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Water for health

Long before the advent of modern medical care, industrialized countries decreased their levels of water-related disease through good water management. Yet, even in these countries, outbreaks of water-borne disease continue to occur, sometimes with lethal consequences. In developing countries, preventable water-related disease blights the lives of the poor. Diseases resulting from bad hygiene rank among the leading causes of ill-health.

3.4 million people, mostly children, die annually from water-related diseases. Most of these illnesses and deaths can be prevented through simple, inexpensive measures.

The poor are more susceptible to ill-health than are the well-off. They lack adequate supplies of safe water and safe methods of disposing of their wastes. Lack of water and sanitation create ideal conditions under which faecal oral diseases thrive.

Similar inequities in access to safe water, especially in rural areas, force women in developing countries to spend hours every day fetching water, causing an enormous drain on their energy, productive potential and health. The lack of good quality, reliable water puts people's health at risk and may force them to extract water from alternative, unsafe sources, exposing them to diseases such as diarrhoea or dysentery, cholera and typhoid. Traditional wells may become polluted with agrochemical residues as irrigated agriculture intensifies.

Everyone benefits from good sanitation. But girls are among those who benefit the most. Girls often miss out on an education because they have to help with the household chores and, when money is scarce, it's usually the boys who get chosen to go to school. An important reason why girls drop out of school in developing countries is because of lack of sanitation facilities. The school attendance by girls increases when separate latrines for girls and boys are installed as evidenced by our government's initiative towards swaccha bharat creating thousands of toilets.

Easy, low-cost methods for improving health do exist and can be applied collectively or individually. Water can be purified by means of chlorination and solar-thermal techniques. People can stay healthy by simply washing their hands with soap and water. Government policies can support local initiatives.

What we now know is that even in conditions of very poor sanitation and hygiene where people are collecting whatever water is available to use as household water supply as in urban slums, if the water is chlorinated, the water is improved microbiologically and you can find statistically significant decreases in diarrhoeal disease.

The Maldives adopted a national control programme using chlorination in wells and oral rehydration salts for the treatment of diarrhoea, as well as use of rainwater for drinking. 20 years later all the islands in the country are self-sufficient with their own community rainwater collection system tanks. Deaths due to diarrhoea are now a thing of the past.

Sodis was pioneered in Lebanon in the 1980s. It is a simple water-treatment method which uses the sun, throw-away plastic soft-drink bottles and a black surface. Further research was carried out and promoted by the Swiss
Federal Institute for Environmental Science and Technology on Sodis. Transparent bottles are filled with water and placed horizontally on a flat surface in sunlight for about five hours. The illness causing micro-organisms (pathogens) in the polluted water succumb to the killing effect of the ultraviolet light in the solar radiation. The process is enhanced when the solar water disinfection is combined with a “solar thermal water treatment” which makes use of the fact that the colour black absorbs light. This is accomplished by painting the bottom half of the bottle black or placing it on black-painted corrugated iron or plastic sheets. Anecdotal evidence has been gathered indicating that people have less diarrhoea.

Valerie Curtis, Lecturer in Hygiene Promotion at the London School of Hygiene and Tropical Medicine participated in a major three-year study in India, the Netherlands, the United Kingdom and West Africa to learn what motivates good hygiene practices. “All it requires is soap and motivation” washing hands with soap would probably save half of the deaths from diarrhoeal diseases,” but that’s more easily said than done. Of people at Lucknow only 46% washed hands with soap and water and only 21% mothers cleaned hands with soap and water after cleaning their babies. The results are interesting and in many ways unexpected.

The research finds that hygiene is a common value around the world. Nobody likes dirt. But, people’s hygienic practices have less to do with health than with social and aesthetic considerations. Mothers want to keep their babies clean because they believe it is a loving, caring thing to do and will make their babies socially acceptable. One Indian mother explains “If my child is dirty, no one will hold him in their arms, no one will love him. And, so I keep my child clean.”

There has to be a rethinking of the traditional “scolding, moralistic” approach to hygiene, which hasn’t worked. A number of studies show that people are turned off by dire warnings that they will face disease and death if they don’t change, “their filthy ways”. Often I have come across people when told that reason for their ill health and recurrent illness is improper hygiene they felt they were being accused of being “filthy dogs”.

Infectious diseases know no borders. Malaria-bearing mosquitoes have been known to hitch rides on airplanes departing from Africa or Asia and unwittingly infecting an individual from a non-endemic country. Since the wild polio-virus can travel from one country to another, the global campaign to eradicate this crippling disease will not succeed until polio has been eliminated in every country of the world. These are some of the grim realities of a more integrated world. The multibillion dollar tourist industry for a safer and cleaner environment could, if effectively channeled, contribute also to development for the benefit of the poor.

Safe water and proper sanitation are the answer to majority of gastrointestinal problems in developing countries. It’s this reason that I have touched upon this most neglected problem on the eve of a gastrocon. We have to realize this fact that as much as we neglect this problem more and more it will backfire upon us, on our health.

Water is one of the earth’s most precious and threatened resources

Health is one of each person’s most precious resources

We need to protect and enhance them both

Water for Health( WHO)

Prof. Atul Kr Gupta
Editor-in-Chief
It is a great privilege and honor to edit the Special Issue of “The Child and Newborn” on Pediatric Gastroenterology, Hepatology and Nutrition. This Special Issue is primarily based on the lectures delivered by the renowned International and National experts in the 3rd Annual Conference of Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition at Kolkata.

I am sure that the readers will be enriched by the knowledge, wisdom and information about the office practices and recent advances that are presented in these articles.

It gives me and the entire editorial team immense pleasure to be able to present these pearls of wisdom to you in form of this Special Issue.

**Sutapa Ganguly, MD(Ped), FIAP**
Professor of Paediatrics & Principal
CSS College of Obs., Gyne and Child Health
Descriptive Epidemiology of Acute Diarrhoeal Disease and Outbreaks
In North 24 Parganas District, West Bengal, 2010-2014

Falguni Debnath
National Institute of Cholera and Enteric Diseases, Kolkata.

Introduction
There was 45% increase in acute diarrheal disease (ADD) outbreaks from 2010 (n=4) to 2013 (n=14) of all outbreaks in District North 24 Parganas of West Bengal. The District ADD data were also not analyzed so far. In this context, we conducted a descriptive study by analyzing the secondary data on ADD and its outbreaks from 2010 – 2014. Our study objectives were to describe incidence of ADD by blocks, by gender over time, describe ADD specific mortality and case fatality over time, correlate incidence of ADD with selected factors at block level, describe trends in ADD outbreaks.

Methods
We abstracted data from district communicable disease report, Integrated Disease Surveillance Programme report and Census India, 2011. We calculated incidence, by gender, by blocks, by time using appropriate denominators. We also calculated attack rates, disease specific mortality, case fatality rate. We Calculated descriptive statistics of time-taken to report during outbreaks. We correlated selected block level factors with incidence. Outbreaks were plotted by blocks over time and we created area maps for incidence by blocks.

Results
From 2010 – 2012, Hasnabad block reported highest number of ADD cases. In 2013, Habra II block and in 2014 Amdanga block reported highest ADD incidence. Only in 2014, there was no reported diarrheal deaths. Twenty-eight acute diarrheal outbreaks were reported from 2010 – 2014. In 2013, 14 (20) acute diarrheal outbreaks were reported and only 6 of them got laboratory confirmed. Block and municipal authorities took equal median time of 2 days (IQR= 1 – 3 days) for intimating district Rapid Response Team about occurrence of the outbreak from 1st case reporting.

Conclusions
Consistently few blocks do not report ADD cases. Among the blocks, where proportion of households who don’t have access to improved water source was more, incidence of ADD was also more. All the ADD outbreaks were not laboratory confirmed. Time taken to report outbreaks was similar in when outbreaks occurred either in blocks or municipalities.

Introduction:
Acute diarrheal disease is one of the leading causes of morbidity and mortality in under five age group children throughout the world. It accounts for an estimated 9.9% of the 7.6 million deaths among under five age group children in 2010. Children in developing countries are worst affected. In India diarrhea contributes 10% to the mortality among under 5 age group (2013) and in all age group it contributes 6% to the mortality. Diarrhea is the second leading cause of death in under five children in India.

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The scenario is same in West Bengal. The state contributed highest numbers of diarrheal cases to the national burden of diarrhea in 2013. If we look among the districts of West Bengal, North 24 Parganas continues to contribute large no of acute diarrheal disease to state burden of diarrhea. In 2012, North 24 Parganas was the second highest contributor of diarrheal cases to the overall diarrheal burden of the state. In 2013 diarrheal deaths have been reported from the district and also the district continues to report sporadic acute diarrheal outbreaks throughout the year. So far no study has been undertaken to quantify the timeliness of intimating about occurrence of diarrheal outbreak to the district epidemic investigation team which is one of the major step to be taken.
in time for better outbreak control.

In this context we retrospectively examined diarrhoea related data of North 24 Parganas district of West Bengal to describe epidemiology of acute diarrheal disease and outbreaks due it from 2010 to 2014.

Methods:

Study settings
District North 24 Parganas is situated in southern West Bengal of eastern India. This district is the most populous district in the state as well as India.

Study Design
We did a retrospective cross sectional study.

Operational definitions
Acute diarrheal disease:
Passage of 3 or more loose stool or watery stools in past 24 hours with or without dehydration

Improved sources of drinking water:
Includes pipe water in to dwelling, piped to yard/plot, public tap/stand-pipe/hand-pump/tube-well/bore-well/covered-well/protected spring, tanker/truck, cart with small tank/drum and packaged/bottled water

Unimproved sources of drinking water:
Unprotected spring well, unprotected dug well, cart with small tank or drum, tanker truck, surface water

Improved water source away from premises
If the source is located beyond 100 meters from the premises in urban areas and beyond 500 meters in rural areas

Acute diarrheal outbreak
We considered acute diarrheal outbreaks for analysis which satisfied IDSP guidelines and we also included those which were treated as acute diarrheal outbreaks by the district health authority.

Time taken to report to District Rapid Response Team
Time taken to report to the District Rapid Response Team or District Epidemic Investigation Team was calculated from the date of onset of the outbreak

Data sources
We abstracted data from district Communicable Disease report and entered in excel. We collected outbreak related data from District IDSP cell. Sanitation & water related data were taken from Census India, 2011. We analyzed the data using excel and SPSS 22(student version) and Epiinfo version 7.

Results:
Incidence of acute diarrheal disease maintained a plateau from 2010 till 2014, ranging in between sixteen to eighteen per thousand populations. Though diarrheal deaths were reported in 2010, 2014 was a diarrhea death free year. Diarrhoeal cases got reported throughout the year between 2010 to 2014. Proportion of acute diarrheal disease cases were equal among males and females but the incidence of acute diarrheal disease ranged from 28 to 31 per thousand populations among females, whereas the incidence of acute diarrheal disease among males ranged from 24 to 28 per thousand populations.

The proportion of acute diarrheal cases required hospitalization increased over time. In 2010 only 8% cases required hospitalization for acute diarrhea, but in 2013 it turned 15% and in 2014 scenario continued to be same. In 2011 and 2012, Hasnabad block reported highest no of cases among 22 blocks of the district and the incidence was 140 and 158 per thousand populations respectively.

In 2013, Minakhan reported highest diarrheal cases with an incidence of 80 per thousand populations. In 2014 Amdanga block reported highest number of acute diarrheal cases with an incidence of 92 per thousand populations.

There was no significant correlation among incidence of acute diarrhea in 22 blocks of the district and distribution of households having improved water sources away from their premises. There was also no significant correlation among diarrheal incidence and proportion of households not having a latrine within premises and proportion of households who practice open air defecation. But We found significant correlation between incidence of diarrheal disease in 22 blocks of the district and proportion of households who were not having access to improved water source with a spearman correlation coefficient of 0.561 which was statistically significant at 0.01 level(2 tailed).

In total the district reported 28 acute diarrheal outbreaks from 2010 to 2014. The were 4(/16) diarrheal outbreaks in 2010, whereas in 2011 it was3(/10). In 2012 there were 2(/12) acute diarrheal outbreaks but in 2013 there were14(/20) acute diarrheal outbreaks. In 2010, total cases in 4 acute diarrheal outbreaks were 629 and 2 deaths were reported. That year the attack rate for 4 acute diarrheal outbreaks was 7.1% with case fatality of 0.3%. In 2011 the attack rate for 3 acute diarrheal outbreaks was 8.5% with case fatality of 0.8%. In 2012, the attack rate for 2 diarrheal outbreaks was 9.5% with case fatality of 0.8%. In 2013 and 2014, the attack rate was 4.2% and 5.9% respectively.

Case fatality was 0.1% in 2013(Table1).

Out of 28 acute diarrheal outbreaks, only in 21 diarrheal outbreaks samples were collected. But out of these 21 outbreaks where samples were collected, 9 outbreak samples
were confirmed for V. cholera.

When we analyzed the data for acute diarrheal outbreaks occurring in blocks and in municipalities separately, 50% of the blocks who reported acute diarrheal outbreaks, the median time interval between outbreak occurrence and intimating the epidemic investigation team came as high as 5 days to as low as 1 day. Barasat two block took a highest median time of 5 days to intimate the district epidemic investigation team during this study period. Baduria, Haroa, Hingalganj took lowest median time of 1 day to intimate the district epidemic investigation team during this study period (Fig 1).

The acute diarrheal outbreaks which occurred in municipal areas of the district, for 50% of those outbreaks, the median time interval between outbreak occurrence and intimating the district epidemic investigation team about the occurrence of outbreak was 2 days. Panihati municipality took a median time of 1 day from outbreak occurrence to intimating the district epidemic investigation team about the occurrence of outbreak. Rajarhat gopalpur and South dum dum municipality took a median time of 4 days from outbreak occurrence to intimating the district epidemic investigation team about the occurrence of outbreak (Fig 2).

Discussion:

This analysis in district North twenty-four Parganas showed that the incidence of acute diarrheal disease did not very much. But females had higher incidence of acute diarrheal disease than males. Though proportion of acute diarrheal cases requiring hospitalization increased from 2010 to 2014, case fatality rate came down and 2014 was a diarrhea death free year.

Place distribution of acute diarrheal disease kept changing through these five years. Through this analysis high acute diarrheal disease burdened blocks got identified and this information can further be utilized for planning preventive strategies. Significant correlation among blocks reporting higher acute diarrheal incidence and blocks with higher proportion of households not having access to improved water sources clearly indicates towards the need of inter sectorial collaborative interventions.

---

### Table 1: Number of acute diarrheal outbreak cases & deaths, North twenty-four Parganas, West Bengal, India, 2010-14

<table>
<thead>
<tr>
<th>Year</th>
<th>No of Cases</th>
<th>Population at risk</th>
<th>No of deaths</th>
<th>Attack rate(%)</th>
<th>Case fatality rate(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>629</td>
<td>8800</td>
<td>2</td>
<td>7.1</td>
<td>0.3</td>
</tr>
<tr>
<td>2011</td>
<td>124</td>
<td>1464</td>
<td>1</td>
<td>8.5</td>
<td>0.8</td>
</tr>
<tr>
<td>2012</td>
<td>119</td>
<td>1250</td>
<td>1</td>
<td>9.5</td>
<td>0.8</td>
</tr>
<tr>
<td>2013</td>
<td>1765</td>
<td>43612</td>
<td>2</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>2014</td>
<td>751</td>
<td>13888</td>
<td>0</td>
<td>5.4</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Fig 1:** Time taken by the blocks to intimate District Rapid Response Team during acute diarrheal outbreaks, North twenty-four Parganas, West Bengal, India, 2010-14

*Block code: Bhat 1, Barasat 1 block; Bhat 2, Barasat 2 block; Bst 1, Basirhat 1 block; Bst 2, Basirhat 2 block*

**Fig 2:** Time taken by the municipalities to intimate District Rapid Response Team during acute diarrheal outbreaks, North twenty-four Parganas, West Bengal, India, 2010-14

*BKP, Barrackpore Municipality; North Du, North Dum Dum Municipality; South Du, South Dum Dum Municipality*
District epidemic investigation team is responsible for organizing swift course of action from getting outbreak intimation to intervention. General assumption is that shorter the delay, better the outbreak control response [6]. But the district epidemic investigation team only can respond in time if the local authority intimates them timely about the occurrence of outbreak. In this analysis we have we found that most of the block or municipal authority took two days or more for just to report to the district epidemic investigation team about occurrence of diarrhoeal outbreak. But reasons which led to take two days or more in intimating the district epidemic investigation team about the occurrence of the acute diarrheal outbreak remained unknown.

Reference
Chronic pain abdomen is a common problem and occurs in 20% children. It is a frustrating experience by child, parent and the pediatrician. Majority of children miss school and college, hence affects their studies. Worldwide pooled prevalence of functional abdominal pain is estimated to be up to 13.5%\textsuperscript{1}. This is multifactorial and indicators are non-specific and accounts for about one-fourth of pediatric gastroenterology outpatient visits. Various etiologies presenting as pain can be classified as anatomical, inflammatory (infectious and non-infectious), metabolic and neoplastic. Broadly it can be segregated into organic and functional, where in former, a particular disease process and organ of involvement can be specifically ascertained and treated with specific therapeutic agent or a surgery, whereas in later, the cause would be more of altered gut-brain interaction\textsuperscript{2,3} with some degree of hypersensitivity of the viscera and abnormal motility\textsuperscript{4}. Since its first description by Apley and Naish\textsuperscript{5}, a host of modification has been taken place due to significant advancements in the understanding of pathogenesis of pain. Nevertheless, the case diagnosis is largely based on the patient’s symptomatology, without much emphasis on detailed investigation\textsuperscript{6,8}. The approach to case of functional abdominal pain are discussed in detail in many reviews\textsuperscript{9,10}, however here we discuss the general approach to a case of pain abdomen in children and their management.

**Types of pain abdomen**

1. **Inflammatory pain (Infectious and non-infectious):**
   Moderate to severe pain and referral to anatomical location of organ of involvement, e.g., appendicitis is characterized by severe pain in right iliac fossa whereas liver abscess presents with pain in the right upper quadrant with fever.

2. **Obstructive pain (Obstruction of hollow viscus):**
   Episodic, severe pain with crescendo-decrescendo pattern described as colicky pain, associated with secondary symptoms e.g., jaundice in case of biliary colic, abdomen distension and vomiting in intestinal colic and pain radiating from loin to groin in ureteric colic. This can be seen due to infectious, inflammatory, anatomical defects or a neoplastic etiology.

3. **Functional pain:**
   It is due to abnormal gut-brain interaction, can be periumbilical, epigastric or left iliac fossa, dull aching pain, episodic without any alarming symptoms.

4. **Referred pain:**
   Pain is due to cardiorespiratory diseases can present as upper abdominal pain due to same segmental innervation.

**Causes of pain abdomen**

A host of conditions present as pain abdomen along other symptoms depending upon the etiology and organ of involvement. Causes of pain abdomen are shown in table 1 and checklist to be followed during evaluation is listed in table 2.

**Differentiating between functional and organic pain**

Always ask and look for the red flag symptoms and signs (alarming symptoms and signs) in a case of chronic pain abdomen. Table 3 shows the selected ‘red flags’. If any of these are present patient need to be evaluated for the possible cause of organic pain\textsuperscript{11}.

**Important causes of organic chronic pain abdomen in children**

There are more than one hundred causes of pain abdomen in children depending upon the organ of involvement, which may be a superficial neuromuscular apparatus related pathology to a deep seated chronic inflammation of the pancreas. However, most common causes are discussed below.

1. **Acid peptic disorder** – This is a spectrum of conditions in which there is acid related injuries at various sites of the upper GI tract. Most common being gastric and duodenal ulcers, followed by GERD. Children present with pain abdomen, localized to epigastric region, following meals.
<table>
<thead>
<tr>
<th>Structural (Organic) Disorders</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appendicitis</td>
</tr>
<tr>
<td></td>
<td>IBD</td>
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<tr>
<td></td>
<td>Eosinophilic gastroenteritis</td>
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<tr>
<td></td>
<td>Pelvic inflammatory diseases</td>
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<tr>
<td></td>
<td>Peritonitis</td>
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<tr>
<td></td>
<td>Cholangitis</td>
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<tr>
<td></td>
<td>hepatitis</td>
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<tr>
<td></td>
<td>Pancreatitis</td>
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<tr>
<td></td>
<td>GERD</td>
</tr>
<tr>
<td></td>
<td>Gallstones</td>
</tr>
<tr>
<td>Vascular</td>
<td>Thrombosis of splanchnic vessels</td>
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<tr>
<td></td>
<td>vasculitis (Medium and small vessels)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Lead poisoning</td>
</tr>
<tr>
<td></td>
<td>Porphyria</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Anterior cutaneous nerve entrapment syndrome</td>
</tr>
<tr>
<td></td>
<td>Myofascial pain syndrome</td>
</tr>
<tr>
<td></td>
<td>Thoracic nerve radiculopathy</td>
</tr>
<tr>
<td>Others</td>
<td>Intestinal malrotation</td>
</tr>
<tr>
<td></td>
<td>Intestinal obstruction</td>
</tr>
<tr>
<td></td>
<td>Hernia</td>
</tr>
<tr>
<td></td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td></td>
<td>Neoplasms</td>
</tr>
<tr>
<td>Functional GI disorders</td>
<td>Functional dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Functional abdominal pain/Functional abdominal pain-NOS</td>
</tr>
<tr>
<td></td>
<td>Abdominal migraine</td>
</tr>
<tr>
<td></td>
<td>Irritable bowel syndrome</td>
</tr>
</tbody>
</table>
Table 2: Checklist during evaluation of a case of pain abdomen

<table>
<thead>
<tr>
<th>Duration</th>
<th>Location</th>
<th>Character of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Duration of each episode</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequency (in day/week/month/year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severity (visual analogue scale)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relation to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Food</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowel movement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of parents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated history (Aggravating and relieving factors)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Water brash</td>
<td></td>
</tr>
<tr>
<td>• Urinary complaints</td>
<td></td>
</tr>
<tr>
<td>• Headache / Migraine</td>
<td></td>
</tr>
<tr>
<td>• Trauma to the abdomen</td>
<td></td>
</tr>
<tr>
<td>• Passing of worms through body orifices</td>
<td></td>
</tr>
<tr>
<td>• Irregular bowel movements</td>
<td></td>
</tr>
<tr>
<td>• Response to antacids, H2-blockers, PPIs &amp; anticholinergics / diversion of attention</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic symptoms</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td>Joint involvement</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Cardiac, respiratory and renal symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• School performance / stress of studies / parents expectation</td>
<td></td>
</tr>
<tr>
<td>• Early waking up to get ready for school</td>
<td></td>
</tr>
<tr>
<td>• Lack of evacuation</td>
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<tr>
<td>• Lack of breakfast / empty stomach / take milk</td>
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<tr>
<td>• Student teacher relationship</td>
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<tr>
<td>• Scolding by the teacher</td>
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<tr>
<td>• Bullying in the school</td>
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<tr>
<td>• Relation with the peers</td>
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<tr>
<td>• Change of school</td>
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<table>
<thead>
<tr>
<th>Personal History</th>
<th>History of habit disorders</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Enuresis</td>
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<tr>
<td></td>
<td>• Encopressis</td>
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<tr>
<td></td>
<td>• Teeth grinding</td>
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<tr>
<td></td>
<td>• Nail biting</td>
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<tr>
<td></td>
<td>• Pica</td>
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<tr>
<td></td>
<td>• Thumb sucking</td>
</tr>
<tr>
<td></td>
<td>• Trichotillomania</td>
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<table>
<thead>
<tr>
<th>Past History</th>
<th>Discord in home</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Emotional attachment &amp; dissociations</td>
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<td></td>
<td>• Marital relations or financial problems</td>
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<td></td>
<td>• Parental separation</td>
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<td></td>
<td>• Recent illness</td>
</tr>
<tr>
<td></td>
<td>• Sexual or physical abuse</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history</th>
<th>Abdominal examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Organomegaly</td>
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<tr>
<td></td>
<td>Ascites</td>
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<tr>
<td></td>
<td>Luminal obstruction</td>
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<tr>
<td></td>
<td>Lumps</td>
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<tr>
<td></td>
<td>Spastic left colon</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Examination</th>
<th>Anthropometry and nutritional status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic signs</td>
<td>LAP</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Icterus</td>
</tr>
<tr>
<td></td>
<td>Bleeding spots</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
</tr>
<tr>
<td></td>
<td>Oral and genital ulcers</td>
</tr>
<tr>
<td>Abdominal examination</td>
<td>Organoomegaly</td>
</tr>
<tr>
<td></td>
<td>Ascites</td>
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<tr>
<td></td>
<td>Luminal obstruction</td>
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<tr>
<td></td>
<td>Lumps</td>
</tr>
<tr>
<td></td>
<td>Spastic left colon</td>
</tr>
<tr>
<td>General examination (for anxiety and other psychological conditions)</td>
<td>Trichotillomania</td>
</tr>
<tr>
<td></td>
<td>Nail biting</td>
</tr>
<tr>
<td></td>
<td>Decreased attention span and interaction</td>
</tr>
</tbody>
</table>
Table 3: “Red Flags” in History and Examination of Chronic Abdominal Pain

<table>
<thead>
<tr>
<th>“Red flags” on history</th>
<th>“Red flags” on physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age less than 4 years</td>
<td>Loss of weight or growth retardation</td>
</tr>
<tr>
<td>Localized pain away from the umbilicus</td>
<td>Anemia</td>
</tr>
<tr>
<td>Pain awakening the child at night</td>
<td>Organomegaly</td>
</tr>
<tr>
<td>Sudden severe excruciating pain</td>
<td>Localized abdominal tenderness, particularly away from the umbilicus</td>
</tr>
<tr>
<td>Family history of metabolic, infectious or peptic ulcer disease</td>
<td>Joint swelling, tenderness or heat Pallor, rash, hemias of the abdominal wall</td>
</tr>
<tr>
<td>Pain associated with changes in bowel habits, dysuria, rash, arthritis</td>
<td>Delayed sexual characteristics</td>
</tr>
<tr>
<td>Occult bleeding</td>
<td>Vaginal discharge</td>
</tr>
<tr>
<td>Repeated vomiting, especially bilious</td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms like recurrent fever, loss of appetite, lethargy</td>
<td></td>
</tr>
</tbody>
</table>

and awakens the patient early in the morning. Younger children have atypical pain which occurs anywhere in the upper abdomen, not related to meal and doesn’t have periodicity. Younger children typically have secondary cause, in form of stressors or drug intake. Gastric ulcers typically occur in cases of extensive burns, head trauma, drugs etc. whereas duodenal ulcer in older children are more likely due to have Helicobacter pylori infection. Acid suppression, prevention of reflux of gastric contents into esophagus by pharmacotherapy or lifestyle modification are the corner stones in management of APD. Duodenal ulcers without predisposing factors should be treated with anti-H.pylori therapy.

