pole of the left kidney using ultrasound guidance and an automated biopsy needle with the patient in a prone position. The CT has generally been used for localization of the kidney prior to kidney biopsy in situations in which localization is unsatisfactory by ultrasound, e.g. very large patient girth, and often when optimal localization is particularly critical, e.g., in a patient with a solitary kidney.

The patient should be cooperative and are asked to inhale when necessary and hold their breath as the needle is advanced in the kidney, which is difficult in children ,and the biopsy is obtained.

All patients should provide informed consent for the biopsy. Possible allergy to local anesthetics and iodine containing solutions should be elicited. Just prior to the procedure,

peripheral intravenous access is placed and the patient is usually placed prone with a pillow under the abdomen(9]. If the patient is pregnant or very obese, the biopsy can be performed in the seated, lateral decubitus, or supine anterolateral position. Some anxious patients may require mild sedation.

Percutaneous renal biopsy is usually performed under ultrasonic guidance with local anesthesia (usually 1 percent lidocaine hydrochloride)[9]. Ultrasonography can localize the desired lower pole site (at which the risk of puncturing a major vessel is minimized), determine renal size, and detect the unexpected presence of cysts that might necessitate using the contralateral kidney.

After the lower pole is localized, a skin mark is made to identify where the biopsy needle will be inserted. The site is then prepped and anesthetized. Under ultrasound guidance, a needle is then used to locate the capsule of the lower pole and to provide anesthesia for the biopsy needle tract.

After a small skin incision is made to facilitate passage, real time ultrasonography is most commonly used to guide the biopsy needle directly into the lower pole[10].

This cumbersome procedure has the advantage of direct visualization of the location of the needle as the core of tissue is obtained.

The use of real-time ultrasound has been compared to the "blind" approach (using ultrasound for localization only). A retrospective study demonstrated a higher diagnostic yield (100 percent versus 84 percent) as well as a lower major hemorrhagic complication rate (0 percent versus 11 percent) in the group using real-time ultrasound[11].

Non percutaneous renal biopsy techniques include open renal biopsy, laparoscopic renal biopsy and transjugular renal biopsy.

**Adequacy of tissue sampling**

It is usual to take two cores of tissue. Only a few glomeruli are required to constitute a sufficient sample size for EM and IF. Therefore, if possible, an area of the biopsy tissue should be identified in which there are recognizable glomeruli, and a small sample of that area, 1 to 3 mm in length, should be sufficient for EM, with a second similar sample allocated for IF. All remaining tissue may then be submitted for LM. This pattern of tissue allocation minimizes the amount of tissue required, and increases the likelihood that maximal information will be obtained. One of these small pieces of tissue is placed in a solution of glutaraldehyde for EM, and the second piece will be placed in Michel's solution for IF examination. The two remaining larger cores are placed in formalin for LM.

The routine immunofluorescence examination of biopsy specimens should include evaluation of IgG, IgM, IgA, C3, C1q, albumin, fibrin, and kappa and lambda immunoglobulin light chains. Special studies, including evaluation of serum amyloid A deposits, IgG subclasses (IgG1-4), and collagen chains (alpha 3.4 and 5) may be helpful in some suspicious cases. Diagnoses that commonly require electron microscopy include minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis,

membranous nephropathy, thin basement membrane disease and Alport syndrome, postinfectious glomerulonephritis, HIV-associated nephropathy, amyloidosis, immunoglobulin deposition diseases, and fibrillary (immunotactoid) glomerulopathy.

**Post biopsy care**

After the procedure the patient should be maintained in the supine position; clinical status, vital signs, and urine color should be monitored over the next 12 to 24 hours[13].

A number of studies have examined the appropriate amount of time that a patient should be observed after the biopsy. Jones and associates found that 66% of complications were apparent within 6 hours and 100% within 12 hours of observation[14].

**Biopsy needle**

A variety of different biopsy needles are available, including manual needles (TruCut disposable, Franklin-Silverman, Vim-Silverman) and automated spring-loaded biopsy needles[15,16].