2. **Pancreatitis (acute recurrent pancreatitis and chronic pancreatitis)** – The incidence of pancreatitis is on rise; majority of cases are implicated to underlying genetic mutations or trauma. Children present with severe, recurring pain abdomen localized to periumbilical or the epigastric region associated with vomiting. Typically pain with amylase or lipase elevation more than 3 times the upper limit of normal or imaging of the pancreas showing evidence of pancreatic inflammation suffice for diagnosis of pancreatitis. In Chronic pancreatitis (CP), there would be evidence of irreversible damage in form of atrophy of the parenchyma or irregular dilatation of the duct with or without calcification. Treatment is depending on the ductal anatomy, where dilated duct requires drainage either by ERCP and stenting of the pancreatic duct (PD) or a surgical drainage. One has to look for secondary causes like hypercalcemia, hyperlipidemia, sphincter of Oddi dysfunction in children with recurrent episodes of pancreatitis.

3. **Celiac disease (CD)** – It is a multisystem autoimmune disorder predominantly involving small intestine due to exposure to dietary gluten (wheat, rye and barley). Typical presentation involves diarrhea, steatorrhea, iron deficiency anemia (IDA), abdominal distention and failure to thrive, however; atypical presentations are becoming more and more common. This is a public health problem has been reported in 1% of the general population suffering from northwestern states of India. Currently available serological markers are excellent screening tools. Tissue transglutaminase (tTG) antibody enzyme-linked immunoassay has emerged as the universally recommended screening test for celiac disease. IgA deficiency has been seen upto the tune of 2-10% in cases of proven CD, thus screening for IgA levels is mandatory and if proven to be IgA deficient then, test based on IgG levels like tTG-IgG based, anti-DGP or HLA-DQ2/DQ8 has to be done along with confirming enteropathy both morphologically and histologically. Treatment is lifelong withdrawal of wheat and wheat products along with nutritional supplementation and vigilance for other autoimmune disorders.

4. **Carbohydrate malabsorption (CM)** – The unabsorbed dietary substances are the substrates for bacterial fermentation. By-products include hydrogen, volatile fatty acids such as acetate, propionate, and butyrate and carbon dioxide. Due to excess of these agents various symptoms like abdominal cramping, bloating with distension of abdomen, diarrhea and excessive flatulence ensues. Malabsorption of lactose followed by fructose and sorbitol is the common sugar implicated with the symptoms. The prevalence of lactose malabsorption
variants widely among different races, with the lowest prevalence found in the Scandinavia and Northwestern Europe. North American Indians have high rates of deficiency. Inhabitants of Southeast Asia, Australian aboriginal population are lactose intolerant. Historical information of symptoms of temporal relationship between lactose intake and onset of symptoms, is found to be poorly predicting the lactose intolerance. Condition can be confirmed by hydrogen breath test. Response to low lactose or lactose free diet further substantiates the lactose intolerance. For fructose intolerance, fruits with high fructose contents like apple (5g/100g of apple) and pears (6.5g/100g of pear) are to be avoided.

5. **Intestinal parasites** – *Giardia lamblia* is the most common small intestinal pathogen, with nearly 30% of carriers presenting with pain abdomen, diarrhea/steatorrhea, flatulence and weight loss secondary to malabsorption. Diagnosis made by cyst or trophozoties in freshly passed stools or a more sensitive ELISA based stool *Giardia antigen* testing.

Other agents like *Ascaris lumbricoides* and *Trichuris Trichiura* are often asymptomatic, but heavy infestation leads to symptoms of pain anorexia, diarrhea, rectal prolapse and bleeding.

6. **Chronic constipation** – Chronic constipation most common referral to a Pediatric Gastroenterologist (upto 25%). This leads to gas formation, colonic distension and painful defecation. At times pain abdomen in the periumbilical or left iliac fossa would be the only presenting complaint, on detailed assessment a history of fecal retentive maneuvering and prolonged straining would be forthcoming. Fecal disimpaction, dietary modification along with maintenance laxative would improve the condition.

8. **Congenital anomalies** – Malrotation of the intestine is the most common intestinal anomaly presenting as intestinal obstruction in first few day of life. However, nearly 50% of the older children with intestinal malrotation present with chronic pain abdomen with or without emesis. Pain is often postprandial and may be accompanied by bilious emesis, diarrhea, or evidence of malabsorption. Other conditions presenting as pain abdomen are gastrointestinal duplications and cysts of mesentery. When these conditions are identified, surgery is mandatory.

9. **Genitourinary disorders** – Uretero-pelvic junction (UPJ) obstruction is established cause of chronic pain abdomen in older children, where nearly 70% of UPJ presents with only pain abdomen in the loin region. Apart from urine analysis, a detailed USG abdomen to look for kidney-ureter-bladder region is mandatory in the evaluation of chronic pain abdomen. Nephrolithiasis due to various causes present as pain abdomen. In one series of 1440 children, 51% presented with only pain abdomen.

10. **Eosinophilic GI disorders** – Eosinophilic infiltration of the mucosa and various other layers of the GI wall is a common phenomenon due to hypersensitivity to various known and unknown antigen. In esophagus eosinophil count more than 15 per HFP is suggestive of eosinophilic esophagitis (EoE). Patients present with pain abdomen, vomiting, growth failure, dysphagia and food impaction. Treatment include withdrawal of the allergic agent and immunosuppression. Eosinophilic gastroenteritis presents with pain abdomen and diarrhea. Treatment of this condition is immunosuppression.

11. **Biliary dyskinesia** – Biliary dyskinesia or hypokinetic GB disease presents with epigastric pain, nausea, vomiting and fatty food intolerance. Diagnosis is made by radiolabeled gallbladder emptying studies. Ejection fraction less than 35% suggest poor contractility and needs further evaluation and management.

**Functional GI disorders:**

Functional GI disorders are the group of disorders presenting with various GI symptomatology due to abnormality in the GI motility, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and central nervous pain sensitization.
Diagnosis of childhood functional abdominal pain disorders –
Diagnosis of functional abdominal pain disorders has been
revised recently in 2016 and a new classification has been
arrived by ROME IV group separately for infants, toddlers and
children and adolescents given in table 4.

Functional Abdominal Pain Disorders (FAPD)
ROME IV has adapted functional abdominal pain disorders
rather than abdominal pain related functional gastrointestinal
disorders, which include, functional dyspepsia (FD), irritable
bowel syndrome (IBS), abdominal migraine and functional
abdominal pain– not-otherwise specified. The diagnostic
criteria for various FAPDs are shown in table 5.

Functional Dyspepsia (FD):
This is a heterogeneous disorder arising out of various
abnormalities of the gastroduodenal function due to abnormal
gastric motility, visceral hypersensitivity, low grade mucosal
inflammation in a genetically predisposed individual.
According to various community studies, the prevalence
ranges from 0.2% to 10%. The diagnostic criteria and
character of pain is shown in table 5. Upper GI endoscopy is
not routinely required for exclusion of other diseases of upper
digestive tract, except in cases of family history of peptic
symptoms, evidence of H. pylori gastritis in near relative, age
of child more than 10 years and symptoms for more than 6
months. Various agents have been tried with varying degree of
response like omeprazole, low dose tricyclic antidepressants,
famotidine, domperidone and cyproheptadine. In refractory
cases gastric electric stimulation has been attempted with
some success.

Table 4: Functional Gastrointestinal Disorders: Children and
Adolescents (ROME IV)

<table>
<thead>
<tr>
<th>H1. Functional nausea and vomiting disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1a. Cyclical vomiting syndrome</td>
</tr>
<tr>
<td>H1b. Functional nausea and functional vomiting</td>
</tr>
<tr>
<td>H1c. Rumination syndrome</td>
</tr>
<tr>
<td>H1d. Aerophagia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>H2. Functional abdominal pain syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2a. Functional dyspepsia</td>
</tr>
<tr>
<td>H2b. Irritable bowel syndrome</td>
</tr>
<tr>
<td>H2c. Abdominal migraine</td>
</tr>
<tr>
<td>H2d. Functional abdominal pain– not otherwise specified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H3. Functional defecation disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3a. Functional constipation</td>
</tr>
<tr>
<td>H3b. Non-retentive fecal incontinence</td>
</tr>
</tbody>
</table>

Irritable Bowel Syndrome:
Pain associated with varying degrees of constipation or
diarrhea due to altered gut-brain reciprocation of the senses
due to abnormal visceral sensitivity. IBS patients tends to have
rectal hypersensitivity, and this may be related child’s
psychological status like associated anxiety, depression and
impulsiveness. Noxious early life exposure has bearing on
the development of IBS. The prevalence varies from 1.2% to
5.4% according to various studies. The diagnostic criteria
are shown in table 5. No much RCTs are available in children,
but available evidence suggests laxatives, probiotics,
peppermint oil, dietary modification with FODMAPs are
beneficial. In resistance cases behavior therapy is helpful.

Abdominal Migraine:
Abdominal migraine, cyclical vomiting syndrome and migraine
headaches share pathophysiological mechanisms as well as
being episodic, self-limiting and stereotypical with symptom
free interval between attacks. Children with abdominal
migraine and classical migraine report almost similar triggers
(stress, fatigue and travel), associated symptoms (anorexia,
nausea and vomiting), and relieving factors (rest and sleep).
Increased activity of excitatory amino acids has been found in
patients with classical migraine, possibly explaining the
efficacy of certain medications that increase gamma amino
butyric acid. Diagnostic criteria are shown in table 5. The
association of nonspecific prodromal symptoms, such as
behavior or mood changes, photophobia and vasomotor
symptoms, similar to those experienced by children with
headaches, and history of relief of symptoms with antimigraine
therapy supports the diagnosis. Various agents like oral
pizotifen, amitriptyline, propranolol and cyproheptadine has
been tried.

Functional Abdominal Pain—Not Otherwise Specified:
These are group of children who do not qualify for the diagnosis
of any other FAPDs. They have a different risk profile. They do
not have rectal hypersensitivity as seen in patients with IBS,
have lower antral contraction and slower emptying rate of a
liquid meal compared to controls. There is evidence for the
association between psychological distress. The stressful
situation like parental divorce, hospitalization, bullying and
childhood abuse. Children frequently report nonspecific and
extra-intestinal somatic symptoms that do not necessarily
require laboratory or radiological investigation. Often for
reassurance, limited diagnostic work up is performed. For
treatment amitriptyline, citalopram has been used. Hypnotherapy
and cognitive behavioral therapy have provided short and long term benefit in these patients.

Investigations in a case of chronic pain abdomen:
Investigations are directed based on the most probable organ
First line investigation includes complete Hemogram, liver and kidney function tests, stool for ova and cyst and abdominal X ray. Based on the clue and other high risk for particular etiology function investigation are undertaken (Table 6). One should be rationale in ordering the test as it would be traumatic for patient to undergo whole battery of investigations if the clinical probability is low. Table 6 shows various tests that can be ordered in cases of chronic pain abdomen. A simplified and practical approach is given in fig1.

### Conclusion

Chronic pain abdomen is a common GI complain in children. Differentiating organic from functional causes is utmost important. Organic causes are treated according to the etiology. Functional disorders are managed as per consensus guidelines of ROME IV committee. Pediatric onset abdominal pain syndromes are known to persist on to adulthood or progress to other psychosomatic condition. Thus timely recognition and management is crucial.

### Table 5: Diagnostic criteria for Functional Abdominal Pain Disorders (FAPDs)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Functional Dyspepsia</th>
<th>IBS</th>
<th>Abdominal Migraine</th>
<th>FAP-NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durations of symptoms (Mo)</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>No. of days of symptoms</td>
<td>4</td>
<td>4</td>
<td>Twice in 6 months</td>
<td>4</td>
</tr>
<tr>
<td>No. of symptoms present</td>
<td>2-1</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Postprandial fullness</td>
<td>Abdominal pain at least 4 days per month associated with one or more of the following:</td>
<td>Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)</td>
<td>Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses)</td>
<td></td>
</tr>
<tr>
<td>Early satiation</td>
<td>Changes in frequency of stool</td>
<td>Episodes are separated by weeks to months</td>
<td>Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migrane</td>
<td></td>
</tr>
<tr>
<td>Epigastric pain or burning not associated with defecation</td>
<td>A change in form (appearance) of stool in children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)</td>
<td>The pain is incapacitating and interferes with normal activities</td>
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<td></td>
<td></td>
<td>Stereotypical pattern and symptoms in the individual patient</td>
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<tr>
<td></td>
<td></td>
<td>The pain is associated with 2 or more of the following:</td>
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<tr>
<td></td>
<td></td>
<td>a. Anorexia</td>
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<tr>
<td></td>
<td></td>
<td>b. Nausea</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>c. Vomiting</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>d. Headache</td>
<td></td>
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<td></td>
<td></td>
<td>e. Photophobia</td>
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<td></td>
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<td>f. Pallor</td>
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</table>

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out.

### Table 6: Checklist for investigation

#### First order
- Complete blood counts, ESR, CRP
- Liver and renal functions
- Calcium profile
- Stool for ova and cyst for 3 days
- Abdominal Xray
- USG abdomen
- Amylase, lipase

#### Second order
- Endoscopy
- CECT/MRI abdomen
- Testing for Helicobacter pylori infection
- Hydrogen Breath Test for Small Intestinal Bacterial Overgrowth(SIBO) and slow transit
- CXR
- Mantoux

#### Third order
- Positron Emission Tomography (PET)
- Histology of the affected organ
- GI motility studies
Reference

Approach to Functional Constipation in Infants and Children
What a Primary Care Pediatrician should know?

Sankaranarayanan V. S
Department of Pediatric Gastroenterology, Kanchi Kamakoti CHILD Trust Hospital, Chennai,

Abstract

Constipation is a symptom of an underlying disorder presenting approximately 10-25% of all patients in the pediatric gastroenterology clinics. A normal bowel pattern is thought to be a sign of good health. Constipation in children is common, often chronic (more than 2 weeks) and often with consequences (chronic abdominal pain, faecal soiling, Voiding dysfunction, psychosocial stress, behavioral problems and causing distressed quality of life to the patient). Constipation is a common and long-term problem persisting for many months to years in children. Approximately 95% of childhood constipation is functional in nature without any obvious cause presenting as painful passage of dry and hard cause stools with straining (mostly to stop it) due to “stool-withholding manoeuvres”. Evaluation of a child with functional constipation requires a thorough history and physical examination including digital rectal examination in the absence of “red flags” such as fever, vomiting, bloody stools, failure to thrive, anal stenosis, tight anal sphincter and empty rectum warranting investigations to find out the cause. Treatment of functional constipation in children requires a well-designed plan and a team approach involving the child, parents, and a health care provider and involves education of the family about constipation and encopresis, fecal disimpaction, and long-term maintenance therapy of laxatives and behavioral modification. Laxatives such as magnesium hydroxide, lactulose, and mineral oil have been used in children for a long time. A new laxative, polyethylene glycol 3350, has been used as a first line drug successfully in children with constipation and encopresis.

Keywords:
Functional Constipation, Encopresis, Disimpaction, Laxatives

The number of bowel movements a normal child has in a day decreases with age and reaches adult frequencies during the preschool years.

An infant averages three to four stools a day in the first week of life, two stools a day later in infancy and the toddler years, and once a day to every other day after the preschool years. Constipation is particularly common during the introduction of solid foods to the diet, during toilet training, and at school entry. When constipation presents early in life (<6 weeks), be alert for organic disease. Neonates presenting with constipation should be discussed with a senior doctor.

Definition:

For practical clinical purposes, constipation is generally defined as infrequent defecation, painful defecation, or both. In most cases, stools are too large, too hard, not frequent enough, and/or painful to pass.

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The North American Society of Gastroenterology, Hepatology, and Nutrition (NASPGHAN 2014) defines constipation as “a delay or difficulty in defecation, present for 2 weeks or more, and sufficient to cause significant distress to the patient”.

Rome III definition of chronic constipation: Symptoms must include at least two of the following for the past two months.

- Two or fewer defecations per week
- At least 1 episode of fecal incontinence per week in a toilet trained child
- History of excessive stool retention or retentive posturing
- History of painful or hard bowel movements
- Presence of large fecal mass in the rectum
- History of large diameter stools that may obstruct the toilet

Functional constipation: No objective evidence of a pathological condition, no evidence of structural, metabolic or endocrine disease presenting beyond neonatal period with
no “red flags” due to painful bowel movements in an otherwise developmentally normal child who tries to avoid an unpleasant defecation13.

**Intractable Constipation:** Constipation not responding to optimal conventional treatment for at least 3 months13,15.

**Fecal impaction:** A hard mass in the lower abdomen (lumpy abdomen) identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination or excessive stool in the distal colon on abdominal radiography13.

Refrectory constipation is defined as recurrent impaction, not responding to routine use of laxatives, diet and behavioural therapy for atleast 3 months13,15.

**Encopresis (Fecal incontinence):** Encopresis is defined as involuntary loss of stools in inappropriate places after the developmental age of 4 years8.

Obstipation is the absence of passage of both feces and flatus and indicates underlying organic obstruction or pseudo-obstruction

**Functional constipation:** Nearly 90% of children with constipation accounts for functional constipation (cf for organic cause) in the school entry age. The contributing factors are – stool withholding habits after experience of passing painful bowel movement (vide supra sequence of events), denying natural calls in the school or teachers not giving permission to defecate, retentive defecation posturing. Characteristically red flags are absent1,4.

**Consequences**1,4,9: Hard stools are difficult and painful to push \(\rightarrow\) pooping in pain \(\rightarrow\) stool withholding \(\rightarrow\) fecal retention \(\rightarrow\) rectal distension \(\rightarrow\) excessive absorption of fluid and decreased sensory perception \(\rightarrow\) hard stools ?fissure in ano \(\rightarrow\) painful defecation with partial evacuation \(\rightarrow\) vicious cycle \(\rightarrow\) "toilet-o-phobia” \(\rightarrow\) impaction \(\rightarrow\) fecoloma formation \(\rightarrow\) affects toilet training13.

**Common causes:** The common causes of constipation in infants and children are listed in Table 1.

Neuronal intestinal dysplasia, visceral myopathy, Chagas disease, small left colon syndrome, neurofibromatosis are some of the rare causes leading on to pseudo-obstruction

**Symptoms of constipation**1,4,7,11: Awareness about the constipated patients & their perception (NASPGAN, Jpediatr gastroenterol Nutr 1999;29:61 )focussing on “D”) may be useful in arriving at the quick diagnosis in office practice, namely

- Delay (decreased frequency = < stools 3 / wk), Difficulty in defecation by straining to pass ----Dry, large, hard stools( pellety / putty / pasty, pebble),

<table>
<thead>
<tr>
<th>New born</th>
<th>Infants and children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>Poor dietary habits ,lack of fiber</td>
</tr>
<tr>
<td>Under feeding , formula feeds</td>
<td>Weaning formulas</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>Functional / psychogenic</td>
</tr>
<tr>
<td>Low anorectal anomalies eg. Anteriorly placed anus</td>
<td>IBS – Constipation type</td>
</tr>
<tr>
<td>Spinal abnormalities</td>
<td>HIE, Cerebral palsy , Mental retardation</td>
</tr>
<tr>
<td>Meconim plug syndrome</td>
<td>Drugs : antispasmodics,antimotility drugs,phenothiazines,codeine</td>
</tr>
<tr>
<td>Presacral/ pelvic mass</td>
<td>containing cough syrups, vincristine and vinblastine</td>
</tr>
</tbody>
</table>

• Defecation dissatisfaction ,
• Displeasure, no free motion and
• Dysrhythmic toileting x 2 or more weeks and
• Daily but constipated-
• Digital manoeuver assistance ?
• Soiling: 90% of functional constipation, may be mistaken for diarrhea. Child should never be blamed for soiling (Nice guidelines),rectal bleeding and urinary symptoms – 10 %
• Timing of meconium passage – most infants pass meconium <24hours
• Painful/ frightening precipitant
• Straining
• Stool withholding manoeuvers : Refusal to sit in the toilet /toilet refusal ( toileto-phobia), hiding while defaecating ,stands with crisscross poisture ,often rocks back and forth ,try to rub anus against pointed object ,screams (often face turns red) –until at least a bowel movement finally takes place
• Faecal or urinary incontinence, day or night
• Weight loss, vomiting or per rectal blood loss – suggests possible organic disease
• Stool description
• **Learning points** – Constipation is common during : the introduction of solids to the diet,
• toilet training and at school entry & precipitated by episodes of dehydration / intercurrent illness5.

**Assessment of a child with constipation:** A careful or atleast a brief history and thorough physical examination including per rectal examination will suffice to diagnose functional constipation provided there are no “red flags”.

“Red flags” suggesting organic cause of constipation are failure to thrive, abdominal distension, lack of lumbo-sacral curve, sacral agenesis, flat buttocks, patulous / anteriorly placed anus, tight empty rectum, gush of air and liquid stool on withdrawal of finger per rectal examination and absent anal wink or cremastic reflex and lower limb weakness. A summary of warning signs for organic causes of constipation are as follows (Table 2A).

**Physical exam**:

- Any dysmorphism, bony abnormality?
- Height and weight – failure to thrive?
- Abdomen – distension / faecal lumps?
- Spine – deep sacral cleft or tuft of hair or visible spinal dysraphism?
- Neurology – Neurological assessment of lower limbs
- Anal area – visually examine for fissures, fecal soiling, anal reflex & PR if required?

**Learning point** – Avoid per rectal examination during anal pain episodes

A summary of the rectal examination during the evaluation of chronic constipation follows (Table 2B).

### Table 2A. Warning Signs for Organic Causes of Constipation in Infants and Children

<table>
<thead>
<tr>
<th>Warning signs or symptoms</th>
<th>Suggested diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passage of meconium more than 48 hours after delivery, small-caliber stools, failure to thrive, fever, bloody diarrhea, bilious vomiting, tight anal sphincter, and empty rectum with palpable abdominal fecal mass</td>
<td>Hirschsprung’s disease</td>
</tr>
<tr>
<td>Abdominal distension, bilious vomiting, ileus</td>
<td>Pseudo-obstruction</td>
</tr>
<tr>
<td>Decrease in lower extremity reflexes or muscular tone, absence of anal wink, presence of pionidal dimple or hair tuft</td>
<td>Spinal cord abnormalities: tethered cord, spinal cord tumor, myelomeningocele</td>
</tr>
<tr>
<td>Fatigue, cold intolerance, bradycardia, poor growth</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Polyuria, polydipsia</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Diarrhea, rash, failure to thrive, fever, recurrent pneumonia</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Diarrhea after wheat is introduced into diet</td>
<td>Gluten enteropathy</td>
</tr>
<tr>
<td>Abnormal position or appearance of anus on physical examination</td>
<td>Congenital anorectal malformations: imperforate anus, anal stenosis, anteriorly displaced anus</td>
</tr>
</tbody>
</table>

### Table 2B. Components of comprehensive rectal examination

<table>
<thead>
<tr>
<th>Technique</th>
<th>Potential abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection(at rest)</td>
<td>Faecal soiling, Anal fissure, prolated rectum, external pile mass, blood stain</td>
</tr>
<tr>
<td>Inspection (with Valsalva)</td>
<td>Patulous anus, rectal prolapse, internal pile mass</td>
</tr>
<tr>
<td>Anal wink</td>
<td>Sacral nerve dysfunction</td>
</tr>
<tr>
<td>Palpation (anal canal)</td>
<td>Anal fissure, thrombosed external pile mass, abscess, ulcer, sphincter tone, finger gnp test in functional constipation, polyp, stenosis / stricture</td>
</tr>
<tr>
<td>Palpation (rectum)</td>
<td>Faecal mass, polyp</td>
</tr>
<tr>
<td>Palpation (rectum and abdomen, with Valsalva)</td>
<td>Incomplete anal sphincter contraction, Paradoxical anal sphincter contraction, absence of anal sphincter contraction, incomplete perineal descent</td>
</tr>
</tbody>
</table>
Table 3. Difference between Hirschsprung disease (HD) and functional constipation

<table>
<thead>
<tr>
<th>Functional constipation</th>
<th>Hirschsprung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More common</strong></td>
<td><strong>Less common</strong></td>
</tr>
<tr>
<td>Meconium history – NORMAL</td>
<td>Delayed passage</td>
</tr>
<tr>
<td>Onset beyond infancy</td>
<td>From birth</td>
</tr>
<tr>
<td>Fecal soiling</td>
<td>Spurious diarrhoea</td>
</tr>
<tr>
<td>Abdominal distension - rare</td>
<td>Common</td>
</tr>
<tr>
<td>Loaded rectum</td>
<td>Empty rectum, gripe, finger, gush of air and fluid on release</td>
</tr>
<tr>
<td>FTT /enterocolitis – rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

- USG abdomen: Post void residual urine in bladder, bladder wall thickening
- Colonic monometry in refractory constipation
  Rectal mucosal biopsy in Hirschprung’s, Intestinal neuronal dysplasia and Solitary rectal ulcer
  Don’t forget: Screening for hypothyroid, diabetes mellitus, lead poisoning, celiac, hypercalcemia

**Treatment**: The main steps in the management of constipation are:
- Ensure there is no organic cause, treat if found
- Diet, Fluid, Exercise, Toilet training
- Pharmacotherapy
- Disimpaction
- Maintenance – prevention of reimpaction
- Behavior therapy
- Education & reeducation (counseling)

**Disimpaction**: Ideal to get second opinion before starting disimpaction. Use correct doses of laxatives. Check preparations before use.

Polyethylene glycol (PEG) lavage solution for evacuation of impacted stools in the colorectum is only the first line drug preferred as it is noninvasive in a dose of 1-1.5 g/kg/day, given over 4 hours for at least 3-6 days or 20-25 ml/kg/hour as a reconstituted solution by naso-gastric tube up to 1000 ml/hr until clear colonic content is evacuated and under supervision in small children; Ryle’s tube may be required for administration. Single dose of prokinetic and intravenous fluids may be needed in some children.

**Enema**: is faster but invasive and tendency for hospital and defecation phobia not preferred by most; Proctoclysis (sodium phosphate enema) 2.5 ml/kg maximum up to 133 ml/dose for 3-6 days especially if PEG is not available for disimpaction.

**Digital disimpaction**: Ideal for children refractory to all measures.

---

A. Plain x-ray abdomen showing colon loaded with feces in a child with fecal impaction
B. Habitual constipation
C. Hirschsprung disease
occasionally helpful
For infants, glycerine suppositories are recommended instead of enemas and lavage. Consultation with a pediatric gastroenterologist or pediatric surgeon is appropriate if the child's history or examination findings suggest an underlying organic cause (e.g., Hirschsprung disease). Also seek consultation when the child fails routine therapy or when management is otherwise complex.

**Constipation: maintenance treatment**
- Inform parents the need for long term treatment and regular follow up to make sure faecal impaction does not become reestablished soon after disimpaction of stools or as a first step, if there is no disimpaction.
- Maintenance medication, diet, fluid intake and exercise, toilet training to be continued for several weeks after regular bowel habits are established.
- Medication: PEG 3350 with electrolytes if no faecal impaction.

Dose: Half the dose used for disimpaction regimen (1 gm/kg/day)
Dose can be adjustable depending on symptoms & response
Side effects: Nausea, vomiting and bloating (osmotic effect)
Add stimulant laxative (lactulose / lactitol for hard stools) if PEG is not effective
- No abrupt stoppage of treatment
- Reduce dose gradually over a period of months depending on stool consistency and frequency. Initial weekly review for 2 to 3 weeks with parents & stool diary helpful.

**Education:**
- Explain physiological basis of constipation and soiling. NICE recommend that the child should never be blamed for soiling.
- Need to adhere to long term medication and a regular toilet pattern
- Avoid antispasmodic and antidiarrhoeal drugs for pain & fluid faecal soiling (pseudodiarrhoea)
- If needed, meeting with teacher in school
- As optimum dose is unpredictable for any child, initial weekly meeting for 2-3 weeks is suggested to help family titrate the dose.

Maintenance therapy is aimed to avoid reimpaction and to ensure regular passage of stools by diet, laxatives and behavioural therapy. We train the care givers a simplified use of stool diary and recording of daily stool and defecation details.
each meal. Follow the routine every day, even during holidays and vacations.

Be supportive. Reward your child’s efforts, not results. Give children small rewards for trying to move their bowels. Possible rewards include stickers or a special book or game that’s only available after (or possibly during) toilet time and don’t punish a child who has soiled his or her underwear.

Diet in constipation includes fiber containing items like sprouted whole grains, pulses, beans, sorbitol rich fruits (apple with peel, guava, pomegranate, pear, and prune juice), green leafy vegetables and water. Fiber intake is recommended over 2 years of age and the dose is calculated as age in years plus 5 g/day. Involvement of dietician is beneficial.

**Behavioural therapy** – Aim scheduled toileting to establish a regular bowel habit, maintenance and discussion of a bowel diary, and use of encouragement and rewards systems includes proper toilet training, after feeds, three times daily for 5-10 minutes. Pre-toilet training can be started soon after one year of age though ideally after 2 years of age. One word, one person, one year, one stool/day, one sitting posture policy is ideal. School teachers are informed about the child’s problem.

**Laxatives**

Many children require laxative therapy for months to years. The choice of the medication depends on the child’s preference, safety, cost, ease of administration, and the practitioner’s experience. Laxatives such as lubricants, osmotic and stimulants for maintenance are required for a longer period even over years to regulate the bowel habits and hence the need for explaining to this parents at the onset.

**Follow-up schedule**

- Weekly, Fortnightly, Monthly till normal bowel habit is attained. Followed by 2-3 monthly x 1 or 2 years. Record during visits: stool history, associated symptoms, per abdominal and rectal examination. Monthly follow up till regular bowel movement is achieved. Check diary, physical and rectal examination. Laxative dose is to be adjusted

**Yearly follow-up.**

Points to be remembered while treating infants with constipation are to exclude organic causes such as HD, cystic fibrosis, cretinism, etc to avoid mineral oil, stimulant laxatives and glycerine enemas for fecal impaction. Stool softeners like sorbitol containing juices, lactulose or lactitol and polyethylene glycol (PEG) and magraco are recommended in infants.

Don’t forget to look for the related comorbidities such as early satiety/small meals/ poor appetite, Recurrent abdominal pain/ irritability, Urinary tract infections, Voiding dysfunction ,Enuresis, Encopresis, Psychological effects, Quality of life – suboptimal[7,10,11].

**Refractory constipation**[10,15]

More than 30% of children at primary care paediatrician level with refractory constipation with recurrent impaction, not responding to routine use of laxatives, diet and behavioural therapy for atleast 3months[15] needs evaluation of organic diseases and timely referral for specific investigations such as rectal biopsy or to rule out anatomic defects by referral to pediatric surgeons or pediatric gastroenterologists for anorectal manometry, metabolic screen (hypothyroidism, cystic fibrosis, hypercalcemia, celiac disease, lead poisoning, mental retardation, etc.), colonic transit time (CTT) study, colonic manometry or ileo-colonoscopy, planning work for spinal dysraphism by MRI of lumbosacral spine and brain[15].

These patients, especially school-going children, may need to be diagnosed whether they are functional or organic, or irritable bowel syndrome (IBS)-constipating type or if functional whether they are of slow transit or normal transit type or pelvic floor dysfunction(rectoanal dyskinesia) which needs biofeedback training, a challenging task in our set -up[15].

**Do’s and Don’ts in costipation management:**

- Do not perform a rectal exam in acute painful stage
- Anal inspection is a must
- Investigations not needed as a routine
- Look for urinary infection (voiding dysfunction)
- Reassure parents on safety of laxatives
- Avoid rectal medications if possible
- Avoid antispasmodics for abdominal colic
- Stress on periodic and longterm followup
- During disimpaction treatment overflow of the laxative by passing the impacted dry stool may be mistakenly interpreted as a complication of laxative in use.

**Key messages**

- Constipation is a common problem in children and often presents as chronic periumbilical pain with difficulty and delay in passing dry stools.
- Nearly 95% is of functional and often does not need any investigation; diagnosis is invariably clinical including per rectal examination and long term follow up(months to years) is essential.
- Management includes drugs, diet modification, toilet training and regular follow up and behavioural therapy.
- Refractory cases need referral to the pediatric gastroenterologist to further work up (such as CTT) to know the cause and for management guidance.
### Table 4: Laxatives: dose and side effects (Modified from NASPHAGAN Position Statement\textsuperscript{15}

<table>
<thead>
<tr>
<th>Laxative</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubricant: Mineral oil</td>
<td>1-5ml/kg/day or 1-2g/kg once daily or in divided doses for a short period only</td>
<td>Do not give to infants. Anal leakage, lipid pneumonia</td>
</tr>
<tr>
<td>Osmotic: Lactulose or Lactitol or Sorbitol</td>
<td>1-3 ml/kg/day in two doses</td>
<td>Bloating, cramps and diarrhea</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>5-10ml/kg/day (Laxo PEG FC 17g/50ml) or 1-1.5g/kg/3-6 d</td>
<td>Nausea, vomiting, cramps, diarrhea</td>
</tr>
<tr>
<td>Magnesium hydroxide(Milk of Magnesia)</td>
<td>1-3ml/kg/day in 1-2 doses</td>
<td>Hypermagnesemia, hypophosphatemia, hypocalcemia</td>
</tr>
<tr>
<td>Stimulant: Bisacodyl</td>
<td>&gt;2 years: 5-10 mg daily oral. 5mg per rectally</td>
<td>Cramps, diarrhea, anal irritation</td>
</tr>
<tr>
<td>Senna</td>
<td>&gt;6 years 5-15 ml/day (8.8mg/5ml) 2-6 years 2.5-7.5 ml/day</td>
<td>Melanosis coli, hepatitis</td>
</tr>
</tbody>
</table>

The dose of laxative has to be adjusted individually aiming at 1-2 soft stools/day and not merely liquid stools in a day\textsuperscript{15} (in a child with stool retentive habits where the liquid laxative often by-passes the impacted dry, pasty, hard stools in the rectosigmoid colon and comes out as a fluid which is invariably mistaken as a good response to the laxative or laxative induced diarrhea when the attending paediatrician is forced to change the drug or reduce the dose of laxative and precipitate further impaction and abdominal colic with lumpy abdomen causing pain among patient, parents and paediatrician – indicating the right time for referral to the pediatric gastroenterologist)

### Reference

11. IAP – ISPGHAN Module – Constipation in children
Gastroesophageal reflux (GER) is common in ‘normal’ population. When GER causes changes in lifestyle of the patient, it is called gastroesophageal reflux disease (GERD). While GER is physiological, GERD is pathological. It is important to distinguish between these two and use investigative resources on GERD only.

GERD is common in infants and children in the developed world. Most neurologically normal children with GER have an excellent prognosis. Only children with ‘red flag’ signs require intervention. Combinations of clinical and investigational data often help in management and prognostication of these children. The goal of this article is to provide a critical overview into the clinical spectrum, and investigations of GERD leading to therapeutic decision making; from, as far as possible, Indian perspective.

**Incidence and epidemiology:**

Generally, GERD in divided into two types, infant and adult. The exact incidences of GERD in various age groups are not known.

All babies have GER by adult standard, and grow out of this by 2 years of age. Those who continue to have reflux symptoms after 2 years of age are likely to have adult type GERD. This was somewhat corroborated in a recent collaborative practice based study. Vomiting, the most common manifestation, was seen in 50% infants in their first 3 months of life, 67% of 4 months olds and 5% of those between 10 and 12 months. The peak incidence of vomiting (67%) was found at 4 months. It decreased dramatically to 21% between 6 and 7 months of age. Parents perceived the vomiting to be a ‘problem’ based on frequency (>1/day) and volume (>30ml) of regurgitation, incidence of increased crying or fussiness, reported discomfort with regurgitation and back arching. The ‘problem’ regurgitation peaked at 6 months of age (23%) rapidly decreasing to 14% at 7 months of age. Only 0.2% of these children were treated with medications.

Adult type GER appears to be a life-long disease, punctuated by exacerbation and remissions. These children can keep well for years in between exacerbations. The symptoms are better articulated and hence well defined in this group. In children between 3-17 years, heartburn, epigastric pain and regurgitation were reported in approximately 1 to 3.5%. Epigastric pain was reported in 7.2% of 3 to 9 year olds while between 5.2 to 8.2% of 10-17 years old self reported these symptoms. Only 1.3% of the 10-17 years old used over the counter medications.

It is difficult to comment on the incidence of gastroesophageal reflux disease in Asia in general and India in particular due to shortage of objective data. The incidence of GERD seems to be increasing in adults (up to 39%) with Indian ‘race’ being vulnerable in a multiethnic population. A community-based study in Japan revealed significant regurgitation in 47.1% of 1 month olds, 28.8% at 4 months and 6.4% at 7 months of age. This data is comparable to those reported from the USA. In a tertiary care based study from India, regurgitation and/or vomiting was reported in 54.6% of infants below 6 months, 15% among those between 6 and 12 months and 10.2% in infants between 1 and 2 years of age. In children undergoing gastroesophageal scintigraphy for lower respiratory tract infection, incidence of GER was 1.7 times higher in children below 18 months of age when compared to those above 18 months. A recent study has suggested a weekly reflux incidence of up to 17% in older children.

A fascinating fact is the gradual increase in the incidence of reflux since the second world war in the Western Countries and now recognition of GERD in India with conceivably improved standard of living. Increased average feeding volume, use of car seats and increased parental attention due to smaller families have been cited as the possible cause. One can possibly add advent and availability of trained pediatric gastroenterologists looking for work to that list!

Children with compromised neurological conditions such as cerebral palsy/mental retardation are at high risk of having complicated gastroesophageal reflux. It is estimated that about one third of such children will have significant GERD. In this discussion, we will primarily focus on neurologically compromised conditions.
normal children.

To summarize, gastroesophageal reflux is common in infants, most of them outgrow reflux as they grow older. The incidence of GERD in infants in Asia, based on the limited amount of data from India and Japan, appears to be similar to those reported from USA. In older children less than 10% report symptoms suggestive of GERD.

**Clinical spectrum**

**Infants:**

As in adults, majority of the children with gastroesophageal reflux escape medical attention. According to the iceberg model (Figure-1), only 9% of the infants with GER get medical attention. Vomiting and spitting up are the most frequent symptoms in these children. In infants, even minor reflux manifest as vomiting due to low volume of esophageal lumen. Majority of these babies grow and develops normally with episodic vomiting. These babies are called ‘happy spitters (the underwater section of the ‘iceberg’). However, excessive vomiting, nonspecific response to esophageal pain as well as esophageal symptoms due to esophagitis, growth failure and unique respiratory complications such as apnea, ALTE, reactive airway disease, stridor and recurrent pneumonia constitute the so called ‘red flag signs’ (Table-1)).

These babies may need detailed evaluation. Most of these infants, as discussed above, grow out of reflux. Their chance of having reflux as an adult is unknown. However, about 5 % of children continue to have symptoms beyond 2 years of age and are less likely to grow out of it.

**Children above 2 years:**

Older children present with heartburn, abdominal pain, regurgitation and complications such as Barrett’s esophagus, stricture and possibly asthma. Their symptoms can be episodic with intermittent apparent disease free period.

The common clinical presentations of GER in infants and older children are given in Table 1. Some of these, especially the respiratory symptom in infants will be discussed in detail with a critical review of available pediatric literature.

![Figure 1: Gastroesophageal Reflux in Infants and Children](image)

**Table 1: Presentation of Gastroesophageal reflux**

<table>
<thead>
<tr>
<th>In infants</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent vomiting</td>
</tr>
<tr>
<td></td>
<td>Regurgitation</td>
</tr>
<tr>
<td><strong>Constitutional</strong></td>
<td>Failure to thrive</td>
</tr>
<tr>
<td></td>
<td>Non specific</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Crying episodes</td>
</tr>
<tr>
<td><strong>Esophageal symptoms</strong></td>
<td>Poor feeding/interrupted feeding</td>
</tr>
<tr>
<td></td>
<td>Arching back</td>
</tr>
<tr>
<td></td>
<td>Posturing (Sandifer’s syndrome)</td>
</tr>
<tr>
<td></td>
<td>Hematemesis</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td><strong>Respiratory symptoms</strong></td>
<td>Apnea</td>
</tr>
<tr>
<td></td>
<td>Acute life threatening episodes (ALTE)</td>
</tr>
<tr>
<td></td>
<td>Reactive airway disease</td>
</tr>
<tr>
<td></td>
<td>Coughing/choking</td>
</tr>
<tr>
<td></td>
<td>Stridor</td>
</tr>
<tr>
<td></td>
<td>Recurrent pneumonia</td>
</tr>
</tbody>
</table>

- **In Older children**
  - Heart burn
  - Abdominal pain
  - Regurgitation
  - Asthma
  - Dysphagia/odynophagia
  - Chronic anemia/ hematemesis
  - Food impaction

**Investigations**

The goals of investigation (Table-2) can be summarized as

1. To document GER when reflux is clinically occult or to document effectiveness of treatment.
2. To establish a cause and effect relationship between reflux and symptoms such as irritability, heart burn, coughing, choking etc. This includes diagnosing non erosive reflux disease (NERD) and functional heartburn (Figure 4).
3. To exclude exacerbating causes such as gastric emptying delay, anatomical abnormalities
4. To document tissue damage due to reflux and to exclude associated conditions that can have an impact on treatment and prognosis. These include looking for reflux or eosinophilic esophagitis, esophageal strictures, H, Pylori, Barrett’s esophagitis etc.
Table 2: Investigations for GERD in Children

<table>
<thead>
<tr>
<th>Goal</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Documenting reflux</td>
<td>Multichannel Intraluminal Impedance Study</td>
</tr>
<tr>
<td></td>
<td>Long term pH monitoring of the esophagus</td>
</tr>
<tr>
<td></td>
<td>Upper GI barium (see text)</td>
</tr>
<tr>
<td></td>
<td>Scintigraphy</td>
</tr>
<tr>
<td>2. Documenting tissue damage/effects of GERD</td>
<td>Upper GI endoscopy</td>
</tr>
<tr>
<td></td>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td></td>
<td>Occult blood in stool</td>
</tr>
<tr>
<td></td>
<td>Scintiscan (lung scan, see text)</td>
</tr>
<tr>
<td>3. Establishing GER as etiology of episodic symptoms</td>
<td>Long term pH monitoring of the esophagus</td>
</tr>
<tr>
<td></td>
<td>Sleep study (polygraph)</td>
</tr>
<tr>
<td>4. Documenting associated aggravating conditions</td>
<td></td>
</tr>
<tr>
<td>i) Anatomical gastric outlet obstruction</td>
<td>Upper GI barium</td>
</tr>
<tr>
<td>ii) Gastric emptying delay</td>
<td>Scintiscan</td>
</tr>
<tr>
<td>5. Provocative tests (Obsolete)</td>
<td>Bernstein’s test (pediatric modification)</td>
</tr>
<tr>
<td>6. Associated conditions affecting management</td>
<td>Esophageal motility</td>
</tr>
</tbody>
</table>

All these goals are not required to be met even in the most complicated patient. Investigation has to be tailored to individual patient so that the results are of therapeutic and/or prognostic value.

The major investigative tools will be discussed briefly followed by a discussion on investigative approach.

**Barium upper GI x-ray:**

It is probably the most commonly ordered investigation in GER. This test is NOT for documentation of reflux. As reflux is known to be intermittent, absence of reflux during barium study does not rule out GER.

On the other hand, healthy adults have about 22 refluxes per day. So one or two reflux episodes seen during the study period do not establish GER either. This study lacks both sensitivity and specificity for GER. However, an incidental finding of reflux with aspiration and/or features of esophagitis may suggest severe reflux. This study is commonly ordered to exclude associated anatomical abnormalities such as tracheoesophageal fistulas and to exclude gastric outlet obstruction, microgastria and malrotation. It can also provide crude indication of esophageal motility (achalasia, tertiary waves or hypoperistalsis). Functional gastric emptying delay may not be apparent in barium studies.
Upper Gastrointestinal endoscopy and biopsy:

It reveals esophagitis, presence of complications such as stricture or Barrett’s esophagus, associated acid peptic disease, H. Pylori infection (which may affect peptic esophagitis) and other unrelated problems. Peptic esophagitis is a reliable indicator of GERD. However, it may have to be distinguished from eosinophilic esophagitis. At times these two conditions may co-exist. Unlike adults, a normal appearing esophageal mucosa does not rule out esophagitis, especially in young children. About 95% of the children with biopsy proven esophagitis have abnormal pH study. However, in selected population of patients, only 50% with GER by pH probe study had esophagitis. Severity of reflux, as detected by pH probe study, does not correlate with presence of esophagitis. Similarly grade of severity of esophagitis does not correlate with clinical symptoms.