The size of the needle determines the amount of core tissue obtained and also the complications following biopsy. The size of the needle used is a matter of judgment, a decision to be made by the operating physician, balancing benefits of information to be obtained,against possibly increased risks of a) a larger bore needle versus b) more sticks with a smaller bore needle. In a study by Pellegrini et al, biopsies were performed under ultrasound imaging, using a semiautomated and thin needle (20 gauge in children with age under 5 years and 18 gauge for those over 5 years. Diagnostically adequate tissue was retrieved in 38 of 40 biopsy procedures (95%).

**Complications**

Serious complications of renal biopsy are uncommon. The risk of complications will vary from centre to centre based on experience and other technical factors.

The most common complication of kidney biopsy is bleeding. In a recently published study evaluating the safety of pediatric renal biopsy 227 patients aged 18 years or less who underwent percutaneous native kidney biopsy were analysed. Perirenal haematoma occurred in 58 patients (25%) and macroscopic haematuria occurred in 46 patients (20%)[17].

In a series from India with 250 nephrotic children younger than 18 years old who had renal biopsy from January 1988 to December2002, mild (16.0%) and gross (16.8%) hematuria and subcapsular hematoma (6.0%) were the common complications. Fifty-five percent of the children had no complications. Only two children (0.8%) had biopsy site infection[18].

In a series from Sweden, 109 children and adolescents, aged 0.1-19.8 (mean 9.9) years underwent119 biopsies. 24-h post-biopsy ultrasonography disclosed a small haematoma of the biopsied kidney in 26% of the cases. No correlation was seen between the occurrence of haematoma and (treated) prolonged bleeding time or a decrease in the haemoglobin level. No major complications occurred. Newly developed macroscopic

haematuria was reported by 7% and micturition pain by 7% of patients. Painful body movements were reported by 37%[19].

A Brief audit on percutaneous renal biopsies performed at Institute of Child Health, Kolkata revealed the following data[20].

1. Total number of kidney biopsies done were 30. Out of the 30 patients, 23 patients were male the rest female.

2. Indication of renal biopsy are shown in table 1. The commonest indication for biopsy in this pediatric population was SRNS, similar to previous Indian data. This is followed by SDNS, lupus nephritis and nephritic syndrome. Biopsy was also done for AKI, HSP with nephritis and to see the Tacrolimus toxicity in one patient.

Table 1. Indication of renal biopsy

| Indication | No. of patients |
|---|---|
| SRNS | 14 |
| SDNS | 4 |
| SLE | 3 |
| AKI | 2 |
| Nephritic syndrome | 3 |
| Drug toxicity (Tacrolimus) | 1 |
| HSP | 1 |
| Persistent hematuria with proteinuria | 2 |

3. Results:

Histopatholgical diagnosis by LM and IF as shown in table 2, revealed majority as primary glomerular disease with most having minimal change disease followed by focal segmental glomeruloscleroisis. Lupus nephritis and IgA Nephropathy were the other histological findings. EM was not done on any specimen.

**Table 2.** Histopathological diagram

| Histopathology | No. of pt |
|---|---|
| MCNS | 8 |
| FSGS | 7 |
| LUPUS nephritis 2 | 1 |
| Lupus nephritis 4 | 2 |
| IgA Nephropathy | 2 |
| DPGN | 3 |
| Pauci immune GN | 1 |
| Mesengioproliferative GN | 2 |
| Collapsing Glomerulopathy | 2 |
| HSP Nephritis | 1 |

4. Major complications were extremely rare as shown in table 3. Most patients complained of pain over the biopsy site for next 24- 48 hrs, which was relieved with paracetamol. Hematuria though common , could be managed conservatively.

Transient gross hematuria seen in 13 patients,resolved within 24 hours. Hypertension was seen in only two patients. Only one patient required blood transfusion. There was no mortality.

**Table 3.** Complications following renal biopsy.

| Complication | No. of patients |
|---|---|
| Gross hematuria < 24 hrs | 13 |
| Gross hematuria > 24 hrs | 2 |
| Hypotension | 1 |
| Hypertension | 2 |
| Shock | 0 |
| Pain over biopsy site | 26 |

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## *Neurodevelopmental Clinic*

Neurodevelopment clinic is held every **Friday 12 noon** onwards. All types of developmental delay, cerebral palsy, speech delay, poor scholastic performance, autism, ADHD are dealt in this clinic.