Long term intraluminal pH study of the esophagus:

This test involves putting a pH sensing probe inside the esophagus and continuous sampling of intraluminal pH for a prolonged period (usually 24 hours). The data is stored in a portable computer (Digitrapper®), downloaded to a PC and analyzed with special software. The graphical record of the intraluminal pH can be correlated in real time with events such as apnea, heartburn etc. Numerical analysis allows calculations of various parameters such as number of refluxes, long reflux episodes, percentage of time the intraluminal pH fell below 4 etc. Generally, event correlation with reflux episodes, documentation of low intraluminal pH for a high percentage of time of the total duration of the study and long reflux episodes (longer than 5 Minutes) are thought to be indicative of presence and severity of reflux. A detailed discussion of the pH study is beyond the scope of this article. Suffice it to say that though proclaimed as the gold standard for GER, the technique, duration and interpretation of data varies greatly among experts. The accepted norms are based on small number of patients and may not be universally applicable. Reproducibility of the data is also doubtful.

However, this test is still a useful diagnostic tool in the hands of an experienced clinician. Two most valuable uses of pH probe studies are:

1. Documenting the correlation between fall of esophageal pH and episodic symptoms such as crying, coughing, arching back etc. and
2. To evaluate adequacy of acid suppression during treatment with antacids.

Several scores are popular for differentiating normal pH probe study from abnormal ones. In our opinion, both Johnson-DeMeester and Boixs-Ochoa scores are statistically flawed. Both are based on paremtric treatment of reflux data which are now to be non-parametric. The only pH reflux parameter that has shown any consistency in reflux index (percentage of time pH is below 4). Even then there is controversy what should be the upper limit of normal (5% or 10%).

Multichannel Intraluminal Impedance (MII) – pH study:

In our institution pH probe study is being replaced by Multichannel Intraluminal Impedance (MII) study of the esophagus. This study addresses two major weaknesses of a traditional pH probe study. First, it can detect refluxes that are not acidic (non-acid refluxes) and secondly this study can document the extent of the proximal migration of the refluxate in the esophageal lumen. This technique also offers simultaneous conventional pH metry.

Physics of MII study:

Impedance of a ‘channel’ (the area between 2 electrodes) changes depending on what is connecting the electrodes. If these two electrodes are lying in the esophageal lumen, then normally they will be connected by esophageal wall, air and some saliva. All these materials have low conductance. So the impedance in the channel will be high. However, when the refluxate arrives at this channel, the conductance will improve due to the high electrolyte content of the refluxate. The Na+, K+, Cl- etc. ions in gastric content will facilitate passage of electricity between the two electrodes. So the impedance of the channel will fall. When the refluxate leaves the channel, the impedance will regain its baseline highvalue (Figure -2). Thereby a wave pattern is created representing passage of the refluxate through the channel. When simultaneous recording of impedance is made in multiple channels along the esophagus, the migration and proximal extent of the reflux episode is seen graphically (Figure 3).

Detection of reflux by MII is not dependent on the pH of the refluxate. It is dependant on the physical mass of the refluxate causing changes in the electrical property in the esophageal lumen. This study is capable of detecting refluxes that are not acidic. As a rule, MII detects more refluxes than a traditional pH probe study. There is controversy on how to interpret the ‘excess’ refluxes. MII also allows the investigator to define the upper limit of proximal migration of the reflux (Figure 3). This study is particularly useful for extra esophageal reflux symptoms often associated with non-acid reflux.

Scintigraphy:

This test involves feeding technetium-labeled formula or food and scanning the areas of interest such as the stomach, esophagus and lung. Scintigraphy can detect non-acid reflux as well. The sensitivity of nuclear scan in detecting GER has varied widely in reported literature (between 15 and 59%) with
Organ is empty
High impedance
Bolus Movement
Organ is empty
High impedance
Ionic bolus spanning segment Low impedance

Figure 2: Reflux detected by change of impedance.

Figure 3: Snapshot of a MII study

relatively high specificity (83 to 100%)\textsuperscript{17}. The role of scintigraphy in detecting GER is not clear. We commonly use scintigraphy for gastric emptying study, a common association with GER in young children\textsuperscript{18}. Another potential benefit of this study is the ability to detect aspiration of gastric contents into the airway. However, our experience has not been encouraging with this aspect of the scan.

Specific Clinical Conditions:

Apnea and acute life threatening episodes (ALTE) and Apnea – It is presumed that acid reflux causes apnea by an esophagolaryngreal reflex as well as possibly by mechanical obstruction of the airway. An obstructive or a mixture of obstructive and central pattern of apnea has been described as the hallmark of GER associated apnea. Gastroesophageal reflux has been reported in as much as 70% of children with apnea\textsuperscript{20}. However, mere co-existence of reflux and apnea does not establish the cause and effect relationship. In a recent study gastroesophageal reflux preceded apnea in only 6.4% of the infants. Most of the GER and apnea episodes were not linked chronologically. In fact, most of the GER occurred following apnea, thereby raising the possibility of apnea causing GER\textsuperscript{21}. In selected groups such as post feeding apnea and awake apnea, the GER associated apneas were more frequent\textsuperscript{22}.

The association between ALTE and GER follows the same logic as apnea. The picture is made more complicated by the infrequent and unpredictable occurrence of ALTE. Mere documentation of GER does not guarantee that treatment of GER will prevent further occurrence of ALTE. However due to the potential for mortality and emotive nature of sudden infant death syndrome, clinicians are often under pressure to treat the potential etiology aggressively.

In summary, there is no convincing evidence that GER is the primary cause of apnea and ALTE in most of the infants. However, GER may play a significant role in a subgroup of these patients.

Clinical approach:

History is probably the most useful tool in establishing a relationship between GER and apnea/ALTE. A careful review of chronology of events, relationship with feeds, presence of feeds in the upper respiratory tract and larynx are important pointers towards this association. We have abandoned doing the pH probe studies to document reflux in infants with apnea. If no anatomical abnormality is detected by barium study, a therapeutic trial with antacids and prokinetic (Table -4) may be attempted. Gastric emptying study is recommended but is seldom useful to make therapeutic decisions. Most of these babies have a delayed gastric emptying with doubtful improvement after prokinetics such as metoclopramide. I do not advise prokinetics routinely because of its potential side effects and doubtful clinical efficacy. Continuous transpyloric (TP) feeding is a novel way of treating these infants. TP feeding is expected to eliminate gastroesophageal reflux. A significant improvement on TP feeding and recurrence of apnea on resumption of oral feeding is a practical approach to establish GER as the etiology of apnea\textsuperscript{23}. In some cases swallowing disorders may have to be ruled out with the help of an experienced speech pathologist.

Asthma

Gastroesophageal reflux has been suspected to be one of the etiologies of asthma. It is suspected that GER associated esophagobronchial reflex and/or microaspiration may lead to bronchospasm. There had been anecdotal reports of
resolution of asthma on treatment of GER. Asthma itself can also cause GER. In a comprehensive evidence based medicine (EBM) review, no overall improvement was noticed in the asthmatic subjects with GER (but who were not recruited for GER associated respiratory symptoms) on antireflux medication. The number of pediatric subjects in qualifying studies was too small to make any conclusion in children. While this review suggests lack of appropriately designed studies in children, it does not rule out GER as the cause of asthma in a subgroup of patients. As mentioned above, asthma and GER can exist as co-morbidity without any etiological association. Recently, non-acid reflux has been postulated as another etiology in asthma and other respiratory associations. Recently, non-acid reflux has been postulated as another etiology in asthma and other respiratory complications of GER.

The approach to GER related asthma has to be individualized based on clinical parameters such as presence of reflux symptoms, association with feeds, severity of asthma, response to conventional treatment and presence or absence of extraneous factors. In infants, a therapeutic trial of antireflux medications may be attempted. If GER is strongly suspected to be the cause of reactive airway disease, simultaneous upper gastrointestinal endoscopy (to look for esophagitis) and bronchoscopy with bronchoalveolar lavage (for lipid-laden macrophages) may be attempted to link GER with asthma. Long-term pH monitoring of the esophagus may reveal association between wheezing episodes and fall of intraluminal pH. However, multichannel intraluminal impedance (MII) study of the esophagus provides a much-detailed picture of the gastroesophageal reflux. This pH independent technique not only detects reflux, but also documents the extent of proximal migration of the reflux episode. Children with large number of refluxes with proximal migration are at an increased risk of microaspiration leading to reactive airway disease. Gastric scintigraphy, to document aspiration of gastric content into the lungs, has been postulated as a useful investigation. In our institution, this test has not been of great diagnostic value. Generally speaking, GERD, if documented, should be aggressively treated in an asthmatic.

Recurrent Pneumonia

Theoretically GER can cause recurrent aspirations leading to pneumonia. This is more likely to happen in a neurologically impaired child. In a recent study, only 5% of recurrent pneumonia in children was found to be due to GER. An association between feeding and respiratory symptoms was common in these children. Oropharyngeal incoordination (common in neurologically impaired children) and immune deficiency were the two most common causes. In an appropriate clinical setting, an approach similar to those for asthma may have to be adopted to link GER with recurrent pneumonia. If such a link is established, surgical treatment may have to be undertaken as aspiration can be life threatening and non-acid reflux (after treatment with antacids) can cause severe pneumonia.

Esophageal symptoms

Infants – infants can show non-specific reaction to esophageal pain such as excessive crying and irritability. These may have to be distinguished from colic, behavioral pattern and neurological abnormalities. Arching back, refusal or poor feeding and posturing (Sandifer's syndrome) are more specific of esophagitis in infants. However, a frustrated child often withdraws from the caregiver, mimicking arching back. Poor feeding may be due to any illness and seizure disorders can produce Sandifer’s syndrome like picture. Anemia, heme positive stool and hematemeses complete the clinical picture. GER is more likely to produce a constellation of symptoms with vomiting/regurgitation being the common denominator.

Older children – Heart burn, odynophagia, dysphagia and regurgitation are common symptoms of GERD. Occasionally chronic or recurrent gastrointestinal bleedings may be the presenting symptom. Food impaction in esophagus may indicate stricture formation or severe inflammation. Other types of esophagitis such as eosinophilic esophagitis can mimic peptic esophagitis.

Recently the concept of Non Erosive Reflux Disease (NERD) and Functional Heartburn have been introduced. Except for lack of visible inflammation and erosions on endoscopy, there are no difference between erosive esophagitis and NERD. A pH probe or preferably MII-pH study is required to distinguish different types of heartburn.

Failure to thrive

A static or decreasing weight (when serial weights are done) or less accurately a weight below 5th percentile (when single weight measurement is available), with vomiting is a cause of concern. Other causes of vomiting and failure to thrive should be ruled out, bilious vomiting is an emergency, an upper gastrointestinal contrast imaging (preferably with water soluble dye) should be ordered immediately to rule out malrotation or other causes of post ampulla small bowel obstruction. This test may also have to be ordered in refractory unexplained non bilious vomiting for other anatomical abnormalities of the upper gastrointestinal tract or intermittently symptomatic partial malrotation (a controversial issue).

The intake and amount lost due to vomiting are to be accurately measured and a gross calorie count done to explain the growth failure. This is often a difficult task and may require a short observational admission. The inpatient stay also allows for documentation of feeding practices and teaching appropriate techniques to the care giver.
H2 blocker (ranitidine 6 mg/kg/day) with anti-reflux measures, continuous nasogastric and if ineffective nasoduodenal feeds may be tried in that order. An endoscopy may have to done, at the discretion of the gastroenterologist looking for other unusual causes of vomiting such as refractory GERD, eosinophilic esophagitis, viral or fungal infection of the upper GI tract.

Reference
Step-up vs top-down is a phrase used in the management of patients with Inflammatory Bowel disease (IBD) that represents therapeutic strategies which start at opposite ends.

Step-up refers to a strategy of matching the intensity of therapy to the severity of disease. The conventional approach to IBD treatment is the so-called ‘step-up’ strategy, with sequential escalation of drugs depending on disease severity, location and response to treatment. In this treatment paradigm, biologics are considered the final line after 5-aminosalicylates, steroids, exclusive enteral nutrition, immunomodulators and more potent immunosuppressants such as cyclosporine and tacrolimus.

Top-down refers to the early initiation of intensive therapy in every patient, assuming that complications of disease can be avoided and function and quality of life will be improved by such rigorous therapy. Attaining deep remission or mucosal healing was considered an essential step in effective management. Efficacy studies examining the early use of immunomodulators such as thiopurines in children have formed the basis of what is now known as “top-down” therapy. This term equates to “aggressive initial therapy” with “disease modifying agents” such as biologics, often in combination with immunomodulators.

Problems and drawbacks with step up approach

In the conventional therapy or step up approach steroids are the pivotal drug in the management of more than 60% of children. Though remission is attained the long term outcome at the end of 1 year is disappointing, many require additional treatment and more than 30-40% became steroid dependent. Growth retardation is a unique feature of pediatric IBD (P-IBD) and this problem gets further aggravated in those on long term steroids and is an important drawback of steroid therapy. In adults more than 30% on conventional therapy require surgery by the end of one year. There is also a great disparity between the clinical response and mucosal healing. The uncontrolled persistent inflammation progresses to fibrosis and further tissue damage. The lack of expected response and disparity between clinical and colonoscopic findings result in variable protocols. Immunomodulators such as azathiopurine, 6-mercaptopurine and methotrexate were introduced about two decades ago as steroid sparing agents and were included in the protocol for the management of P-IBD. However mucosal healing and catch up growth were not observed as desired even after the introduction of immunomodulators.

The goals of therapy

Over the last two decades there has been a redefining of the goals of therapy in IBD. In the Step up approach with conservative use of immunomodulators the goals were to induce remission, maintain remission, promote growth, prevent complications, optimize surgical outcomes and improve quality-of-life. Additional goals such as steroid free remission, disease modification, mucosal healing, pharmaco-economics, disease prevention and improvement in quality-of-life were included. This change in vision brought about the recommendation of Top down approach with earlier use of immunomodulators and biologics regime.

Need for top down therapy in pediatric IBD?

It is now well recognized that children with PIBD have a different phenotype compared to the adult onset IBD. Pancolitis is more often (70-90%) seen in children with Ulcerative Colitis (UC) and there is extension of the disease with time. The majority of children with Crohn’s disease (CD) have a moderate to severe presentation and complications such as perianal fistulae, stricture and abscesses is seen in 30% and 60% of children at 10 year follow up. Though pediatricians were aware of the need of a drug which would address these problematic issues there was a reluctance all over the world among pediatricians to escalate therapies because it was
perceived as “unsafe “

Importance of mucosal healing

It is obvious that protracted mucosal inflammation will result in a greater probability of progressing to penetrating disease resulting in fistulae and perforation. The deep ulcers may heal and perpetuate fibrosis causing strictures and there by progressing to irreversible damage. Cosnes et al documented the natural history of Crohn’s disease and clearly showed that the pathological sequence in CD is an initial inflammatory response followed by penetrating and structuring disease. The early use of drugs that are able to heal the mucosa was considered to be of utmost importance and this led to therapies such as enteral nutrition, azathioprine, infliximab which are able to achieve mucosal healing rather than treatments such as steroids or mesalazine that merely ameliorate symptoms with no improvement in mucosal damage.

Biologics and mucosal healing

Tumour Necrosis Factor α is an important pro-inflammatory molecule in the pathogenesis of IBD and mediates the initiation, perpetuation and disorganization of the mucosal inflammatory process and the subsequent abnormal tissue repair in IBD. Biological agents selectively target specific sites in the complex cascade of cytokine and chemokine effector molecules that comprise the end result of immune system activation. In children with Crohn’s disease, biologic agent infliximab has been associated with documented mucosal healing 75% which is maintained for a long time (up to 2 years) thus altering the natural course of the disease. The biologics used in pediatrics are alpha (TNF-α), Infliximab (Remicade), a mouse-human chimera, adalimumab (Humira) a fully humanised molecule, and certolizumab (Cimzia), a polyethylene-glycolated antibody-binding fragment. Natalizumab (Tysabri), an α–integrin monoclonal antibody, has also been used in the management of pediatric CD. Vedolizumab an anti-α 4β 7 integrin monoclonal Ab has also been tried in severe ulcerative colitis to helped in deferring or postponing surgery.

The benefits of top-down strategy include earlier disease stabilization, with limitation of disease progression and prevention of complications such as strictures and fistulae. In an open randomized trial comparing early introduction of combined immunosuppression with azathioprine and infliximab vs. conventional therapy, D’Haens et al demonstrated superior rates of remission with combined therapy at 61.5% compared with 42.2%. In children, the ‘top-down’ approach may be especially advantageous as it allows avoidance of the adverse effects of steroid therapy. A top-down approach with anti-TNF-α therapy is associated with lower risks of concomitant corticosteroid use, lower rates of discontinuation of steroids and switch to anti-TNF-α and Crohn’s disease related surgery when compared with the step-up approach. Infliximab also improves height velocity in children if provided during early puberty. The use of biologics in pediatric IBD has transformed treatment outcomes and quality of life in many children. Not only do biologics facilitate mucosal healing in both luminal and fistulizing disease, but also they improve growth and quality of life in children with IBD by achieving steroid-sparing remission.

Biologics in pediatric Crohn’s disease The REACH trial

A randomized multi-center open label trial, evaluated the outcomes of induction therapy with infliximab in 112 patients. Clinical response and remission, was achieved as defined by the PCDAI score, in 88% and 59% of patients respectively at 10 weeks. When evaluating 22 sub-group of patients with fistulizing disease at baseline, 41% of patients attained partial or complete response 2 weeks after the initial infusion and 68% achieved complete response by week 54.

Data comparing a step-up with a top-down treatment strategy in pediatric patients are limited. A retrospective study in Asia by Lee et al compared three treatment strategies in 36 newly diagnosed pediatric CD patients. At 1 year follow-up, patients treated initially with IFX and azathioprine had lower rates of relapse (as defined by a PCDAI >10) compared to those initially treated with steroids + azathioprine (23% vs. 62%, p=0.047) or steroids + mesalamine (23% vs. 80%, p=0.012).

Biologics in pediatric Ulcerative Colitis

Unlike pediatric Crohn’s Disease, data on the use of IFX in pediatric ulcerative colitis is limited. Turner et al described a cohort of 128 UC patients hospitalized for a severe flare, 33 of which underwent treatment with IFX for disease refractory to steroids. Short-term response (Pediatric Ulcerative Colitis Activity Index [PUCAI] <35) was seen in 76% of patients with 55% maintaining long term response and remaining colectomy free. Patients with new onset disease and those with a shorter duration of disease activity were more likely to respond to IFX than those with a longer disease history. Despite its short-term efficacy, infliximab does not modify the long-term surgical rate of paediatric acute severe colitis.

Biologics in growth and development :The REACH study demonstrated significant improvements in height z-scores at 30 (mean improvement in z-score of 0.3; P < 0.001) and 54
week (mean improvement in z-score of 0.5; P < 0.001) follow-up. This improvement in linear growth was related to inhibition of TNF-alpha effects on osteoblasts as well as coupling of bone formation and resorption.

**Concerns with Biologics**

i) *Immunogenicity and infusion reactions* – The formation of antibodies to infliximab (ATI) has been seen in 3–35% of IFX treated pediatric patients and is thought to impact clinical efficacy as well as increase the risk for both acute infusion reactions (AIR) and delayed type III hypersensitivity reactions (serumsickness).

ii) *Autoimmunity* – Cezard JP et al documented that 17% developed positive ANAs, 4% anti-double stranded antibodies and 2% anti-tissue antibodies. The significance of these asymptomatic antibodies is unclear since they often disappear within 6 months of stopping treatment.

iii) *Infections* – Overall infection rate of 17.7% with 2.8% of treated patients suffering from serious infections. Opportunistic infections or reactivation of latent TB and chronic viral infections such as hepatitis B and herpes zoster is of major concern.

iv) Malignancy Concern arises for the occurrence of malignancy with an increased incidence of non-Hodgkins lymphoma with the use of anti-TNF agents and immunomodulators. Another particularly serious type of lymphoma, hepatosplenic T-cell lymphoma (HSTCL), has been reported in inflammatory bowel disease patients. However IFX therapy does not appear to significantly impact the rate of lymphoma in pediatric patients.

v) *Loss of Response* – The loss of response is an important drawback which may be as high as 25 -40% and attributed to the occurrence of immune allergic reactions.

Several other rare side effects such as Psoriasis psoriasiform lesions, anemia, neutropenia, transaminitis arthralgias/joint pain, pancreatitis basal cell carcinoma bradycardia, cardiac insufficiency, cardiomyopathy and prolonged QTC resulting in death have been reported.

**Rational of step up therapy**

The step-up approach bases its rationale on avoiding overtreatment of patients with milder disease, where risks of aggressive medical therapy may outweigh the benefits. Hence, the difficulty lies in identifying those with a more severe disease, who would be unlikely to respond to standard treatment but are likely to benefit from biologics. It is therefore imperative to identify the high risk groups where it may be rational to start top down therapy rather than expose those with low risk to aggressive therapy.

**High Risk groups in pediatric IBD**

Children with the following features may be considered as high risk and need aggressive therapy where it may be rational for considering top down therapy.

- Deep colonic ulcerations on endoscopy
- Persistent severe disease despite adequate induction therapy
- Extensive (pan-enteric) disease
- Marked growth retardation N-2.5 (minus 2.5) height Z scores
- Severe osteoporosis
- Strictureng and penetrating disease (B2 and/or B3 disease behavior) at onset
- Severe perianal disease

**Indications for Biologicals**

The definite indications for induction:

- Moderate to severe inflammatory CD with inadequate response to conventional therapy
- Fistulizing Crohn’s disease with draining enterocutaneous or perianal fistula

The definite indications for maintenance therapy

- Inflammatory or fistulizing Crohn’s disease that responded to induction therapy with infliximab but failed maintenance with one or more of immunosuppressives.
- Steroid treated CD that failed attempt at steroid sparing with one or more immunosuppressives agents.
- Patients with inflammatory or fistulizing CD who have NOT failed to conventional treatment BUT require quick recovery or have a severe presentation.
- Extraintestinal manifestations of CD.
- Moderate to severe UC NOT responding to conventional treatment
- Severe, steroid refractory UC.
- Growth failure.

Conclusion: In conclusion it is not rational to start all children with IBD with top down down approach. A select group will however benefit from this early aggressive therapy.

**Messages:**

- There is no “one size fits all” in IBD therapy. Children
should be evaluated in detail regarding age, phenotype and presence of high risk predictors

- Indiscriminate TOP-DOWN approach does NOT seem to be appropriate for ALL patients with either moderate to severe CD or severe UC.
- Early identification of the high risk group of patients who will ultimately require biologic therapy for long-term maintenance of remission is essential.
- Early therapy not only with Biologics BUT early use of immunomodulators and re-evaluation of surgical timing is beneficial
- Risk-benefit assessment will favor use of biologic agents in severe Crohn's disease and Ulcerative Colitis.