# HbH Disease: A Case Study

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## Introduction

The generic term α thalassaemia encompasses all of those conditions in which there is a deficit in the production of the alpha -globin chains of haemoglobin (Hb). Alpha-thalassaemia is inherited as an autosomal recessive disorder characterized by microcytic hypochromic anaemia, and a clinical phenotype varying from almost asymptomatic to a lethal haemolytic anaemia. Normal individuals have two α-genes on each chromosome 16 (aa/aa). The normal complement of four functional alpha globin genes may be decreased by 1 (-a/aa), 2 (--/aa,(cis) or -a/-a(trans)), 3(--/-a) or all 4 (--/-- ) copies of the genes, explaining the clinical variation and increasing severity of the disease. The most severe form of alpha thalassaemia is Hb Barts hydrops foetalis where there are no functional a-globin genes (--/--) and results in the condition where death occurs in utero or within a few hours of birth[1].

Patients with alpha-thalassaemia intermedia with only one functional α-globin gene (--/-a) develop chronic haemolytic anaemia of variable severity. Underproduction of a globin chains gives rise to excess ß-like globin chains which form ?4 tetramers, called Hb Bart's (in foetal life) and ß4 tetramers, called HbH (in adult life). The condition characterized by the presence of HbH in the peripheral blood is referred to as HbH disease. The type of mutation influences the clinical severity of HbH disease. Non-deletional HbH disease is more severe than the deletional type[2].

In this case report, a case of HbH disease is presented where HPLC served as a rapid and accurate tool in the early detection and management of the hemoglobin disorder.

## Case Report

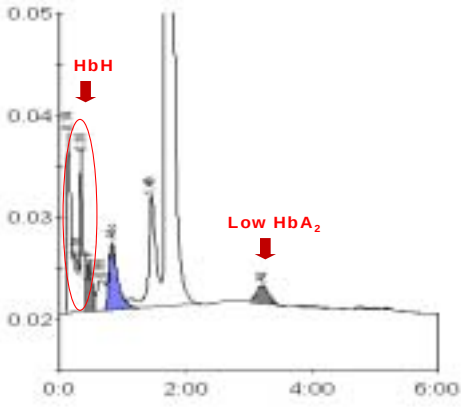
A 1-year 11 month old female child presented with mild pallor, generalized malaise with fever, but without hepatosplenomegaly. Child was born term, of a non consanguineous marriage, with uneventful perinatal and neonatal period, and with normal developmental milestones. There was history of previous admission at 9 months of age with diarrhea, vomiting and anemia. There was no family history of thalassaemia. The haematology work-up included a full blood picture, thalassaemia screen tests and a liver profile. Blood specimens were drawn into tubes (Becton Dickinson Vacutainer Systems) containing dipotassium ethylene diamine tetraacetic acid (EDTA) for full blood picture and thalassaemia diagnosis (quantification of Hb subtypes), into plain tubes for serum ferritin and liver profile studies.

Thalassaemia screen using cation exchange high performance liquid chromatography (HPLC) was performed. She was noted to

have moderate anaemia with a haemoglobin level of 7.9 gm/dl (normal range 11.5-13.5 gm/dl), hypochromic-microcytic red cell indices (MCH of 16.7 pg and MCV of 54.0 fl), and a thalassaemia peripheral blood film (anisopoikilocytosis, hypochromia, tear drop and, target cells). A specimen collected in EDTA was analyzed on the Bio-Rad D10 HPLC Hb analyzer (Bio-Rad Laboratories) to determine the distribution of Hb subtypes with the use of the ß-thalassaemia short program. The Hb subtypes noted were HbA, HbF, $HbA_2$ and a sharp peak, before the start of integration, in the first minute of elution which indicates HbH as shown Figure 1. The serum ferritin was 34 µg/L (normal 13-150 µg/L). The bilirubin and liver enzymes were normal.

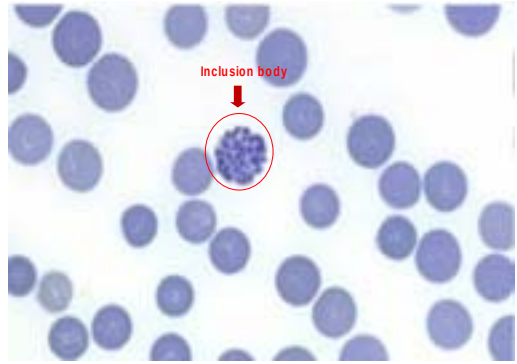
Figure 1: HPLC chromatogram obtained on Bio-Rad D10 ß-thal short program for HbH. A sharp peak (circled), before the start of integration, in the first minute of elution indicates HbH, HbF concentration = 1.1%, HbA concentration = 80.2%, HbA2 concentration = 1.3% (normal 2.0-3.5%)

Y axis: percentage of Hb subtypes, X axis: retention time in minutes (RT)




| Fraction | Retention time(minutes) | % | Normal Range(%) >12 months |
|---|---|---|---|
| HbF | 0.46 | 1.1 | |
| HbA | 1.71 | 80.2 | |
| HbA2 | 3.18 | 1.3 | 1.9 -3.5 |
| Area | 1710022 | | |

Figure 2: An inclusion body positive cell seen in Brilliant Cresyl Blue stained red cells of an alpha thalassemia patient




## Discussion

HbH disease is seen most commonly in the Asian population (South East Asia, Mediterranean, and parts of Middle East)[2].

The predominant features in HbH disease are anaemia (2.6-13.3 g/dl) with variable amounts of HbH (0.8-40%), in the peripheral blood. The patients usually have splenomegaly (which may be severe) and occasionally this is complicated by hypersplenism. Jaundice may be present in variable degrees and children may show growth retardation and may have mild hemolytic facies. Other complications include infections, leg ulcers, gall stones, folic acid deficiency and acute haemolytic episodes in response to drugs and infections[3]. Older patients often have some degree of iron overload. The severity of the clinical features

is related to the molecular basis of the disease. Patients with non-deletional types are more severely affected than those with the common deletional types of HbH disease[4].

As was in our case, the clinical diagnosis of HbH disease (milder form) is often made only after the detection of complications, such as exacerbations of the anaemia induced by infections, growth failure (in children) or findings of splenomegaly.

The first line laboratory workup should include a complete blood count with red cell indices; findings show pronounced microcytic hypochromic anaemia. The degree of microcytic (low MCV), hypochromic (low MCH) anaemia (low Hb) depends roughly on the number of a genes mutated and correlates well with the reduction in α-chain synthesis[2,5,6].

HPLC (or Hb electrophoresis) is of particular importance to demonstrate HbH in individuals with HbH disease. HbH is fast moving haemoglobins appearing on electrophoresis or HPLC. Careful examination of the chromatogram reveals the presence of HbH. Furthermore, a reduction in the level of $HbA_2$ is distinctive in patients with HbH disease (see Figure 1)[2,5,6,7].

HbH is prone to oxidation leading to the formation of intracellular inclusions. These can be visualized by staining the peripheral blood cells with 1% Brilliant Cresyl Blue in a reticulocyte preparation. The typical inclusion-body cells have a golf-ball like appearance with stippling regularly distributed over a blue stained background (see Figure 2)[8].

Presentation of HbH disease overlaps with iron deficiency anemia and iron studies should also be meticulously carried out to rule out iron deficiency status.

Confirmation of disease is with DNA analysis for common mutations using Gap-PCR. Screening of family members is recommended and should be essential for parents of an affected child, for genetic counseling. When one parent carries ao thalassaemia (--/aa) and the other carries an a+ thalassaemia (-a/aa) the risk of their offspring having HbH disease is 1:4 (25%). If the carrier of a+ thalassaemia is a homozygote the risk of HbH disease is 1:2 (50%)[2,5].

Patients may require intermittent transfusion therapy especially during intercurrent illness. Chronic transfusion therapy is rarely needed in this group. However, patients with non-deletional types of HbH disease may have moderately severe splenomegaly and require more regular transfusion and ultimately splenectomy. Iron overload is uncommon in HbH disease patients (compared to beta-thalassaemia) but has been recorded in older patients (>45 years). The prognosis for patients with HbH is good as many patients appear to lead a normal life in all respects. Some even remain undiagnosed throughout their lives. Complications need to be managed well for better outcome, especially the problem of iron overload for those with severe HbH disease[3,9].