Reference


Answer to Quiz

1. Esophageal Atresia
2. Duodenal Atresia (Double bubble appearance)
3. Congenital Diaphragmatic Hernia (Left)
4. Achalasia Cardia (Rat tail appearance)
5. Gastroesophageal Reflux
6. Congenital Hypertrophic Pyloric Stenosis
7. Intussusception
8. Hirschprung’s Disease
9. Anal Atresia
Eosinophilic esophagitis (EE) is a chronic, allergen and immune mediated condition that is characterized by the abnormal infiltration of eosinophils in the esophageal mucosa. EE has now evolved as a distinct disease process with unique clinical and pathophysiologic characteristics. It was first described in literature in 1970. Primary EE, rarely diagnosed until the mid-1990s, currently represents an important esophageal disorder, particularly in children, but increasingly in adults. The emergence of this disease has paralleled the increasing incidence of allergies and asthma.

An incidence of 1.5 per 10,000 and a prevalence of 5 per 10,000 is described due to heightened awareness and an overall rise in number of cases. If untreated EE can have significant effects on children including growth changes, chronic pain and irreversible fibrosis. Early diagnosis of disease is needed for effective treatment interventions, prevention of complications and improved quality of life for patients.

Diagnosis of EE
EE is a clinicopathological disease characterized by
1. Symptoms
2. Endoscopy
3. Typical Histopathology
4. Exclusion of other disorders associated with similar clinical, histological, or endoscopic features, especially GERD. (Use of high dose proton pump inhibitor treatment or normal pH monitoring).

Symptoms
Whereas younger children with EE frequently present with GERD-like symptoms, feeding problems, abdominal pain, vomiting and chest pain adolescents and adults present with obstructive presentations such as dysphagia or food impactions, with or without strictures.

The degree to which these presentations represent actual structural obstruction versus dysmotility is unclear and appears to vary among patients. Esophageal biopsy of patients without any GI symptoms, such as some patients presenting for evaluation of respiratory symptoms, has disclosed unsuspected EE.

Children presenting with feeding problem and emesis, abdominal pain are often treated with an adequate dose of proton pump inhibitor for 2 months. But if symptoms persist despite adequate compliance after 2 months children must be evaluated by endoscopy to exclude eosinophilic esophagitis (EE).

Peripheral eosinophilia (>700 cells/mm3) has been reported in children with EE. Furthermore, specific immunoglobulin E (IgE) antibodies to foods may be found in children with EE identifying sensitization to foods which may (or may not) be the causative foods of the disease.

Endoscopy
Endoscopy performed by a trained pediatric gastroenterologist is needed to diagnose EE.

Normal mucosa appears smooth with no irregularities. In EE.
1. Typical features include mucosa that appears erythematous, dull and thickened.
2. White plaques or eosinophilic abscesses can be present
3. With more chronic inflammation, linear furrows or circumferential rings can be seen
4. Luminal narrowing and strictures, fortunately are rare findings in children

Extra care should be taken to perform biopsy or dilatation to prevent perforation.

Studies have shown the diagnostic sensitivity to be 84% with 2 biopsies, but increases to 97% and 100% with 3 and 6 respectively which is likely due to the patchy pattern of inflammation. Sampling both proximal and distal levels aids
in distinguishing between EE and GERD. Approximately 10% of EE patients demonstrate no obvious macroscopic changes. Conversely, of the patients who exhibit gross features suggestive of disease, less than 40% actually have histologic evidence of EE. Given the above, multiple biopsies from more than one level should be obtained during endoscopy, even in the setting of grossly normal appearing tissue.

ESPGHAN & NAPGHAN (position paper on EE)\(^5\) recommendations are as follows:

In symptomatic children with histological findings of esophageal eosinophilia, a trial of PPIs is recommended for 8 weeks. A second Esophagogastroduodenoscopy (EGD) should be performed under PPI therapy in all children, even if symptoms resolve. If histology is still suggestive of EE and other causes of esophageal eosinophilia are unlikely, then the diagnosis of EE can be made. If the first endoscopy is performed after the patient has already had an adequate trial of PPI, the diagnosis of EE can also be made and specific treatment for EE be initiated.

Endoscopic ultrasound (EUS)

EUS has also been found to be a useful tool in EE management. Changes of the esophageal wall diameter following therapy have shown to correlate well with histologic improvement. Meanwhile, a lack of esophageal wall diameter changes is suggestive of an incomplete response to therapy even when mucosal biopsies may be negative for EE by histologic criteria. Moreover, EUS is useful in differentiating reflux esophagitis with EE. Histologic changes in untreated GERD can be difficult to differentiate from EE. Esophageal wall thickening involving all 3 layers of the esophagus (mucosa, submucosa and muscularis propria) is not typically seen in GERD [eosinophilic and allergic disorder].

Histology

The main histological findings are dense eosinophilia of the esophageal mucosa, which tends to be panesophageal, basal zone hyperplasia, lamina propria fibrosis, and sometimes eosinophilic microabcesses. A diagnostic criteria of > 15 eosinophil/High power feld is defined to diagnose EE. It should be noted, that the size of a high-power field has not been standardized. This may alter the sensitivity/specificity of the lower threshold of diagnosis at 15 eosinophils/hpf. Furthermore, it should be considered that diagnostic biopsies are predominantly or entirely epithelial and as such may underestimate deeper disease activity, particularly as eosinophil recruitment begins within the subepithelial compartment. Moreover, esophageal wall thickening, subepithelial fibrosis, and neural dysfunction occur beneath the epithelium. This recruitment pattern has implications for both diagnosis and treatment\(^2\).

Management

The goal of the treatment should ideally be both the resolution of symptoms and the normalization of the macroscopic and microscopic abnormalities. Although there are no follow-up studies assessing the long-term consequences of persisting esophageal eosinophilia in asymptomatic patients, the possibility of esophageal fibrosis and narrowing cannot be excluded. Moreover, patient-reported outcome measures may be difficult to assess in children, particularly in infants, and young or learning-disabled children who are unable to provide accurate information on their symptoms. Hence, at present, histology with absolute eosinophil counts remains the best marker objective measure of the inflammatory disease activity.

Diet

Food allergens are the most frequent culprit of inflammation, as the vast majority of pediatric cases resolve with elemental diets. Diet elimination involves the collaboration with the pediatric allergist to identify foods most likely driving inflammation.

Different dietary approach is described amino acid–based formula (AAF) for complete removal of food allergens from the diet targeted elimination diet (TED), which removes foods based on a suggestive history of food triggers and results of specific IgEs, SP(skin prick test), and APT (Atopy Patch test) or Blood test using Immunocap Allergy testing(where available)

The most commonly identified allergen shown to improve avoidance is cow's milk, in 75% of cases. A major challenge for patients and families is when multiple foods are identified. In a practical sense, multi-food avoidance is highly impractical and makes achieving a nutritionally complete diet a challenge. An alternative approach is a six-food elimination diet. By empirically eliminating the most commonly allergenic foods—cow's milk, soy, nuts, eggs, wheat and seafood-75% efficacy in symptom reduction and histologic inflammation was reported in one pediatrics study. Elemental diet is highly efficacious in reducing inflammation.

Medications

Corticosteroids are often used when food allergens are not properly identified, diet modification is not practical for the patient or proves to be insufficient, and when disease is very severe.
Corticosteroids
Swallowed fluticasone spray or budesonide liquid prepared as a slurry acting directly on esophageal mucosa have shown to be effective anti-inflammatory agents with less side-effects of systemic drugs. Fluticasone spray achieved significant improvement in histology and symptomatology in comparison to placebo. A pediatric randomized control trial showed almost 70% patients had <6 eosinophils/HPF following 3 months of budesonide use. One study also suggest that budesonide may beneficially reverse fibrosis. Unfortunately, discontinuation of steroids leads to recurrence of inflammation in the vast majority of patients. Fortunately, the low side-effect profile does allow chronic use as a maintenance medication in some patients with large excretion of drug retrieved in stool. Additionally, absorbed budesonide has the advantage of high first-pass metabolism. The most common side effect is localized oral or esophageal candidiasis, noted in about 20% of patients. Overall, long-term studies are limited.

Despite oral corticosteroids being extremely effective at symptom control, they are infrequently used in patients with EE because of their systemic adverse effects; however, systemic corticosteroids can be used for extremely severe symptoms, for example, when immediate relief of the patient's symptoms is required.

The ESPGHAN & NASGHAN (Position Paper) recommendations are as follows:

1. Swallowed FP (Fluticasone Propionate) or OVB (Oral Viscous Budesonide) for a minimum of 4 weeks and a maximum of 12 weeks can be a treatment option either alone or in combination with an elimination diet.

2. Systemic oral corticosteroids are only recommended when rapid relief is required for symptoms such as severe dysphagia, dehydration, weight loss, or esophageal strictures, or where the diagnosis is certain and other treatments have failed.

3. The efficacy of the drug treatment should be monitored by assessment of symptoms and evaluation of endoscopic and histological response.

4. Histologic remission is followed by drug titration and discontinuation of treatment.

5. In case of symptoms persistence or recurrence, endoscopy and biopsies for the histological assessment of the esophagus are necessary.

6. Long-term follow-up of asymptomatic patients remains individualized and depends on local practice

Other treatments
Neither cromolyn sodium nor leukotriene receptor antagonists are recommended as treatment for children with EE.

Immunomodulators and Biologics
Because corticosteroids fail to induce a long-lasting remission in patients with EE, immunomodulation has been considered as a potential means of providing some maintenance efficacy. Azathioprine and Infliximab has been tried with very limited efficacy

Anti–Interleukin-5 Therapy (Mepolizumab)
Clinical trials have described reduced peripheral eosinophil counts and clinical benefit with mepolizumab in certain eosinophilic disorders.

Anti–IgE Therapy (Omalizumab)
The humanized anti-IgE monoclonal antibody omalizumab, known to be effective therapy against allergic rhinitis and asthma, has also been described to have positive effects in EG by improving peripheral and tissue eosinophilia, serum IgE, and symptom scores.

Furthermore, local treatment, targeted at inhibition of IL-4 and -13 in the lung, substantially diminished the symptoms of asthma.

But neither currently available immunomodulators nor biological agents can be recommended for treatment in children with EE.

Esophageal Dilatation
Esophageal dilatation is only recommended in highly selected cases with severe esophageal narrowing that persists despite other forms of treatment. In all of the cases, esophageal dilatation must be accompanied by medical treatment of EE.

Present problems
The lack of appropriate biomarkers to evaluate response to treatment and detect early relapse may require repeat endoscopy and biopsy during the course of the disease. Such biomarkers are under evaluation now.

Conclusion
EE is a chronic, relapsing inflammatory disease of the esophagus, requiring prolonged therapy but there is poor correlation between clinical symptoms and histological measures, making absolute recommendations for monitoring impossible. The disease course is unpredictable and long-term complications are unknown. Treatment should be
individualized and must not create more morbidity for the patient and family than the disease itself. However adequate treatment can lead to improved growth and symptom relief and potentially, avoidance of long-term complications in children.

**Reference**


**Abbreviation:**

EE – Eosinophilic Esophagitis  
GERD – Gastroesophageal Reflux Disease

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**Eosinophilic Esophagitis vs GERD**

<table>
<thead>
<tr>
<th>Characteristic features</th>
<th>EE</th>
<th>GERD</th>
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<tbody>
<tr>
<td>Clinical</td>
<td></td>
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<tr>
<td>Prevalence of atopy</td>
<td>Very high</td>
<td>Normal (possibly increased)</td>
</tr>
<tr>
<td>Prevalence of food sensitization</td>
<td>Very high</td>
<td>Normal (possibly increased)</td>
</tr>
<tr>
<td>Sex preference</td>
<td>Male</td>
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<tr>
<td>Abdominal pain and vomiting</td>
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<td>Food impaction</td>
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<td>Uncommon</td>
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<tr>
<td>Investigative findings</td>
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<td></td>
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<td>pH probe</td>
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<td>Abnormal</td>
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<tr>
<td>Endoscopic furrowing</td>
<td>Very common</td>
<td>Occasional</td>
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<td>Histopathology</td>
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<td>Involvement of proximal esophagus</td>
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</tr>
<tr>
<td>Epithelial hyperplasia</td>
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<tr>
<td>Esophinal levels in mucosa</td>
<td>&gt;24/hpf</td>
<td>0-7/hpf</td>
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<td>Treatment</td>
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<td></td>
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<td>H2-blockers</td>
<td>Sometimes helpful</td>
<td>Helpful</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Sometimes helpful</td>
<td>Helpful</td>
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<tr>
<td>Glucocorticoids</td>
<td>Helpful</td>
<td>Not helpful</td>
</tr>
<tr>
<td>Specific food antigen elimination</td>
<td>Sometimes helpful</td>
<td>Not helpful*</td>
</tr>
<tr>
<td>Elemental diet</td>
<td>Helpful</td>
<td>Not helpful*</td>
</tr>
</tbody>
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Inflammatory bowel disease (IBD) is a group of disorders characterized by chronic intestinal inflammation. Pediatric inflammatory bowel disease (P-IBD) constitutes about 20-25% of all IBD in the West and is an important cause of morbidity in children and adolescents. It is classified into 3 main types based on the clinical and pathological features:

- Crohn's disease (CD)
- Ulcerative colitis (UC)
- IBD-unclassified (IBDU) - is a term used to describe IBD patients with colonic involvement who cannot be classified as UC or CD. It is seen more often in children than adults (12.7% vs. 6.0%). If patients cannot be classified as UC or CD even after histology of resected colon then they are labeled as “indeterminate colitis”.

Several epidemiologic studies have shown a rising trend in P-IBD, more in CD as compared to UC. In a systemic review of 28 pediatric studies from 1950 to 2009 across 32 countries, 60% of studies showed a significant increase in CD incidence and 20% increase in UC. There has been an increase in the incidence of IBD even in the Asia Pacific region. Data from India on Pediatric-IBD (P-IBD) is sparse with no population based study on prevalence of CD/ UC in children. In a study from Southern India, IBD constituted 33 out of 100,000 new children attending the hospital. P-IBD accounted for approximately 7% of all new cases of IBD seen annually at tertiary referral centre in south India. In a recent multicentre experience of IBD in 267 Indian children (boys 49 %), 44% had UC, 52% had CD and 4% had IBDU. In Northern India, UC was more common, while in South CD was more common than UC.

Depending on the age of the child at presentation, P-IBD is further classified (Fig 1).

This classification assumes importance as IBD in children is different from that in adults.

Children with Crohn’s disease more often have colonic involvement, UpperGI involvement and perianal disease in comparison to adults with CD. Pancolonic disease is significantly more common in children with UC as compared to adults.

The most common age of presentation of IBD in children is between 10 to 14 years. About 10% of all pediatric IBD occurs in children < 6 years of age and 1% in infants. The younger children with IBD, especially those <2 years of age are often characterized by severe disease, lack of response to the standard IBD therapy and poor outcome. This is a special group which may be having various monogenic disorders/ immunodeficiency states like defect in IL-10 and IL-10R pathway and needs detailed etiologic work-up. This assumes even more importance as the treatment in some of these monogenic diseases is different and rewarding like bone marrow transplantation in IL-10R defects.

In the largest Indian data of pediatric IBD of 267 children, the disease distribution was as follows:

**Ulcerative colitis**
- E1 (Proctocolitis) : 4%, E2 (Left sided colitis) : 28%, E3 (Pancolitis): 68%

**Crohn’s disease**
- L1 (Ileal): 8%, L2 (Colonic):18%, L3 (Ileocolonic): 69%
- L4 (UGI: focal active gastritis or granuloma) -12%
- Perianal lesions: 18.8%

The clinical features in patients with UC and CD (Fig 2).
Growth failure is a common problem in children with IBD and may precede clinical evidence of bowel disease by a few years. Growth failure in IBD is characterized by delayed skeletal maturation, delayed onset of puberty and reduced lean body mass. It was more common in CD than UC (93/122 (75.3%) vs. 50/120 (41.6%) in the Indian experience.

Extra intestinal manifestations have been reported in 6-30% children with IBD. In the Indian study, 71/267 (26.5%) children had EIMs with aphthous ulcers (11.6%), being most common followed by arthralgia/arthritis (10.8%), Erythema nodosum in 3.7% and uveitis (0.3%).

Diagnosis and Treatment of IBD: the Porto criteria should be followed for evaluation of IBD children and a complete workup is required in order to make a definite diagnosis, differentiate between CD and UC and also from other disorders like intestinal tuberculosis.

In the step-up therapy of IBD, 6-12% children required biologics and 4-8% surgery as shown in (Fig 3).

Overall, P-IBD is now being seen more often both by paediatricians and pediatric gastroenterologists of our country. Keeping in mind the complexities of diagnosis and need of long-term management with immuno-suppressants/biologics, these patients are best treated by a multidisciplinary team of paediatrician, pediatric gastroenterologist, surgeon, radiologist, pathologist and dietician.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset of symptom</td>
<td>10.2 ± 4.4 years</td>
<td>11.02 ± 4.5 years</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>51:42(1:1.2)</td>
<td>58.64 (1:0.9)</td>
</tr>
<tr>
<td>Duration of symptom</td>
<td>7.6 months</td>
<td>12.1 months</td>
</tr>
<tr>
<td>Fever</td>
<td>11.8%</td>
<td>39.3%</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>90.3%</td>
<td>37.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>69.9 %</td>
<td>48.4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>58.1%</td>
<td>73.8%</td>
</tr>
<tr>
<td>Anemia</td>
<td>43 %</td>
<td>64.7%</td>
</tr>
</tbody>
</table>

Fig 2. showing clinical features in UC and CD

Suggested Reading
Introduction:
Neonatal intestinal obstruction (NIO) is one of the commonest reasons for admission to neonatal unit. The approximate incidence of NIO is 1 in 2000 live birth. Classically, babies present with bilious vomiting, abdominal distension and no or delayed passage of meconium. Early diagnosis and management is very important to prevent clinical deterioration, aspiration pneumonia, sepsis and biochemical and hematological derangements.

The presentation may vary from subtle clinical findings to massive abdominal distension with hemodynamic collapse. Careful evaluation regarding history and physical examination often help to diagnose. Concomitant resuscitation is integral part of its management.

The outcome has been improved by means of antenatal and perinatal diagnosis, neonatal intensive care, safer anesthesia and refined surgical skills. Prematurity, associated congenital malformations and sepsis are the major causes of death.

Spectrum of neonatal intestinal Obstruction:

1. High obstruction
   A) Gastric outlet obstruction
      a. Pyloric atresia
      b. Hypertrophic pyloric stenosis
      c. Antral web
   B) Duodenal obstruction
      a. Duodenal atresia
      b. Duodenal stenosis
      c. Annular pancreas
      d. Preduodenal portal vein
      e. Malrotation

2. Low obstruction
   A) Distal small bowel obstruction
      a. Ileal atresia
      b. Meconium ileus [complicated and uncomplicated]
   B) Colonic obstruction
      a. Colonic atresia
      b. Dysmotility states:
         i. Meconium plug
         ii. Small left colon syndrome
         iii. Hirschsprung disease
         iv. Hirschsprung variants
   C) Uncommon causes of obstruction
      a. Intussusception
      b. Meckel’s diverticulum

-30% of infants presenting with neonatal intestinal obstruction have atresia or stenosis. Duodenal atresia is the commonest, followed by jejunal atresia and ileal atresia.

Analyzing the admission records of two neonatal units in two tertiary care centers in Kolkata we found the following causes for intestinal obstruction: anorectal malformations, Hirschsprung’s disease, malrotation with or without midgut volvulus, atresias (duodenal, jejunal, ileal and colonic), NEC. Other rare causes were neonatal intussusception, duodenal and jejunal diaphragm, ileal and rectal duplication cysts, meconium ileum, congenital diaphragmatic hernia.

Pathophysiology:
Neonatal intestinal obstruction occurs in ~ 1 in 2000 live births. It may result from:
• Intrinsic developmental defects;
• Insults acquired in utero, after the formation of normal bowel;
• Abnormalities of peristalsis and/or abnormal intestinal contents.

The hallmark features of intestinal atresia or stenosis are marked dilation of the proximal segment and collapse of the distal segment beyond the obstruction.

**History and clinical features:**

Careful history can reveal a lot of things which may guide to a definitive diagnosis. There are some cardinal features which are described in brief below:

1. **Maternal polyhydramnios:**
   Usually associated with high intestinal obstruction (Obstruction above the level of mid jejunum).

2. **Family history:**
   Important in certain disease condition such as Jejunal atresia (Type IIIB, familial form of multiple atresia etc. are autosomal recessive disorders. History of cystic fibrosis in meconium ileus and meconium plug syndrome. Family history of Hirschsprung’s disease and total colonic agangliosis is also known entity. Babies born from diabetic mother have chance to develop small left colon syndrome.

3. **Clinical signs and symptoms:**
   a. **Vomiting** –
      One of the most important cardinal sign of obstruction. Bilious vomiting of any volume is suggestive of obstruction. The onset, amount of vomitus and nature of vomiting depend upon the level of obstruction. Non bilious projectile forceful repeated vomiting is suggestive of hypertrophic pyloric stenosis and pyloric atresia. Copious, forceful bilious vomiting seen in early life in case of duodenal atresia, high jejunal atresia. Maltrotation patients are also presented with bilious vomiting. Vomiting is delayed in distal intestinal obstruction like distal ileal atresia, meconium ileus, Hirschsprung’s disease, colonic atresia etc.
   b. **Abdominal distension** –
      It may appear early or late. Complicated meconium ileus with antenatal perforation, meconium pseudocyst present with abdominal distension since birth. Distension of abdomen also depends upon level of obstruction. High obstruction leads to less distension where as low obstruction presents with gradual and severe distension if not diagnosed early. Massive distension often results in perforation. Visible gastric peristalsis is often seen in gastric outlet obstruction.

   c. **Meconium** –
      Normally >90% newborn passes meconium within 24 hrs of birth and 94-98% by 48 hrs. Delayed passage is classically seen in Hirschsprung’s disease and others like small left colon syndrome. Failure to pass meconium occurs in colonic atresia, rectal atresia and anorectal malformation. Blood in stool is seen in volvulus associated with mialrotation and NEC. Passage of white/ greenish meconium pellets are seen in meconium ileus.
   d. **Features of perforation and peritonitis** –
      It is a delayed presentation of obstruction. Babies are often in shock with hemodynamic instability.

**Epidemiology:**

1. 40% - Duodeal atresia
2. 35% - Junal atresia
3. 25% - Ileal atresia

**High bowel obstruction:**

1. **Pyloric atresia** –
   A rare (1 in 1 million live birth) autosomal genetic defect and is strongly associated with epidermolysis bullosa. Case is unknown. It constitute <1% of all GI atresia.

2. **Duodenal atresia** –
   Complete obstruction results from congenital failure of recanalization that normally occurs during 9–11 weeks of gestational age. It is frequently associated with other congenital anomalies, such as additional intestinal atresias, congenital heart disease, or as a part of the VACTERL association. >30% of cases occur in patients with the diagnosis of trisomy 21. Abdominal X-ray shows "double bubble sign". In cases of complete atresia rest of the abdomen is gasless. Three types are present. Open or laparoscopic duodenoduodenostomy is the procedure of choice.

3. **Duodenal stenosis with annular pancreas:**
   Partial duodenal obstruction is usually caused by duodenal stenosis, with or without annular pancreas. In duodenal stenosis there is also intestinal gas seen distal to the proximal duodenum. Upper gastrointestinal contrast study is diagnostic. Open or laparoscopic duodenoduodenostomy is the procedure of choice.

4. **Duodenal web:**
   Here a congenital obstructing membrane with a central pinhole aperture is present. Long-term pressure of peristalsis against the stenotic segment of the duodenum may lead to distal stretching of the web, forming windsock deformity. Upper
gastrointestinal finding is a faint radiolucent membrane. Open or endoscopic excision of web is treatment of choice.