HbH disease is an under-diagnosed entity in the Indian subcontinent. We feel that a careful evaluation for HbH on the HPLC would help in rapidly and accurately diagnosing these cases.

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## MRI Department, Institute of Child Health, Calcutta

### How long it is open?

It is open from 9 a.m. to 7pm on weekdays. On Sunday, it is open from 9am to 1pm.

### What is the usual time required for MRI scan?

About 30 minutes.

### How an appointment is made?

It is usually done at the reception of MRI department by personal visit or by telephone. Telephone No.s **(033)2289-3526 and (033)6526-6969**.

### What preparation is needed for MRI?

Usually no preparation is needed. For MRCP study 4-6 hours fasting is needed. For children, oral sedation is usually required. In some hyperactive, restless patients anesthesia is needed. We have fully equipped setup for anesthesia and extremely competent anesthetist for such patients. About 6 hours of fasting is needed prior to anesthesia.

# Urticaria Pigmentosa- A Rare Presentation

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**Abstract:**

Urticaria pigmentosa is a group of rare disorder that includes systemic mastocytosis at it's spectrum. The term mastocytosis refers to a spectrum of rare disorders characterised by increased number of mast cells in the skin and in some instances, in other organs[1,4]. We present this case for its early presentation in a child and the prompt use of biopsy to arrive at the correct diagnosis of this disorder.

**Introduction**

Urticaria Pigmentosa is an uncommon skin disease primarily affecting children although it may be seen in adults. The common presentation includes pruritic macules and papules with gradual worsening of symptoms. It is the localised form of the group of disorders involving the mast cells called systemic mastocytosis.

**Case Report**

A 1 yr male child presented with multiple oval, red brown, nonscaling papules all over the body which were itchy more during evening. On examination, the child was developmentally normal with no organomegaly or systemic manifestations of any diseases. Routine blood tests were essentially normal and so a punch biopsy was done from one lesion on the trunk on the second visit itself.

Biopsy showed a bit of skin tissue having dense lymphomononuclear cells infiltrate in the dermis with unremarkable epidermis and subcutaneous stroma. H and E stain showed the cells having granular abundant cytoplasm with round to oval bland nucleus. Metachromatic stain (Toulidine Blue) demonstrates metachromatic granules in the cytoplasm of these cells brilliantly.

A diagnosis of localised cutaneous mastocytosis (Urticaria Pigmentosa) was established. The child was treated with mast cell stabilizers to which he responded dramatically.

Discussion: Urticaria Pigmentosa belongs to a group of disorders characterised by early and excessive degranulation of mast cells that leads to exagerated inflammatory responses even to normal stimulus[2,3]. UP is localised form of this group of mastocytosis and mainly affects children in about 50% of cases[5]. In more than 90% cases, this is due to mutation in c-kit oncogene and hence may be considered to be a neoplastic process6.

Systemic mastocytosis is a group of diseases characterised by early degranulation of mast cells in various organs in response to inappropriate stimulus or even in the absence of stimulus resulting in liberation of inflammatory mediators giving rise to a variety of effects[7]. The histologic picture in

urticaria pigmentosa is highly variable and varies from a subtle increase in the numbers of spindle shaped to stellate shaped mast cells around superficial dermal vessels, to a large numbers of tightly packed , round to oval mast cells in the upper to mid dermis(fig.1)[3]. Mast cells may be difficult to differentiate from lymphocytes in routine H&E stained sections(fig.2) and special metachromatic stains(toulidine blue-Fig 3.) must be used to visualise their granules[1].

Urticaria Pigmentosa is a rare disease and diagnosis is usually delayed due to the reluctance of the treating physician to do a biopsy[7]. We advocate the early institution of biopsy to arrive at a definite diagnosis in this type of lesions.

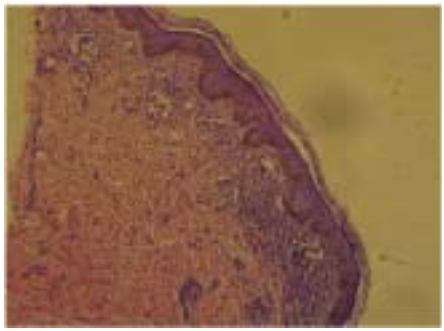

**Fig.1** H&E stain(10X)

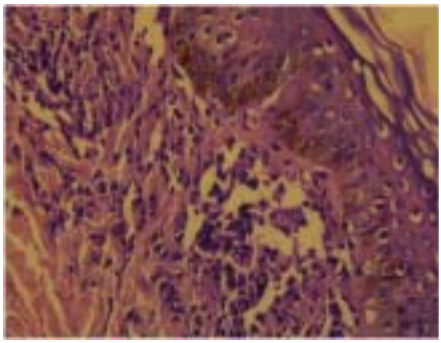

**Fig 2.** H&E stain (40x)

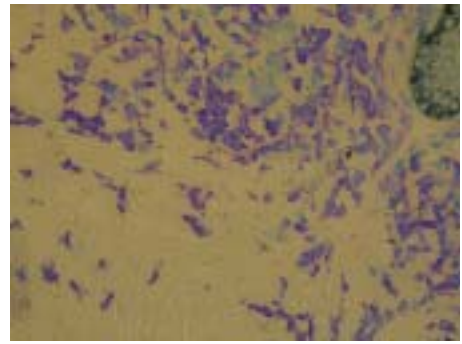

**Fig 3.** Touldine blue stain (40X)

**Reference :**


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# Journal Scan

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*1.The RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014 May 4; [e-pub ahead of print].*

***Has the RIVUR been crossed?*** Many of us have been eagerly waiting for the outcome of this mega trial looking at whether antibiotic prophylaxis works in vesico-ureteric refluxes (VUR). Researchers at 19 U.S. centers randomized 607 children (age range, 2–71 months) with a first (91%) or second febrile (86%) or symptomatic UTI and VUR (grades I–IV) to receive daily prophylaxis with trimethoprim-sulfamethoxazole or placebo. At 2-year follow-up, febrile/symptomatic UTI recurred in 15% of prophylaxis recipients versus 27% of placebo recipients. At any point in time, prophylaxis reduced the risk for recurrent UTI by 50% overall, and even more in children who had fever with their first UTI (59%) or who were toilet-trained and had bladder/bowel dysfunction (79%). The study concluded that eight children with recent UTI and VUR needed to receive prophylaxis to prevent one recurrent UTI. Renal scarring incidence at follow-up was similar in the prophylaxis and placebo groups (12% and 10%). The flip side was a higher incidence of trimethoprim-sulfamethoxazole resistance in the prophylaxis group (63% vs. 19%). So now the debate is, as the editorialists in the same edition noted, whether preventing recurrent UTIs is worth risking antimicrobial resistance and potential microbiome alterations since it seems the renal damage is not altered.

2a. *Wu S, Baker C, Lang ME, Schrager SM, Liley FF, Papa C et al. Nebulized Hypertonic Saline for Bronchiolitis: A Randomized Clinical Trial. JAMA Pediatr. 2014 May 26. doi: 10.1001/jamapediatrics.2014.301. [Epub ahead of print]*

2b. *Florin TA, Shaw KN, Kittick M, Yakscoe S, Zorc JJ. Nebulized Hypertonic Saline for Bronchiolitis in the Emergency Department: A Randomized Clinical Trial. JAMA Pediatr. 2014 May 26. doi: 10.1001/jamapediatrics.2013.5306. [Epub ahead of print]*