5. Malrotation:
Malrotation refers to abnormal or incomplete intestinal rotation during embryonic development. Normally, physiologic bowel rotation (270° around the axis of the superior mesenteric artery) leads to duodenal-jejunal and ileocecal junctions that are appropriately situated in the left upper and right lower quadrants, respectively. This normal physiologic bowel rotation results in a broad attachment of the intestines to the mesentery, which prevents bowel from twisting around the mesentery. In malrotation, different degrees of abnormal location of these two key intestinal segments produce a narrower mesenteric attachment, which places the small bowel at risk for twisting around its pedicle, a condition known as “midgut volvulus.”

Midgut volvulus causes both mechanical obstruction and arterial occlusion of the mesenteric vessels. If untreated, midgut volvulus will progress to bowel ischemia and eventual infarction. Furthermore, a malpositioned portion of intestine is often associated with abnormal peritoneal fibrous bands (Ladd bands), which are anomalous fibrous connections that typically extend from the malpositioned cecum across the duodenum to attach to the peritoneum and liver. These anomalous fibrous bands may also contribute to bowel obstruction or be solely responsible for it.

Although a newborn with isolated malrotation may be completely asymptomatic, the development of midgut volvulus typically produces bilious emesis. The abdominal X-ray is usually nonspecific. Upper gastrointestinal contrast series is the diagnostic procedure. The classical film shows an abnormal course of the duodenum that fails to cross the midline combined with a circular duodenal configuration (corkscrew appearance).

6. Jejunal Atresia:
Incidence is ~1 in 5000 live births with equal male and female distribution. Babies are usually premature. Intrauterine ischemic insult is the cause, which can be a primary vascular cause or secondary to a volvulus. Babies present with bilious vomiting and abdominal distension. X-ray abdomen shows few air fluid levels. Classical film is shown as “triple bubble sign”. The proximal loop is frequently disproportionately dilated. There are four types. Resection of some length of proximal bowel or tapering jeunoplasty with end to end anastomosis is treatment of choice.

Low Intestinal Obstruction:
Small-Bowel Involvement
1. Ileal atresia –
Common cause of low intestinal obstruction in neonates, with an estimated incidence of 1 in 5000 live births. The cause is thought to be related to an intrauterine ischemic insult. Babies present with bilious vomiting and abdominal distension. Multiple air-filled distended small-bowel loops are seen in X-ray.

2. Meconium ileus –
~20% of cases of neonatal intestinal obstruction. Caused by intraluminal obstruction of the colon and distal small bowel from abnormal concretions of meconium, this condition is virtually always the earliest clinical manifestation of cystic fibrosis. Occlusion of the distal small bowel results in mechanical obstruction with subsequent distention of the more proximal bowel loops. Meconium ileus may be complicated by volvulus, perforation, or peritonitis. Intrauterine perforation may lead to meconium peritonitis (chemical type), and peritoneal calcifications may be seen postnatally. Abdominal radiographs in neonates with meconium ileus usually show a pattern of low intestinal obstruction that is characterized by multiple bowel loop dilatations. Despite the marked intestinal dilatations, there is often a relative lack of air-fluid levels within the dilated bowel loops because of the abnormally thick intraluminal meconium. A contrast enema study typically shows an micro colon, within which are multiple small filling defects representing meconium concretions. If there is reflux of contrast material beyond the ileocecal valve, multiple small filling defects (soap bubble sign) also may be seen in the terminal ileum.

Large-Bowel Involvement
1. Meconium plug or small left colon syndrome:
The underlying cause is thought to be related to immaturity of the colonic ganglion cells (myenteric nerve plexus). Functional immaturity of the colon is the most common diagnosis in neonates who fail to pass meconium stool for more than 48 hours. An increased incidence of functional immaturity of the colon has been reported in infants of diabetic mothers and mothers who received magnesium sulfate for preeclampsia during pregnancy. A diagnostic enema is usually therapeutic and leads to the passage of discrete meconium plugs and resolution of the intestinal obstruction.

2. Hirschsprung’s disease:
Arrest of neuronal (ganglion) cell migration to the distal bowel before the 12th week of gestational age leads to this entity.
Because the intestinal ganglion cells migrate in a craniocaudal direction, the area of aganglionosis always extends distally from the point of neuronal arrest to the anus. The segment of aganglionosis is typically continuous and most commonly involves the rectum and a portion of the sigmoid colon. Occasionally, the migration abnormality of ganglion cells is more extensive and the aganglionic segment extends for a variable distance proximal to the sigmoid colon (long segment disease, which accounts for about 25% of cases). The process can also affect the entire colon (total colonic aganglionosis) and, rarely, a portion of the small intestine. Contrast enema is usually performed for diagnosis of transition zone. In equivocal cases rectal biopsy and ano-rectal manometry are usually required for definitive diagnosis.

3. Colonic atresia:
Relatively rare type, resulting from an intrauterine vascular insult and is typically located in the colon proximal to splenic flexure. Affected neonates generally present with abdominal distension with absence of air in the rectum.

4. Anal atresia and anorectal malformations:
Anal atresia, also known as “imperforate anus,” is a condition of unknown cause in which there is absence of a normal anal opening. With an estimated incidence of 1 in 5000 live births, anal atresia affects boys and girls with similar frequency. Anal atresia is associated with other congenital anomalies, including vertebral, cardiac, renal, and limb anomalies.

As reported from PGI, Chandigarh, the commonest cause of neonatal obstruction (other than Hirschsprung disease and anorectal malformations) was intestinal atresias. Other than anorectal malformations and Hirschsprung disease, we have also encountered similar spectrum of NIO.

Conclusion
Careful antenatal ultrasonography helps us to detect fetal intestinal obstruction particularly atresias. Early transport to tertiary care center, prompt resuscitation followed by definitive surgical repair is mainstay of management. Good post operative support is essential for better survival.

Reference

Request
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Cholelithiasis in Children

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The overall prevalence of gall stone (GS) disease in most developed nations including US, UK, Italy and other Scandinavian countries is between 10% to 20%.

The prevalence increases with age in both males and females. The large majority of these are asymptomatic1. In India, Kuroo et al2 have reported a 6.1% (men 3.1% and women 9.6%) prevalence of GS in subjects above 15 years of age from Kashmir and North India. Prevalence of GS is seven times more frequent in North India than in South India.

We have very meager information about GS in children. Cholelithiasis and choledocolithiasis have been increasingly diagnosed in the recent years due to widespread use of ultrasonography3.

Gall stone distribution in Children

The distribution of GS types in children differs from adult population, with cholesterol stones being the most common type of stones in adults and black pigment stone being most common type in children.

Black pigment stones make up 48% of GS in children. They are formed when bile becomes supersaturated with Ca-bilirubinate, the calcium salt of unconjugated bilirubin. Black pigment stones are commonly formed in hemolytic disorders and can also develop in parenteral nutrition. Calcium carbonate stones which are rare in adults are more common in children accounting for 24% of GS in children4.

Cholesterol stones are formed from cholesterol supersaturation of bile and are composed of 70-100% cholesterol with an admixture of protein, bilirubin and carbonate. These account for most of the GS in adults but make up only about 21% stones in children5,6.

Brown pigment stones are rare, and contribute 3% of GS in children and form in the presence of biliary stasis and bacterial infection. They are composed of calcium bilirubinate and the calcium salts of fatty acids and occur more often in bile ducts than in the gall bladder.

The remaining portion of GS in children consists of protein dominant stones, which make up 5% of GS in these patients. Microlithy are GS smaller than 3 mm: can form within intrahepatic and extrahepatic biliary tree; may lead to biliary colic cholecystitis, and pancreatitis; can persist after cholecystectomy and are difficult to diagnose as they are often missed an ultrasonography.

Biliary sludge is made up of precipitates of cholesterol monohydrate crystals, bilirubinate, Ca phosphate, Ca carbonate and calcium salts of fatty acids which are embedded in biliary mucin to form sludge.

Etiology

Cholelithiasis in children has various causes. Hemolytic disease, hepatobiliary disease, obesity; prolonged parenteral nutrition, abdominal surgery particularly ileal resection, Crohn’s disease, sepsis and pregnancy in adolescent girls may lead to increased incidence of GS in pediatric population.

Less prominent risk factors include acute renal failure, prolonged fasting, low calorie diets, and rapid weight loss. Biliary psedolithiasis or reversible cholecystitis may be associated with the use of certain medications, most commonly, ceftriaxone.

Genetic conditions, such as progressive familial intrahepatic cholestasis type S, predisposes to GS formation. Defects in ABCB4 gene have been increasingly recognized in both adults and children with recurrent cholestasis and cholesterol GS5,6.

Pathophysiology

The complications of cholelithiasis in children are similar to those in adults. Cholelithiasis primarily affects gall bladder and may cause irritation of the GB mucosa causing chronic calculus cholecystitis and symptoms of biliary colic.

If a gallstone obstructs the cystic duct, acute cholecystitis with
distension of GB wall and spillage of bile. If gall stone migrate from the GB into the cystic duct and main biliary ductal system, further complication may occur such as choledocholithiasis, biliary obstruction with or without cholangitis and gall stone pancreatitis.

**Presentation**

33-40% of children are asymptomatic. In symptomatic patients pain in the right upper quadrant (RUQ) is the most common presenting symptom and may be accompanied by nausea and vomiting.

Gall stones should be considered in the work up of non-specific, intermittent abdominal pain in children with risk factors, which include chronic hemolysis, obesity, ileal disease, a family history of childhood gall stones, parenteral nutrition. Also cholelithiasis should be considered in children with jaundice and low grade elevations, of transaminases. Older children may localize their pain to the right upper quadrant (RUQ).

A meticulous physical examination include visualization and palpation of abdomen. Pain in RUQ is common. Murphy’ sign (expiratory arrest with palpation in the RUQ) is thought to be pathognomonic. Hepatomegaly and splenomegaly may be a clue to venous congestion or a hemolytic process that may be a predisposing factor for cholelithiasis. Obesity should also be noted as it is an important risk factor for cholesterol stones.

**Work up:**

Laboratory tests should include a complete blood count, gamma glutamyl transferase (GGT), amylase, urinalysis, direct and indirect bilirubin, alkaline phosphatase and transaminase levels. All laboratory results in simple cholelithiasis are within the reference ranges. They are abnormal in more complex disease process including biliary obstruction and cholecystitis. Abnormal results on liver function tests or CBC count suggests infection, obstruction or both.

**USG:**

USG is the study of choice in patients with uncomplicated cholecystitis. It can be used to identify location of the stone, thickening of GB wall, presence of sludge and pericholecystic fluid. Ultrasonographic Murphy sign (expiratory arrest with pressure from sonographic probe in RUQ) aids in the diagnosis of cholelithiasis.

Plain radiography in pediatric patients with cholelithiasis is seldom useful because GS except calcium carbonate stones are not radio-opaque. However, Radionuclide Scanning with Imidodiacetic derivatives is also used to assess GB filling and bile excretion particularly in response to cholecystokinin or a fatty meal.

**Cholangiopancreatography**

In children with suspected hepatobiliary complications, magnetic resonance cholangiopancreatography (MRCP) or Endoscopic retrograde Cholangiopancreatography (ERCP) can help delineate the anatomy of the extrahepatic and intrahepatic biliary tree, identify the presence of ductal stones, and provide a therapeutic mode of remaining stone or decompressing the biliary tract. As a noninvasive alternative, the MRCP has demonstrated promise in the elevation of choledocholithiasis.

**Approach to the management**

Treatment of simple cholelithiasis is symptomatic. Surgical removal of an asymptomatic GS is currently not recommended.

A Prospective study was conducted on 41 children having non pigmented gallstones, with non-specific or no symptoms for 21 months. Of these 50% remained asymptomatic, 32% experienced definite improvement in symptoms, 18% had continued symptoms but none had any biliary complication. This observation was substantiated by another study of 82 children with cholelithiasis who were followed up for 4.6 years.

Children with gall stones can be divided into two groups. Those with typical symptoms should have their gall bladder removed. Asymptomatic children or children with non-specific symptoms can undergo safe follow up. These children will require regular follow up till their adulthood to determine their lifetime risk of developing symptoms.

Laparoscopic cholecystectomy is currently the criterion standard in the treatment of symptomatic cholelithiasis. It has been proven to be safe and effective in children with low rate of postoperative complications.

**Ursodeoxycholic Acid (UDCA)**

It is helpful in medical management of cholelithiasis. One study in whom pediatric patients received 20 mg/kg/d of UDCA for a median period of 13 months demonstrated resolution of clinical discomfort in 83.7% of patients. However complete disappearance of GS was observed in 7.2% and cholelithiasis recurred in 50% of these patients.

UDCA has not been approved by US food and drug administration for use in pediatric patients. However, there is a big history of use as an adjunctive therapy in the adolescents with cystic fibrosis and in infants and children with a hereditary
cholestasis syndrome biliary atresia, and cholestasis associated with perenteral nutrition.

The primary disadvantage of UDCA is high incidence of gallstone recurrence. So the treatment is not recommended in patient with symptomatic cholelithiasis.

Management of cholelithiasis in hemolytic disease

Screening with USG is recommended at and around five years of age, screening is also necessary before splenectomy and cholecystectomy can be combined in the presence of GS. There is a survival benefit over splenectomy alone in hereditary spherocytosis. There is no advantage of doing cholecystectomy with splenectomy if there are no gall stones in these patients who are not at an increased risk of cholelithiasis after splenectomy.

In sickle-cell disease prophylactic cholecystectomy is recommended even for asymptomatic gallstone as it is difficult to differentiate acute abdominal crisis from acute cholecystitis; and the morbidity and mortality of emergency cholecystectomy in this setting is much higher than in elective cholecystectomy. Proper hydration during the perioperative period is essential to avoid sickling and hemoglobin S should be decreased to at least 30% and hemoglobin to be increased to 13%.

Choledocholithiasis

Common bile duct stones are associated with gall stones except in hemolytic diseases where these may be the primary stones. CBD stones account for 10% of gall stones. Clinical presentation of choledocholithiasis comprises jaundice, cholangitis and gall stone pancreatitis. A CBD stone should be suspected in a child with hyperbilirubinemia (total bilirubin >1.3 mg/dl) and/or a dilated CBD on US (>6mm).

Different approaches are available for the treatment of combined cholecystocholedocholithiasis including totally laparoscopic (TL) treatment, simultaneous laparoendoscopic treatment, and sequential treatments (ST) combining endoscopic tetrograde cholangiopancreatography (ERCP) and endoscopic sphincterectomy (ES) with cholecystectomy. The most appropriate method of investigation and management of CBD stones seems to be laparoscopic cholecystectomy (LC) with intraoperative cholangiogram (IOC) followed by ERCP.

Reference

Definition
The name acute recurrent pancreatitis (ARP) is preferred over recurrent acute pancreatitis (RAP) as the connotation of RAP in children is different. Recently the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPiRE)\(^1\) has defined ARP as two or more distinct episodes of acute pancreatitis (AP) along with complete resolution of pain (= 1-month pain free interval between the diagnosis of AP) or complete normalization of serum pancreatic enzyme levels along with complete resolution of pain irrespective of specific time interval between AP episodes\(^1\). In adults baseline MRCP or ERCP is required in all cases of ARP to rule out the presence of chronic pancreatitis (CP) as they can manifest as ARP\(^2\). Symptom-based definition has problem as it is difficult to differentiate ARP and chronic pancreatitis (CP) clinically. In a recent study on 155 cases of ARP and 146 cases of CP in children, Kumar et al\(^3\) showed that 81% of children in both ARP and CP presented with pancreatitis related abdominal pain and there was no difference between them as far as episodic pain is concerned. In the same study it has also been shown that initial imaging in ARP group showed changes of florid CP on MRCP and ERCP in as many as 23% of cases. Hence, if we follow the INSPPiRE definition of ARP\(^1\) then there is always a possibility of including cases with underlying CP. We recommend the use of MRCP as baseline in all cases of ARP to rule out the presence of CP.

Epidemiology
Pancreatitis used to be uncommon in children but in recent times there are reports to suggest an increasing incidence of acute pancreatitis in children like in adults\(^4-9\). Acute pancreatitis (AP) is an event and expected to recover completely after the first attack. However, a proportion (10% to 30%) of AP goes on to have a second or more attacks of pancreatitis (ARP)\(^10\). What predicts the progression of AP to ARP is not known. There is scarcity of published information about ARP in children. So far there are only three single center studies comprised of 19, 25 and 78 cases\(^10-12\) and a recent multicenter study on 155 children\(^3\). All these studies have focused on one-time information about its clinical spectrum. The natural history of ARP has not yet been studied in children. We have recently analyzed our experience of 93 cases of ARP with long-term follow up data\(^13\).

Etiology of ARP in children (table 1): In adults, gallstones and alcohol are the two major causes of ARP but in children biliopancreatic structural/obstructive causes are shown to be important. In a study of 19 cases of ARP in children, Sanchez-Ramirez et al\(^10\) have shown that 25% cases were due to biliopancreatic obstruction like gallstones and pancreas divisum, 37% idiopathic, 30% familial/genetic and the remaining 13% were due to metabolic/drugs. Su et al\(^11\) in their study of 25 case of ARP in children have shown that 50% cases were due to biliopancreatic structural/obstructive causes. Lucidi et al\(^12\) in a study of 78 young patients with ARP have documented biliopancreatic structural/obstructive causes in 26%, genetic causes in 42% and 27% were idiopathic. The recent study by Kumar et al\(^3\) also showed obstructive causes in 33%, genetic mutations in 48% of cases. In our study\(^13\) of 93 cases we have documented obstructive causes in 23% of cases and 75% were idiopathic. Nevertheless, 10 of 22 (45%) idiopathic cases, in whom mutation analysis was performed, were shown to be SPINK1 mutation positive. Hence, even in India a vast majority of ‘so-called’ idiopathic causes were having genetic predisposition for pancreatitis.

Approach to a patient with ARP – The basic difference in approach to a child with ARP from that of an adult is that MRCP/CT scan is done as a first step in adults to rule out underlying chronic pancreatitis/malignancy\(^2\) whereas in children it is done in the 2nd step to diagnose pancreaticobiliary obstructive causes\(^1\). If structural, metabolic and autoimmune
Table 1: Etiology of ARP in children

**Structural causes (25-30%)**
Choledochal cysts, gallstones, pancreas divisum, duodenal duplication, annular pancreas, pancreaticobiliary malunion, sphincter of Oddi dysfunction etc.

**Metabolic**
Hyperlipidemia, hypercalcemia

**Autoimmune pancreatitis**
Type II with normal IgG4 is common in children

**Genetic (40-50%)**
SPINK1, PRSS1, CFTR, CTRC

**Idiopathic (30-40%)**

30-40% pancreatitis is ruled out in 1st and 2nd step then genetic mutation studies are indicated before putting a label of idiopathic. The suggested algorithmic approach to a child with ARP in given in figure 1.14

However, we believe that MRCP should be the first line and not the 2nd line investigation and genetic mutations analysis should be 2nd line. Considering the rarity of autoimmune pancreatitis, it should be the 3rd line investigation.

**Natural history of ARP in children (ARP to CP)** – Adult studies have shown that idiopathic ARP and ARP with genetic predisposition often progress to chronic pancreatitis (CP) in long run15-17. In a study of 75 adults with ARP, Garg et al15 have shown that 47% had progressed to CP on follow-up. Similarly, Whitcomb DC16 and Keim V17 described idiopathic ARP as a transition phase between acute and chronic pancreatitis as they have shown that genetically predisposed cases of AP over many years develop CP after going through the phase of ARP. However, there is no information in children to say ARP is nothing but a transition phase between AP and CP as there is no long-term follow-up study in children. We have analyzed our long-term follow-up data of 93 cases and showed that over a median follow-up period of 2 years almost half (42%) of ARP cases progressed to CP and idiopathic etiology, longer duration of follow-up and presence of genetic mutations were strongly associated with progression.

**Genetic predisposition and the risk of progression to chronic pancreatitis** – There is strong association between genetic predisposition and progression of pancreatitis to CP. It has been shown that most patients with pancreatitis causing genetic mutations present with AP in childhood and progress to CP through a transition phase of ARP over many years16,17. Kumar et al18 in their study of 301 pediatric cases of ARP and CP showed that genetic predisposition was found in 50% in ARP and 75% in CP. The most common identified mutation in ARP was CFTR (34%) and PRSS1 (46%) in CP. They also suggested that PRSS1 or SPINK1 mutations in children are important risk factors for progression of ARP to CP as there was clustering of these mutations in CP group. Lucidi et al19 also showed that almost half of their 78 cases of ARP had one or the other genetic mutations (CFTR in 39.6%, SPINK1 in 7.1% and PRSS1 in 4.5%). Though CFTR mutations are common in Europe and America, it is the SPINK1 which is shown to be common in Asia especially in India. Studies in adults, especially from India and our own study in children, showed that almost half of the cases of idiopathic chronic

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**Fig. 1: Approach to acute recurrent pancreatitis in children**14

1st step: USG, LFT, Lipid profile, serum calcium, autoimmune markers (anti-plasminogen binding protein), IgG4

2nd step: MRCP [pancreaticobiliary structural causes and choledocholithiasis]

3rd step: genetic mutations study
Pancreatitis were associated with SPINK1 gene mutations but PRSS1 and major CFTR gene mutations were extremely uncommon18-22. SPINK1 gene is known as a disease modifier23 and is probably not responsible for initiation of pancreatitis but mutation of SPINK1 leads to disease progression. Children with mutations in SPINK1 who had an episode of pancreatitis of unknown etiology (may be some environmental factor) had a higher risk of developing chronic pancreatitis. In a recent study, Aoun E et al24 showed that SPINK1 N34S polymorphism was not associated with the sentinel acute attack but it substantially increased the risk of recurrent attacks. Hence it is important to get genetic mutation analysis done in all cases of so-called “idiopathic” ARP to predict their progression to CP and that may help in taking some preventive measures like avoidance of alcohol and smoking to modify the disease progression.

Conclusions: MRCP should be done at diagnosis in all cases to rule out the presence of CP and to detect the treatable structural causes. Genetic mutation study should be done as a second line investigation as it predicts the progression. All ARP cases especially idiopathic one and cases with genetic mutations should be followed closely to detect CP early.

Reference
Recent Trends In Liver Transplantation

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Introduction

Paediatric liver transplantation (LT) has dramatically changed the prognosis for many infants and children with liver failure and metabolic diseases. Survival rates are 90% at one-year and 75% at 15-20 years with good quality life. Key to this improved survival has been better preoperative management of hepatic complications and intensive nutritional support, particularly in infants; innovative surgical techniques to expand the donor pool; and improved postoperative immunosuppression and management. The success of this complex procedure has led to a significant increase in the number of children undergoing liver transplantation worldwide including the developing world.

As the focus moves from ensuring immediate survival and the prevention and management of early post-operative complications, there is a need to address long-term outcome and quality of life, the factors that influence them and realistically evaluate what needs to change so that pediatric recipients will become adults.

Indications For Liver Transplantation

Liver transplantation is now accepted therapy for acute or chronic liver failure (Table 1).

Chronic liver failure:
The commonest indication for LT is biliary atresia, accounting for 50% of children requiring transplantation in the U.S and 74% in Europe. The outcome of Alagille’s Syndrome which is an autosomal dominant multisystem disorder and Progressive Familial Intrahepatic Cholestasis (PFIC 1-4) is more variable as many children have compensated liver disease. Liver transplantation is indicated for cirrhosis and portal hypertension, malnutrition and growth failure or for intractable pruritus resistant to maximum medical therapy or biliary diversion.

Metabolic liver disease:
Tyrosinemia type I is an autosomal recessive disorder due to a defect of fumaryl acetoacetase (FAA) in which liver transplantation is only indicated for the development of acute or chronic liver failure unresponsive to Nitidine or hepatocellular carcinoma.

Wilson’s disease is a rare indication for liver transplantation in childhood. Early diagnosis and therapy with penicillamine or zinc should be curative, but transplantation is indicated for those children who present with advanced liver disease (Wilson’s score >6), fulminant liver failure or who have progressive hepatic disease despite penicillamine therapy.

Most children with glycogen storage type I do not require liver transplantation except for those who develop multiple hepatic adenomas or with poor metabolic control. Children with glycogen storage type III and IV progress to cirrhosis with portal hypertension and require transplantation.

Auto-Immune Liver Disease Type I and II:
Most children with auto-immune liver disease type I or type II respond to immunosuppression with Prednisolone or Azathioprine and transplantation is only required in 20% who do not respond, or who present with fulminant hepatic failure.

Timing of Transplantation:
The timing of liver transplantation for children with chronic liver failure is based on the rate of decline of liver function, development of malnutrition despite intensive nutritional support, social and motor developmental delay or severe hepatic complications such as chronic hepatic encephalopathy, refractory ascites, intractable pruritus or recurrent variceal bleeding. Hepatopulmonary syndrome secondary to pulmonary shunting is an important indication for liver transplantation.

Acute Liver Failure
Liver transplantation is indicated for acute liver failure due to fulminant hepatitis or secondary to an inborn error of
metabolism (Table 1). Children should be referred early to a specialist unit with facilities for transplantation.

Children with a poor prognosis include:

1. Indeterminate hepatitis
2. Development of grade III or IV hepatic coma
3. Reduction in hepatic size in association with falling transaminases and increasing bilirubin (> 300 µmol/l or > 16 mg/dl).
4. Persistent severe coagulopathy (>50 seconds over control, INR >4).

**Inborn Errors Of Hepatic Metabolism**:

Certain inborn errors of metabolism are secondary to hepatic enzyme deficiencies and transplantation is indicated if the hepatic enzyme deficiency leads to irreversible liver disease/liver failure and/or hepatoma or severe extrahepatic disease.

**Hepatic Tumours**:

Benign tumours including haemangiomias or haemoangioendotheliomas, adenomas or focal nodular hyperplasia rarely require transplantation while malignant hepatic tumours such as hepatoblastoma or hepatocellular carcinoma which are either unresectable or refractory to chemotherapy are considered for liver transplantation as long as there are no extra-hepatic metastases.

**Table 1**

<table>
<thead>
<tr>
<th>I Chronic Liver Failure</th>
<th>Primary immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestatic liver disease</td>
<td></td>
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<tr>
<td>Biliary atresia</td>
<td>Fulminant hepatitis</td>
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<tr>
<td>Alagille syndrome</td>
<td>Auto-immune hepatitis Type I &amp; II</td>
</tr>
<tr>
<td>Progressive familial intrahepatic cholestasis (PFIC)</td>
<td>Paracetamol poisoning</td>
</tr>
<tr>
<td>Metabolic liver disease</td>
<td>Viral hepatitis (A, B or Indeterminate)</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td>Metabolic liver disease</td>
</tr>
<tr>
<td>Tyrosinaemia type I</td>
<td>Tyrosinaemia type I</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Wilson's disease</td>
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<tr>
<td>Cystic fibrosis</td>
<td></td>
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<tr>
<td>Glycogen storage type IV</td>
<td></td>
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<tr>
<td>Chronic hepatitis</td>
<td></td>
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<tr>
<td>Auto-immune Type I &amp; II</td>
<td></td>
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<tr>
<td>Post viral (hepatitis B, C, other)</td>
<td></td>
</tr>
<tr>
<td>Fibropolycystic liver disease +/- Caroli syndrome</td>
<td></td>
</tr>
</tbody>
</table>

| II Acute Liver Failure                |                                           |
| Fulminant hepatitis                   |                                           |
| Auto-immune hepatitis Type I & II     |                                           |
| Paracetamol poisoning                 |                                           |
| Viral hepatitis (A, B or Indeterminate) | Viral hepatitis (A, B or Indeterminate) |
| Metabolic liver disease               | Tyrosinaemia type I                       |
| Wilson's disease                      | Wilson's disease                          |

| III Inborn Errors of Metabolism       |                                           |
| Crigler-Najjar type I                 |                                           |
| Familial hypercholesterolaemia        |                                           |
| Organic acidaemia                     |                                           |
| Urea cycle defects                    |                                           |
| Primary oxalosis                      |                                           |

| IV Hepatic Tumours                    |                                           |
| Benign tumours                        |                                           |
| Unresectable malignant tumours        |                                           |

**Contra-indications For Liver Transplantation**

There are now few contra-indications to transplantation apart from disseminated sepsis, extra-hepatic metastases or multi organ disease which is not reversible following transplantation.

**Liver Transplant Surgery**

Liver grafts are matched by size, blood group and for CMV negative children by CMV status. The development of reduction hepatectomy, living related transplantation and split liver grafts has extended the operation to young children.

**Post Operative Management And Complications**

The key to post-operative management is preventing the known technical complications of vascular thrombosis and biliary complications, providing adequate immunosuppression to avoid rejection while preventing infection.

Current immunosuppression regimes are based on low dose calcineurin inhibitors (e.g. tacrolimus or cyclosporin) with corticosteroids or mycophenolate mofetil (MMF). Induction therapy with the IL-2 receptor antibody Basiliximab has improved rejection rates. Addition of MMF or mTOR (mammalian target of rapamycin) inhibitors allows reduction in steroid and calcineurin inhibitor use and steroid free regimes.
Late Complications Post Transplant

Late complications include CMV or EBV infection, side effects of immunosuppression, post-transplant lymphoproliferative disease (PTLD), late biliary strictures, hepatic artery or portal vein thrombosis. Chronic rejection may occur at any time. Recently, the use of serial protocol liver biopsies has demonstrated the finding of unexplained graft inflammation (“idiopathic” post-transplant hepatitis) and graft fibrosis which increase with time and are thought to have an immune aetiology. The long term consequence of this is being established.

Recurrence disease is less common in children except for autoimmune liver disease, malignant tumours and PFIC-2.

Long Term Survival

Now that the emphasis has moved from immediate survival, and the prevention and management of early post-operative complications, attention has focussed on long term outcome and quality of life, (QoL), reducing the deleterious effects of essential immunosuppression, prevention of chronic infection and rejection and managing a smooth transition from childhood to adolescence and adult life.

Survivors will require regular monitoring both at the specialist centre and with their local hospital in order to ensure early identification of rejection and technical complications, prevention of chronic infection, such as CMV and EBV and reducing the adverse effects of immunosuppression especially renal dysfunction, hypertension, hyperlipidemia and the development of malignancy, such as post-transplant lymphoproliferative disease.

By three months, most children should be on maintenance immunosuppression with a combination of calcineurin inhibitors, steroids and/or MMF and monthly or three monthly assessment of liver function, Calcineurin Inhibitor drug levels, viral PCR, renal function is usually sufficient. 6 monthly or annual monitoring of liver ultrasounds should identify technical issues.

Long term quality of life is good, as nutritional and psychosocial rehabilitation is achieved. It is important to ensure adequate education and encourage a normal life. Some survivors have demonstrated low cognitive achievement which may be related to the early effects of liver disease on the developing brain.

It is important to pay close attention to nutrition, bone metabolism, endocrine function and psychosocial development. The obesity epidemic affects up to 30% of adult liver transplant recipients and may have similar effects in paediatric liver transplant recipients and so appropriate advice on diet and exercise should be given.

Annual or five yearly assessments of cognitive function, educational achievement and patient and family perceptions of quality of life are suggested to allow appropriate intervention.

Finally the management of adolescent transition to adult care, with all the significant issues of non-adherence requires a multidisciplinary team approach to be successful.

Reference

6. Hübscher SG. What is the long-term outcome of the liver allograft? J Hepatol. 2011 Sep;55(3):702-17
Liver Support Therapy In Acute Liver Failure-Role of Hepatocytes

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Extracorporeal liver support systems (ELSS) encompassing artificial and bio-artificial devices have been used for decades, with the aim of supporting patients with acute liver failure (ALF) and acute-on chronic liver failure (AoCLF) as a bridge to recovery (ALF only) or liver transplantation (LT) in an era of organ donation shortages. Although biochemical efficacy has been consistently demonstrated by these devices, translation into clinical and survival benefits has been unclear, due to study limitations and lack of reliable prognostic scoring in liver failure. Consequently, extracorporeal devices are not widely accepted as routine therapy in adult liver failure. Recent large multicentre trials using artificial liver systems have not revealed beneficial outcomes associated with albumin dialysis but plasma exchange practices have shown some potential.

In paediatric liver failure, data on extracorporeal systems is scarce, comprising few reports on albumin dialysis (namely, Molecular Adsorbent Recirculating System; MARS®) and plasma exchange. When extrapolating data from adult studies differences in disease presentation, etiology, prognosis and the suitability and safety of such devices in children must be considered. Hepatocyte transplantation is a biologic liver support system which may yield promising results in paediatric liver failure.

Hepatocyte transplantation (HCT) is the infusion of isolated hepatocytes, predominantly into the portal venous system. Human hepatocytes are isolated, using a collagenase perfusion technique, from donated liver tissue, which is either considered unsuitable for liver transplantation or is unused. These cells can be either used fresh, or cryopreserved for subsequent use. Intraportal injection is the ideal site, however, alternative sites include the spleen and peritoneal cavity. The injected hepatocytes aim to integrate into the liver plates and repopulate the recipient liver. HCT is becoming a promising intervention in liver-based metabolic diseases with the aim of avoiding or postponing LT, and it’s application in ALF is showing promising results.

The clinical role for HCT, to date, has been best demonstrated for inborn metabolic liver diseases, characterised by a single missing hepatic enzyme/protein (e.g. urea cycle defects, Criggler-Najjar Syndrome Type I). Transplanted hepatocytes, usually representing 5-10% of the theoretical liver mass in these specific conditions, have chiefly revealed temporary treatment until transplantation. HCT for ALF and AoCLF is more complicated, due to higher numbers of injected hepatocytes required to achieve adequate liver function, and alternative routes of hepatocyte delivery required due to coagulopathy. Both adult and paediatric cases using HCT in liver failure have been reported.

A multicenter study in the USA nearly two decades ago, documented the effect of splenic artery hepatocyte infusion in patients with ALF (n1=9) and AoCLF (n2=4) including two paediatric patients (6 month old, parenteral nutrition related liver disease and sepsis; 5 month old, idiopathic ALF). An improvement in ammonia, cerebral blood flow, intracranial pressure and HE was seen in patients, however survival outcomes were not significantly different to matched controls (those that did not consent to HCT). Full recovery was seen in one patient with fulminant hepatitis B with grade I HE; the infant with ALF was bridged to LT at day 2 and the infant with AoCLF died of an intracranial haemorrhage.

Intraperitoneal hepatocytes has been used in ALF patients with grade III/IV HE (n=7), including an 8 year old child. In comparison with matched controls, survival was higher in the therapy group (HCT 43% vs 33% control). Three patients showed full recovery, including the child. Several other reports have revealed full recovery after HCT79,80. On application of HCT in cases of severe ALF81, not deemed suitable for LT, although all patients died (n=5), three had improving biochemistry and neurology and survived longer than expected. No significant adverse effects have been reported.

Recently our group has optimized the use of alginate encapsulated human hepatocytes in the treatment of}
liver failure in children. The study population included patients with acute liver failure fulfilling criteria for liver transplantation. In this pilot study 4/8 children (50%) avoided liver transplantation, three patients received liver transplant and retrieved beads showed functioning hepatocytes. One patient died in whom care was withdrawn due to poor cardiac prognosis due to an underlying congenital heart disease.

Editor’s Note

Although liver transplantation has dramatically improved the prognosis for patients with acute or end-stage liver failure, and inherited metabolic disorders, because of the complexity and associated morbidity and mortality of this procedure, hepatocyte transplantation is being explored as a convenient and safer alternative. Transplanting isolated hepatocytes by percutaneous or transhepatic infusion into the portal vein, or injecting into the splenic pulp or the peritoneal cavity, is a less invasive procedure compared with liver transplantation. As the host liver is not removed or resected, the loss of graft function should not worsen liver function. Furthermore, isolated hepatocytes could be, potentially, cryopreserved for ready access. After extensive evaluation in experimental animals, clinical trials of hepatocyte transplantation have been initiated at several institutions for acute or chronic liver failure and inherited metabolic disorders. Hepatocytes transplantation has been explored as a vehicle for ex vivo gene therapy and is being considered for rescuing patients from radiation-induced liver damage resulting from radiotherapy for liver tumors.

Hepatocyte transplantation has been tested most extensively in Gunn rats and Nagase genetically analbuminemic (NAR) rats. In both models, transplantation of normal donor hepatocytes ameliorated the metabolic deficit. When the liver is structurally normal, which is the case in many inherited liver based disorders, hepatocytes injected into the splenic pulp or infused into the portal vein migrate to the liver and become integrated into the hepatic cords within days. These cells become morphologically identical to the host cells and function throughout life, and can be recognized only by virtue of biochemical or genetic markers.

Liver-directed gene therapy is being contemplated for both inherited disorders and acquired conditions, such as infectious and neoplastic diseases, cirrhosis of the liver and immune rejection of transplants. Missing gene products causing inherited diseases could be replaced by transferring genes expressing those proteins. In other cases, specific genes could be overexpressed for therapeutic purposes, such as the overexpression of metalloproteases for the treatment of cirrhosis.

The large size of liver and secretory characteristics of the liver could be exploited to generate “biodrugs” for export out of the hepatocytes. Such proteins include coagulation factors, hormones or vaccines. In some cases, proteins that are normally expressed at extrahepatic sites could be expressed in the liver for specific purposes.

Editor
Perinatal transmission is the commonest mode of acquiring hepatitis B infection in children in developing countries. Unlike in adults, spontaneous seroconversion to an anti HBs state is a rare event (<1%). Most children therefore would benefit from some form of treatment. However, a majority of them are in the immune-tolerant phase, wherein response to currently available drugs is poor.

The goal of treatment of chronic Hepatitis B (CHB) in children is to reduce the risk of progressive liver disease, improve long term survival and also reduce the infectious pool in the community. The ideal end point of treatment should be sustained HBs Ag clearance. This is often very difficult to achieve. Anti HBe seroconversion and sustained suppression of viral replication (undetectable HBV DNA level) is an acceptable end point. The need and rationale for treatment should be discussed carefully with the parents to ensure that the benefits of intervention should outweigh the undesirable effects of the drug therapy.

Factors influencing treatment

The factors which influence the choice of agents include age of the patient, Serum ALT level, Serum HBV DNA level, liver histology at baseline, cost of treatment, family history of Hepatocellular carcinoma (HCC) and presence of co-infections. The two major classes of drugs for treatment of chronic Hepatitis B are interferon (IFN) and Nucleoside. All published guidelines recommend treatment only for children with biochemical evidence of liver injury and serum HBV DNA levels in excess of 20,000 IU/ml. In patients with decompensated liver disease, Nucleoside analogues (NA) are the best choice.

Definitions of treatment response

1. Biochemical response: Normalisation of ALT levels reflecting reduction in histological activity should be monitored every 3 months in first year after treatment and every 6 months thereafter.
2. Serological response: Loss of HBeAg and positive anti Hbe Abs or Loss of HBsAg and positive Anti HBs Abs.
3. Virological response: HBV DNA < 2000IU/ml after 3-6 months of NA or Undetectable after 6 months of IFN
4. Complete response: Sustained HBs Ag loss off treatment on long term
5. Virologic breakthrough: Increase in HBV DNA level >1 log10 IU/ml during therapy.

Antiviral Therapy

Interferon

This has immune modulatory properties, enhancing KLA class I antigen expression on the surface of infected hepatocytes as well as augmenting CD8+ cytotoxic T cell activity. Interferon is given for 6 months to a maximum of 1 year and is not usually associated with drug resistance. It can produce a flu like illness, ocular complications (retinitis/optic neuritis) and leucopenia. The recommended dose is 0.1 MU/kg or 5 to 10 MU/m2 S/C three times a week for 6 months. Pegylated interferon is more potent and requires only once a week dosing. Phase III trials are underway, but it is not yet approved by FDA for children.

Nucleoside and Nucleotide analogues (NA)

They are competitive inhibitors of viral reverse transcriptase and DNA polymerase and interfere with synthesis of HBV DNA. Since they only partially suppress viral replication, prolonged duration of treatment is necessary and thus an increased risk of drug resistance. Seroconversion rates decrease over time and one-fourth of children develop ALT flares after withdrawal.

1. Lamivudine:

This is a potent inhibitor of viral replication. Resistance to the drug increases with the duration of therapy and is more in patients co-infected with HIV. It is only recommended in
Treatment of Chronic hepatitis B (Modified from ESPGHAN guidelines by Sokol et al.)

CHILD WITH CHB

Normal

HBe Ag+

HBV DNA > 20,000 IU/ml

Immuno tolerant phase

Follow-up

HBe Ag+

HBV DNA < 2000 IU/ml

Inactive disease

Follow-up

Persistently elevated ALT

HBe Ag+

HBV DNA > 20,000 IU/ml

Immuno active phase

Liver biopsy

HBeAg -ve chronic hepatitis

HBV DNA < 2000 IU/ml

Mild inflammation / fibrosis (Ishak <3)

No

Family history of HCC

Yes

Treatment

Cost issue

IFN α 6 mo

<12 yrs: Lamivudine
12-16 yr: Tenofovir
>16 yrs: Entecavir

Response

Yes

No
children > 3 years of age at a dose of 3 mg/kg/day as a single dose (Max dose – 100mg). The drug is well tolerated and cheap.

2. Adefovir Dipivoxil:

HBeAg seroconversion is lower than with Lamivudine after the first year of treatment, but rises in the second year. Resistance rates increase with longer duration of therapy. It is effective in lamivudine resistant strains of HBV. It is now recommended in children above 12 years at 10mg/day once daily.

3. Tenofovir:

It is a nucleotide inhibitor and has recently been approved for use in children above 12 years of age in a dose of 300 mg once daily. Phase III trials are on for younger children. It is more effective than adefovir in lamivudine resistant HBV as well as in treatment naïve patients. Resistance has not been reported after up to two years of treatment.

4. Entecavir:

Is a reverse transcriptase inhibitor and approved for use in children above 16 years in a dose of 0.5mg once daily orally. Resistance rate are very low and it is well tolerated. Phase III trials are underway in younger children.

Treatment strategy

For all children with HBeAg positive active hepatitis (elevated ALT), 6 months of IFN is currently the drug of choice. PegIFN may soon become available for use once approved in children. In spite of significant adverse reactions and the high cost, IFN remains the only drug that offers the chances of a sustained virological response without emergence of resistance. It is contraindicated in children with decompensated cirrhosis, pancytopenia, autoimmune diseases and in transplanted patients. Priming with steroids has no proven benefit and combination with lamivudine does not give better seroconversion rates in the long term.

For those unresponsive to IFN, Entecavir is presently the drug of choice in children above 16 years, while Tenofovir is recommended in those 12-16 years. Tenofovir may soon be available for younger children, since it is already approved and widely used in children above 2 years with HIV. Adefovir is no more used, because of the highest risk of resistance with lower response rates. Entecavir or Tenofovir should be continued for at least 12 months after reaching undetectable HBV DNA levels and HBeAg seroconversion. Patients who do not achieve virological remission need long term treatment based on adult safety data. Children below 12 years pose a special challenge, since lamivudine is the only approved drug and it has a high risk of development of resistance. In those who achieve virological remission, Lamivudine should be discontinued 6 months later. These children should be followed up for any relapse, in which case the drug should be restarted or an alternate drug like tenofovir should be started. Available data does not support the use of combination therapy with Lamivudine and adefovir.

NA have traditionally been used only as second line drugs in chronic hepatitis B. It is possible that in the near future, Entecavir and Tenofovir may be available for use as first line drugs in adolescents, in view of their higher genotypic barrier to resistance.

Into the future

Some studies have shown that overall long term outcomes are similar in treated and untreated children with chronic hepatitis B infection. Additional studies are required to verify this finding. Most children with HBV infection in developing countries are in the immunotolerant phase and studies are needed to assess the risk benefit ratio of the newer drugs in such children. Comparative studies on the various NA at all ages would help make optimal treatment algorithms. More data is also required on continuing treatment and probable end point of therapy in children who do not respond to NA.

Reference


Current Treatment Options And Response Rates In Children With Chronic Hepatitis C

Tarun Choudhuri

Abstract
Vertical transmission has become the most common mode of transmission of hepatitis C virus (HCV) in children. The rate of perinatal transmission from an HCV-infected mother to her child ranges from 2% to 5% and the prevalence of HCV in children in developed countries ranges between 0.1% and 0.4%. Spontaneous viral clearance seems to be dependent on the genotype and has been reported between 2.4%-25%. For chronically infected patients, treatment with recombinant polyethylene glycol (PEG)-interferon α-2b and daily rebavirin has now been approved as standard treatment for children 2-17 years of age. In five large prospective studies, a total of 318 children and adolescents aged 3-17 years were treated either with subcutaneous PEG-interferon α-2b at a dose of 1-1.5 µg/kg or 60 µg/m² once a week in combination with oral ribavirin (15mg/kg per day) or PEG-interferon α-2a with ribavirin. Subjects with genotype 1 and 4 received the medication for 48 wk and individuals with genotype 2 and 3 mainly for 24 wk. Overall sustained viral response (SVR) was achieved in 193/318 (60.7%) of treated patients. Stratified for genotype; 120/234 (51%) with genotype 1, 68/73 (93%) with genotype 2/3, and 6/11 (55%) with genotype 4 showed SVR. Relapse rate was between 7.7% and 17%. Overall, treatment was well tolerated; however, notable side effects were present in approximately 20%. According to recent experiences in the treatment of chronic hepatitis C in children and adolescents, a combination of PEG-interferon α with ribavirin has been found to be well tolerated and highly efficacious, particularly in individuals with genotype 2/3. Thus, this treatment can be recommended as standard of care until more effective treatment options will become available for genotype 1 patients.

Key words
Chronic hepatitis C; Treatment; Children; Polyethylene glycol-interferon and ribavirin; Response rate.

Introduction
Combination therapy of polyethylene glycol (PEF)-interferon α-2a or α-2b with ribavirin is standard of care for adults with chronic hepatitis C. Clear benefits in terms of sustained viral response (SVR) and side effect profile have been documented with PEG-interferon α compared with recombinant interferon α with and without ribavirin. An additional advantage of the pegylated form of interferon is the extended serum half-life, which allows a once-weekly administration regimen. Until recently, only recombinant interferon α-2b in combination with ribavirin had been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in children and adolescents. Since December 2008 and September, 2009, respectively, the FDA and EMA approved PEG-interferon α-2b in combination with ribavirin in the United States and Europe for children age 3 years and older. Although most experts believe treatment is beneficial, due to several factors associated with treating young patients with chronic hepatitis C, this topic remains controversial. However, there is no doubt that chronic hepatitis C, remains an epidemiologically important health care issue in children and adolescents. Associated costs in the United States are estimated between $17 and $40 million annually. Effective treatment of chronic hepatitis C virus (HCV) at an early age would help to prevent the long-term sequelae of chronic infection, improve the prognosis of patients, and reduce health care expenditure.

The prevalence of HCV in children in developed countries ranges between 0.1% and 0.4% but may even exceed 10% in some regions of Saudi Arabia and Africa. The rate of perinatal HCV transmission from an infected mother to her child ranges from 2% to 5%. Clinically most relevant are genotypes 1, 2 and 3; considerably less spread is genotype 4. It is estimated...
that there are 1 million individuals aged less than 18 years infected with chronic hepatitis C worldwide. Since early 1990s, transmission of HCV infection has occurred predominantly by parenteral transfusion of blood products or by non-use of disposable syringes. However, transfusion-associated hepatitis C has now become extremely rare in countries with adequate hygienic facilities. Subjects who were particularly at risk such as premature infants, hemophiliacs, patients with thalassemia, and children with malignant diseases or organ transplantations have now reached adulthood and vertical transmission from HCV-infected mothers to their off-springs has become the most common cause of chronic hepatitis C in children. Importantly, in the case of vertical infection, the chronicity rate is very high.