***Utility of nebulised hypertonic saline in Emergency Room for bronchiolitis-CLINCHING evidence of two randomized control trial!!!????:*** Two randomized controlled trials provided conflicting data on the value of nebulized hypertonic saline (HS) for infants with bronchiolitis. Whereas Wu et al concluded that it may even prevent hospitalisation; Florin et al did not report any utility of nebulising with HS in emergency room.. Florin et al studied 62 children (aged 2 months to less than 24 months) with bronchiolitis and persistent respiratory distress after a trial of nebulized albuterol. Half were randomized to receive 3% HS and half to normal saline. The primary outcome was the change in respiratory distress at one hour after the intervention, as determined by the Respiratory Assessment Change Score (RACS). At one hour after HS

or normal saline, the HS group had significantly less improvement in median RACS compared with the normal saline group (-1 vs -5, p=0.01). Criticism of the study by Florin et al has been their use of only a single dose of hypertonic saline, and a small treatment group. In contrast Wu et al studied 408 infants with bronchiolitis (younger than 24 months) who received 3% HS or normal saline up to three times in the emergency department. A lower rate of admission in the HS group was found than the normal saline group (29% vs 43%). The number needed to treat to prevent one hospitalization was eight. But there was no significant between-group difference in length of stay or RDAI score.

The2013 Cochrane meta-analysis done before the publication of this trial did conclude that there is probably no role for HS for patients with bronchiolitis treated in the emergency department, but it may be helpful for inpatients by decreasing their length of hospital stay. The two new RCTs need to be incorporated into an updated systematic review to see whether the overall findings changes or not. Currently maybe we should continue to use HS nebulisation for difficult bronchiolitis admitted in hospital and restrict its routine use in emergency department for research protocols.

*3. Alisi A, Bedogni G, Baviera G, Giorgio V, Porro E, Paris C et al. Randomised clinical trial: The beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2014 Jun;39(11):1276-85. doi: 10.1111/apt.12758. Epub 2014 Apr 16.*

***Yet another use of probiotics!!!*** There are some evidences to suggest that modulation of the gut microbiome with probiotics may have a therapeutic role in Non-Alcoholic Fatty Liver Disease (NAFLD). In the current parallel-arm, double-blind trial, investigators assessed the efficacy of VSL#3, a mixture of eight probiotic strains that has been studied in experimental models of NAFLD. Forty-eight obese (body-mass index >85th percentile) children with biopsy-proven NAFLD and abnormal liver tests were randomized to receive VSL#3 daily (1 packet if aged <10 years; 2 packets if aged =10 years) or placebo for 4 months. The main study outcome was the change in fatty liver severity by ultrasonography at 4 months. At baseline, moderate and severe NAFLD were present in 55% and 45% of the patients in the VSL#3 group and 64% and 36% in the placebo group. The odds ratio of more severe versus less severe steatosis after 4 months of treatment was 0.001 (95% confidence interval, 0.0001–0.02) for the VSL#3 group versus the placebo group. The probabilities of moderate and severe fatty liver after treatment were 9% and 0% in the VSL#3 group compared with 76% and 17% in the placebo group. These results appear to be the first evidence in humans of the potential therapeutic role of probiotics in NAFLD. Further studies are needed with larger sample sizes, longer follow-up, and histologic and clinical primary endpoints.

*4. Minneci PC et al. Feasibility of a nonoperative management strategy for uncomplicated acute appendicitis in children. J Am Coll Surg 2014 Apr 12; [e-pub ahead of print].*

***Good or is it Bad news for our surgical colleagues?*** Urgent appendectomy has been the mainstay of therapy for acute appendicitis. The authors reported a nonrandomized, prospective trial comparing two therapies determined by parental choice: intravenous piperacillin-tazobactam or ciprofloxacin/

metronidazole therapy for at least 24 hours followed by oral antibiotics for 10 days (30 children) versus appendectomy (47 children). Patients were between ages 7 and 17 years, with =48 hours of abdominal pain, white blood cell counts <18,000/μL, and no radiographic evidence of rupture, abscess, or appendiceal fecalith. Immediate and 30-day success rates for nonoperative management were 93% and 90%, respectively. None of the three patients who progressed and underwent subsequent appendectomy had a ruptured appendix. Nonoperative management was associated with significantly longer length of stay (38 vs. 20 hours), but shorter delay before return to school (3 vs. 5 days) and higher scores on parent assessment of child quality of life. It does suggest that proper selection and careful follow up may avoid surgery in a significant number of appendicitis. Long-term follow-up of the nonoperative group will be important to assess risk for relapse.

5. *Lassi ZS, Kumar R, Das JK, Salam RA, Bhutta ZA. Cochrane Database Syst Rev. 2014 May 26;5:CD009576. doi: 10.1002/14651858.CD009576.pub2. Antibiotic therapy versus no antibiotic therapy for children aged two to 59 months with WHO-defined non-severe pneumonia and wheeze.*

***Now, good news for those who prescribe antibiotics frequently!!!.*** In a systematic review and meta-analysis, antibiotic therapy was associated with improved growth in children in low- and middle-income countries. The meta analysis included 4316 children. Type of antibiotic, length of treatment, length of follow-up, and participant age varied among the 10 studies. In pooled analysis, antibiotic use increased weight by 23.8 g/month (95% confidence interval, 4.3-43.3) and height by 0.04 cm/month (95% confidence interval, 0.00-0.07). The effect of antibiotics on weight was greatest in studies conducted in Africa and the effect on height was greatest in younger children. Like all that glitters is not gold we have to appreciate a number of gaps in the meta analysis. The heterogeneity of the trials, absence of information about many factors that affect growth, and concerns about antibiotic resistance limit these results; therefore, routine use of antibiotics as a nutritional therapy should be considered cautiously. Certainly, appropriate use of antibiotic therapy is warranted and may support growth in children in resource-poor settings.

***6.*** *Chamberlain JM et al. Lorazepam vs diazepam for pediatric status epilepticus: A randomized clinical trial. JAMA 2014 Apr 23/30; 311:1652*

***Which one is better?*** Both Lorazepam and Diazepam is advised for status epilepticus in children but is one better than the other? In a double-blind, randomized trial, investigators compared the efficacy and safety of intravenous (IV) diazepam with IV lorazepam in children 3 months to <18 years of age presenting to one of 11 pediatric emergency departments with tonic-clonic status epilepticus. Of 273 children (median age, 3 years), 140 received diazepam (0.2 mg/kg; maximum dose, 8 mg), and 133 received lorazepam (0.1 mg/kg; maximum dose, 4 mg). Additional half doses were given if seizures were ongoing 5 minutes after the initial dose. Cessation of status epilepticus within 10 minutes without recurrence within 30 minutes, as determined by clinical criteria, was similar between treatment groups (72% for diazepam; 73% for lorazepam). The

proportion of patients requiring assisted ventilation was also similar between groups (16% and 18%). Diazepam recipients were less likely to have sedative effects (50%) than those receiving lorazepam (67%) and had a shorter time to recovery from sedation (105 minutes vs. 120 minutes, respectively). Although both seemed to have similar efficacy lorazepam had greater (less desirable) sedative effects. Hence diazepam may be a better choice when there are limited resources for ongoing monitoring and less sedative effect is desired.

*7. Liao YH[1], Lin CL, Wei CC, Tsai PP, Shen WC, Sung FC et al. Subsequent cancer risk of children receiving post voiding cystourethrography: a nationwide population-based retrospective cohort study. Pediatr Nephrol. 2014 May;29(5):885-91. doi: 10.1007/s00467-013-2703-5. Epub 2013 Dec 30.*

***Lastly some grim news!*** In this retrospective study investigators identified 31,908 participants who had underwent VCUG at younger than 18 years of age. For comparison the non-VCUG cohort, was randomly selected among children without VCUG examination histories during 1997-2008, frequency matched for age (every 5 years), sex, geographic region area, parents' occupation, and index year based on a 1:4 ratio. The overall cancer risk of the VCUG cohort was 1.92-fold (95 % CI?=?1.34-2.74) higher than that of the non-VCUG cohort with statistical significance. The genital cancer and urinary system cancer risks of the VCUG cohort were respectively 6.19-fold (95 % CI?=?1.37-28.0) and 5.8-fold (95 % CI?=?1.54-21.9) higher than those of the non-VCUG cohort with statistical significance. The hazard ratios were higher in genital cancer, urinary system cancer (the major radiation exposure area), and cancer of the abdomen, except for the genitourinary system (the minor radiation exposure area), in sequence. Obviously a retrospective study has its limit but this should make everyone think about the necessity of the VCUG before ordering the test.