Children chronically infected with HCV may be at risk for social disintegration and impaired quality of life. A possible psychological burden may be present and some physical impairment has been described. To date, only two rather small studies have been published reporting significantly lower physical and psychosocial scores and worse cognitive functioning compared with non-infected controls.

Natural Course

Spontaneous viral clearance in vertically infected children seems to be dependent on genotype and was found to range from 2.4%-25%. It may be higher in parenterally infected individuals and was reported to reach 35%-45% by adolescence. Children infected with genotype 3 have a higher spontaneous clearance rate than those infected with genotype 1. Beyond the age of 4 years, spontaneous viral clearance seems to become rather unlikely. Patients who do not clear the virus within the first years of life will develop chronic hepatitis C. Overall, the cumulative probability of progression to chronicity is approximately 80%. Most children are clinically asymptomatic or show only mild unspecific symptoms. In roughly 10% of patients, hepatomegaly may be present during the chronic course, alanine aminotransferase (ALT) levels may be normal or intermittently elevated. Only few patients show persistent markedly elevated ALT levels. Inflammatory activity in liver tissue is usually mild and the risk of severe complications is low. However, despite the favourable prognosis during the first and second decade of life, approximately 4%-6% of children will develop evidence of advanced liver fibrosis or cirrhosis. A recently published study in pediatric patients with chronic hepatitis C cured of malignancy reported liver cirrhosis in 5% after three decades of observation. Progression of fibrosis depends on age and additional risk factors such as obesity and alcohol consumption. Thus, progression usually starts beyond the second life decade and there is evidence that it seems to proceed more rapidly in patients with genotype 3.

Large liver transplantation units have reported on children who needed liver transplantation due to progressive HCV infection.

Treatment Options

Many years ago, treatment started in adults with the use of interferons, yielding SVR rates in the 10%-15% range. According to the use of different treatment regimens and small numbers of treated children, it was difficult to compare the response rates in children to those in adults. Overall, SVR seemed to be better in children. Nineteen studies using recombinant a-interferon were published between 1992 and 2003. A meta-analysis of trials with interferon-a monotherapy revealed a wide range (0%-76%), mean 27% of SVR. Subjects infected with genotype 2 and 3 clearly responded better than patients harbouring genotype 1. Based on an increasing number of randomized controlled trials in adults, ribavirin was added to interferon- in treatment trials for children. Between 2000 and 2005, six studies were published all demonstrating an SVR from 27% to 64%. The stratification according to genotypes showed a very good response (>80%) in patients with genotype 2 and 3 and an SVR of approximately 36%-53% in those with genotype 1. Results of an extensive trial in children published by Gonzalez-Peralta led to the approval of recombinant interferon-α-2b in combination with ribavirin. However, when PEG-interferon in combination with ribavirin became the standard of care for adults with chronic hepatitis C, trials in children promptly started. Some advantages were present such a reduced injection frequency to once per week, better SVR, and better interferon tolerance. Interestingly, the sole controlled randomized trial, comparing a pegylated interferon (PEG-interferon-α-2a) with and without additional ribavirin, was only published in 2011. It clearly demonstrated that in the pediatric age group, the addition of ribavirin was necessary to obtain significantly better treatment results. Specifically, in genotype 1 patients, SVR rate was 17% with PEG-interferon monotherapy and 47% in those with genotype 1. Results of an extensive trial in children published by Gonzalez-Peralta led to the approval of recombinant interferon-α-2b in combination with ribavirin.

Upto now, results of seven trails using PEG-interferon α in combination with ribavirin have been reported. SVR rates in patients with genotype 1 from 5 trials with more than 30 patients ranged from 44% to 59%. Achieving SVR in children with genotype 2 and 3 was very successful and yielded rates.
of more 90%. The relapse rate was between 7.7% and 17%. Four trials used PEG-interferon α-2b and two used PEG-interferon α-2a in combination with ribavirin. An additional report presented the retrospective data in 33 treated Japanese children and young adults. SVR rate in these patients was approximately 82%. Pegylated interferon α-2b and ribavirin were approved for patients aged 3 to 17 years of age by the FDA in December 2008 and the EMA in September 2009.

Baseline viral load
Two studies stratified the results in genotype 1 patients according to the viral load before treatment. In the first study, the cut-off level was 600 000 IU/mL: 32% of children with genotype 1 and high viral load (> 600 000 IU/mL) and 73% with low viral load (< 600 000 IU/mL) achieved SVR. In the second trial, the cut-off value was 500 000 IU/mL: 45% of children with genotype 1 and > 500 000 IU/mL and 62% with < 500 000 IU/mL achieved SVR.

Table 1- Most frequent adverse events during polyethylene glycol-interferon treatment in combination with ribavirin and its appraisal of clinical significance

| Interferon α treatment: | Leukopenia, thrombocytopenia – Frequent, not really significant; |
| | If necessary dose reduction |
| | Flu-like symptoms – In all treated patients, not significant |
| | Alopecia – Not significant |
| | Autoimmune thyroiditis – At least 15%, significant, mostly reversible |
| | Acute psychosis, depression – Very seldom before puberty(<1%), rare in adolescents, significant in cases with manifestation; should be under investigation in future trials |
| | Growth delay – Clinically not significant, catch-up growth, but under investigation with relative high priority |
| | Anorexia, weight loss – Mostly not significant with exceptions, normalization after therapy stoppage. |

**Ribavirin**

| Anemia: Mostly clinically not significant with exceptions, reversible |
| Most side effects’ intensity is decreasing after some weeks of treatment. |

**Baseline aminotransferases**

It is remarkable that the level of aminotransferases or histological findings by liver biopsy do not significantly correlate with SVR. However, interestingly, there was a trend towards a slightly better SVR in patients with normal aminotransferases.

**Mode of infection**

There is no significant correlation between SVR and the mode of infection. Nevertheless, it seems that individuals with parenteral infection may have a slightly higher probability to obtain SVR. However, the overall response rate in vertically infected subjects was 55% and in genotype 1 patients 46%, which is comparable to the SVR in adults who are mainly parenterally infected.

**Standard of care**

According to approval, in principle, treatment with interferon α-2b and ribavirin administering injections thrice per week can be performed. However, the majority of experts will prefer once weekly dosing using PEG-interferon. To date in America and Europe, only PEG-interferon α-2b (60µg/m2 per week) in combination with oral ribavirin (15 mg/kg per day) is approved by the FDA and EMA. Patients with genotypes 1 and 4 should be treated for 48 wk, with treatment discontinued at 4-6 mo if there has been no viral response. Patients with genotypes 2 and 3 should be treated for 24 wk irrespective of pre-treatment viral load. In routine clinical practice, there is no need to perform liver biopsy before initiating treatment. In addition, pre-treatment levels of aminotransferases and mode of infection are not predictive for SVR. A five-year follow-up study of children with SVR treated with interferon α and ribavirin showed permanent viral elimination in 98% (Kelly D, personal communication).

**Re-treatment**

Response rates in patients retreated with a standard of care protocol are dependent on the primary treatment regimen. Individuals with previous interferon a monotherapy or recombinant a-interferon in combination with ribavirin may achieve a higher response rate. There are no studies specifically addressing re-treatment except for the trial by Gerner P et al., which has been performed with a natural interferon α in combination with ribavirin. Previously published reports have only include small numbers of children with failed response, demonstrating with a re-treatment response rate of 40%-50% in those with previous interferon a monotherapy. Gerner et al. reported SVR in only 2/18 patients. Thus, re-treatment, particularly in individuals who have been primarily treated with PEG-interferon and ribavirin, remains prognostically difficult and cannot be recommended until new combination treatment options including directly acting antivirals such as protease inhibitors become available.
**Adverse Events**

The majority of treated children and adolescents will tolerate PEG-interferon and ribavirin well. Nevertheless, almost all patients will experience at least one side effect. The clinical significance of adverse events is summarized in Table 1. Most adverse events are mild to moderate, such as flu-like symptoms including fever, anorexia, fatigue, dry skin and moderate hair loss. In some patients, dose reduction of PEG-interferon may be necessary due to decreased white blood cell counts. Severe anemia is very rare; hence, the need for dose reduction of ribavirin is extremely infrequent. The rates of discontinuation of treatment due to adverse events were low in all trials published. Severe psychiatric side effects were rare in pre-pubertal individuals, but may be of significance in affected individuals. Appearance of thyroid autoantibodies and thyroid dysfunction during long-term treatment (>24 wk) has to be considered and carefully monitored. Up to 20% of treated patients, particularly with genotype 1, may have abnormal thyroid stimulating hormone levels or other signs of thyroid dysfunction. Another notable side effect is transient growth impairment. Inhibited growth can be observed in 50%-70% with decrease of growth velocity below the 3rd percentile. Shortly after the end of treatment, catch-up growth usually starts with an increased growth velocity followed by achievement of previous growth velocity levels, which can be observed during the follow-up period. Nevertheless, if possible, treatment during pubertal growth spurt should be avoided.

In addition, weight loss is very common during the treatment phase; however, most patients experience compensatory weight gain after treatment ends. Regarding quality of life, and behavioral, emotional and cognitive outcomes during and after treatment, no significant impairment has been detected in the PEDS-C trial. More follow-up studies are in progress to evaluate long-term sequelae.

**New Developments**

There is no doubt that treatment response in patients with genotype 1 is not entirely satisfactory and improved treatment regimens are desirable. A number of directly acting antiviral agents, designed to target viral encoded proteins essential to the HCV life cycle, are currently under development. Phase III trials in adults have been completed for two protease inhibitors (telaprevir and boceprevir) and have shown a significantly increased viral elimination rate in combination with PEG-interferon and ribavirin. Brand new data indicate that in a considerable number of patients with rapid response, exposure to PEG-interferon and ribavirin may be shortened and response-guided therapy will become the treatment of choice. Approval of telaprevir and boceprevir has been sanctioned by the FDA and EMA in 2011, and pediatric trials will follow in the near future. In adults, genotype 1 non-responders have also demonstrated SVR rates ranging between 59% and 66%, depending on the duration of boceprevir treatment, compared to 20% with standard of care. Given that efficacy data could be extrapolated from adults to children, an approved triple therapy regimen should be expected for non-responders. Nevertheless, they should definitely be included in future pediatric trials.

**Conclusion**

In the children and adolescents, PEG-interferon treatment in combination with ribavirin for 48 wk produces a sustained viral response rate in approximately 50% of adequately treated individuals. Thus, this option can be offered to all patients irrespective of the level of aminotransferases or mode of infection. There is evidence that subjects with low viral load may respond better than patients with high viral load. In

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**Table 2 Indication for Hepatitis C virus treatment in children – pros and cons**

<table>
<thead>
<tr>
<th>In favour of treatment</th>
<th>Deferral might be considered</th>
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<tbody>
<tr>
<td>High response rate, sustained viral response means cure of the disease</td>
<td>Before 3-4 years of age because of possible spontaneous viral elimination</td>
</tr>
<tr>
<td>Prevention of disease progression and social burden</td>
<td>Psychiatric disorder</td>
</tr>
<tr>
<td>Better tolerability and less side effects in younger patients (particularly before puberty)</td>
<td>Low response rate in subjects with genotype 1 and high viral load</td>
</tr>
<tr>
<td>More favourable factors for response in children (e.g., low viral load)</td>
<td>Pubertal growth spurt</td>
</tr>
<tr>
<td>Parents facilitate compliance</td>
<td>More effective treatments in future in genotype 1 non-responders</td>
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</table>
patients infected with genotype 2 or 3, a 90% or even better SVR rate can be achieved. Thus, treatment for 24 wk should be administered in all patients with genotype 2 and 3. According to the approval of the drugs, treatment start is possible beyond three years of age. However, because spontaneous viral elimination may occur within the first 4-5 years of life in vertically infected individuals, watchful waiting for up to five years of age is a justified alternative to an early treatment start. Additionally, different individual and family variables may influence the appropriate time to initiate therapy. An experienced pediatric gastroenterologist should supervise the management of treating these patients. Mid-childhood age before pubertal growth spurt is preferable. Table 2 summarizes pros and cons to indicate or possibly to defer treatment. Adverse events are usually well tolerated, but severe side effects may occur in a small number of patients making dose adjustment necessary. Overall, the encouraging results, particularly in patients with relatively low viral load and / or favourable genotypes and in line with an appropriate consideration of early stopping rules, endorse application of treatment in eligible patients. Re-treatment in non-responding genotype 1 patients should be deferred until a combination of standard care with direct acting antivirals has become available.

Reference

Acute pancreatitis refers to acute inflammation of pancreas secondary to multiple causes. Trauma, drugs, infections, gall stones, biliary structural anomalies, genetic, familial, metabolic abnormalities and systemic illness constitute important causes in pediatric age-group. The diagnosis of acute pancreatitis is based on presence of at least 2 out of the 3 features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum amylase or lipase activity at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) or transabdominal ultrasonography.

The estimated incidence of acute pancreatitis (AP) in children is around 3.6 to 13.2 cases per 100,000/year in the western population and the increase is largely related to increasing awareness about the disease. Outcome of AP in children is mostly favourable, although 15-20% may have severe disease depending on the definition followed. There are various prognostic scoring systems for stratifying the disease in adult population of which the common ones are Ranson, Glasgow, Balthazar CT severity index, APACHE-II score, Atlanta (1992), Revised Atlanta (2012) and Determinant based classification (DBC). Among these Atlanta and revised Atlanta classifications are most commonly used (Table).

There are various problems associated with usage of severity scores, particularly the Atlanta classification, in the pediatric age-group. First, the definition of organ failure is for adult age-group and is not an age-appropriate one. Second, the identification of local complications of acute pancreatitis is sometimes difficult in young children owing to the technically difficult magnetic resonance imaging (MRI) and radiation exposure related to computerized tomography (CT). Third, the incorporation of Ranson’s and APACHE-II in the Atlanta classification, the scores which are meant for adult population, do not carry any meaning in pediatric age-group. Fourth, although the revised Atlanta classification defines the local complications in a better way giving a time limit of 4 weeks for maturation and development of an enhancing wall, the natural history for development of complications may be abbreviated in children and the confusion remains on several occasions in differentiating acute peripancreatic fluid collection (APFC) from acute necrotic collection (ANC) and Pseudocyst from walled-off necrosis (WON) in the pediatric age-group. Fifth, infection which is an important determinant from second week onwards in the natural history of severe acute pancreatitis, is not defined properly in the Atlanta classification for stratification of acute pancreatitis. Lastly, the older Atlanta classification doesn’t give description of moderately severe pancreatitis, the entity which has an intermediate prognosis between mild and severe acute pancreatitis, and needs timely management. This lacuna has been looked up in the Revised Atlanta and Determinant based classification methods.

Various scoring systems have been recently devised for usage in the pediatric population (Table). Of these, the one worth mentioning is by DeBanto et al (Pediatric acute pancreatitis score, PAPS score) which includes 8 parameters and the presence of 3 out of 8 was shown to be associated with severe pancreatitis and associated morbidity and mortality. More recently, age-specific definition for organ failure in pediatric SIRS has been used to better stratify severe pancreatitis in children (Pediatric JPN score).

This was shown to have better sensitivity (80%) than Ranson and DeBanto scores with comparable specificity in labelling severe acute pancreatitis.
Table: Scoring systems for Acute pancreatitis

<table>
<thead>
<tr>
<th>Ranson score</th>
<th><strong>At Admission</strong>*</th>
<th><strong>During initial 48 hours</strong>*</th>
</tr>
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<tbody>
<tr>
<td>Age &gt;55 years</td>
<td>Hematocrit decrease &gt;10%</td>
<td></td>
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<tr>
<td>WBC count &gt;16000/mm³</td>
<td>Blood urea nitrogen increase &gt;5 mg/dL</td>
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<tr>
<td>Blood glucose &gt;200 mg/dL</td>
<td>Serum Calcium &lt;8 mg/dL</td>
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<tr>
<td>Serum LDH &gt;350 IU/L</td>
<td>Arterial pO2 &lt;60 mm Hg</td>
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<tr>
<td>Serum AST &gt;250 IU/L</td>
<td>Serum base deficit &gt;4 meq/L</td>
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<thead>
<tr>
<th>Balthazar CT severity index</th>
<th><strong>Balthazar grade</strong>*</th>
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<tbody>
<tr>
<td>A = 0</td>
<td>Necrosis score:</td>
</tr>
<tr>
<td>B = 1</td>
<td>Absence = 0</td>
</tr>
<tr>
<td>C = 2</td>
<td>Necrosis of upto 33% = 2</td>
</tr>
<tr>
<td>D = 3</td>
<td>Necrosis of 33-50% = 4</td>
</tr>
<tr>
<td>E = 4</td>
<td>Necrosis of &gt;50% = 6</td>
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<tr>
<td><strong>Plus</strong>*</td>
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<table>
<thead>
<tr>
<th>Atlanta Classification (1992)</th>
<th><strong>Presence of organ failure</strong></th>
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</thead>
<tbody>
<tr>
<td>a. Shock: Systolic BP &lt;90 mm Hg</td>
<td>a. Necrosis</td>
</tr>
<tr>
<td>b. Pulmonary insufficiency pO₂ &lt;60 mm Hg</td>
<td>b. Abscess</td>
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<tr>
<td>c. Renal failure: Creatinine &gt;2 mg/dL</td>
<td>c. Pseudocyst</td>
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<tr>
<td>d. Gastrointestinal bleeding: &gt;500 ml/24 hours</td>
<td><strong>Unfavourable early prognostic signs</strong></td>
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<tr>
<td></td>
<td>a. ≥3 of Ranson’s signs, or</td>
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<tr>
<td></td>
<td>b. APACHE-II &gt;8</td>
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<table>
<thead>
<tr>
<th>Revised Atlanta Classification (2012)</th>
<th><strong>Mild pancreatitis:</strong></th>
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<tr>
<td>No organ failure (OF)</td>
<td>Acute peripancreatic fluid collection (APFC): Fluid collections within 4 weeks with no definite wall, homogenous, confined by normal fascial planes in retroperitoneum, mostly sterile and resolve spontaneously.</td>
</tr>
<tr>
<td>No local or systemic complications</td>
<td>Pancreatic pseudocyst (PP): Fluid collection with a well-defined wall developing from a localised collection usually after &gt;4 weeks.</td>
</tr>
<tr>
<td><strong>Moderately severe pancreatitis:</strong></td>
<td>Acute necrotic collection (ANC): Collection with variable amounts of fluid and necrotic tissue within 4 weeks which can involve pancreatic parenchyma and/or peripancreatic tissues. May be multiple and loculated.</td>
</tr>
<tr>
<td>OF that resolves within 48 hours (transient OF)</td>
<td>Walled-off necrosis (WON): Mature encapsulated collection of pancreatic and/or peripancreatic necrosis and with a well-defined enhancing inflammatory wall developing &gt;4 weeks of pancreatitis. May be infected, multiple, and at sites distant from pancreas.</td>
</tr>
<tr>
<td>Local or systemic complications without persistent OF</td>
<td>Infected necrosis: Infected ANC or WON on the basis of clinical course or presence of gas within collection on imaging.</td>
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<tr>
<td><strong>Severe pancreatitis:</strong></td>
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<tr>
<td>Persistent OF (&gt;48 hours)</td>
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</tr>
<tr>
<td>Associated with SIRS</td>
<td></td>
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<tr>
<td>Single or multiple</td>
<td></td>
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<tr>
<td>Determinant based classification (DBC)</td>
<td><strong>Mild AP</strong>: No peripancreatic necrosis AND No OF</td>
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<tr>
<td><strong>Moderate AP</strong>: Sterile peripancreatic necrosis AND/OR Transient OF</td>
<td>Sterile peripancreatic necrosis is absence of proven infection.</td>
</tr>
<tr>
<td><strong>Severe AP</strong>: Infected peripancreatic necrosis OR Persistent OF</td>
<td>Infected peripancreatic necrosis is defined by presence of gas bubbles within necrosis, or positive culture of necrotic fluid.</td>
</tr>
<tr>
<td><strong>Critical AP</strong>: Infected peripancreatic necrosis AND Persistent OF</td>
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</tr>
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</table>

**Peripancreatic necrosis** is nonviable tissue located in or around pancreas; can be solid or semisolid and without a radiologically defined wall. **Sterile peripancreatic necrosis** is absence of proven infection. **Infected peripancreatic necrosis** is defined by presence of gas bubbles within necrosis, or positive culture of necrotic fluid.

**Organ failure** is defined for 3 organ systems (cardiovascular, renal, and respiratory) on the basis of the worst measurement over a 24-hour period (Cardiovascular: need for inotropic agent, Renal: creatinine ≥2.0 mg/dL, Respiratory: PaO2/FiO2 ≤300 mmHg).

**Persistent OF**: persisting >48 hours.

### Scoring systems specifically devised for Pediatric age-group

**Pediatric acute Pancreatitis score (PAPS)**
- Age <7 years
- Weight <23 kg
- WBC >18,500/mm³
- LDH >2000 IU/L
- 48-hour trough calcium <8.3 mg/dl
- Trough albumin <2.6 mg/dl
- Fluid sequestration >75 ml/ kg/48 h
- Rise in blood urea nitrogen >5 mg/dL.

**Score ≥3: Sensitivity 70%, Specificity 79%, NPV 91%**

**Szabo FK, USA**
- High Lipase, High WBC, Low Albulin
- AUROC 0.76

**Bierma MJ, Australia**
- Lipase >7 times ULN & 48 hours trough Calcium <2.15 mmol/L
- Sensitivity 46%, Specificity 89%, NPV 79%, PLR 4.18

**Pediatric JPN score**
- Age <7 years and/or weight <23 kg
- Base excess < -3mEq or shock
- pO2 ≤60 mm Hg or ventilatory requirement
- Blood urea nitrogen ≥40 mg/dl, (or creatinine ≥2 mg/dl or urine volume <0.5ml/kg/hour after fluid resuscitation)
- LDH ≥2 X ULN
- Platelets <1X10⁹/mm³
- Calcium ≤7.5mg/dL
- CRP ≥15 mg/dL
- Pediatric SIRS score >3

**Presence of ≥3 of the 9 criteria**

**Pediatric SIRS and shock criteria:**
- a. Core temp >38.5°C or <36°C
- b. Tachycardia defined as HR >2SD above normal for age, or for children <1 year, bradycardia defined as HR <10th centile for age
- c. Mean RR >2 SD above normal for age
- d. Leukocyte count elevated or decreased for age or >10% immature neutrophils

**Abbreviations:** AP = Acute pancreatitis; HR = Heart rate; OF = Organ failure; RR = respiratory rate; SD = Standard deciation; SIRS = Systemic inflammatory response syndrome; ULN = upper limit of normal.

*For Non-gallstone pancreatitis. The corresponding values for gall-stone pancreatitis are: At admission: Age >70 years, WBC >18000/mm3, Blood glucose >220 mg/dl, Serum LDH >400 IU/L, Serum AST > 250 IU/L; During initial 48 hours: Hematocrit decrease >10%, Blood urea nitrogen increase >2 mg/dl, Serum Calcium <8 mg/dl, Serum base deficit >5 meq/L, Fluid sequestration >4 L.*
Reference


Approach to Acute Pancreatitis

source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4231506/figure/F3/accessed on 18.9.16
Drug Induced Liver Injury (DILI)

Lalit Bharadia
Consultant Pediatric Gastroenterologist, Jaipur

Introduction
One of the primary functions of the liver is the biotransformation of prescription or nonprescription medications, supplements, and herbals into compounds that can be safely metabolized and excreted by the human body. Unfortunately, the liver cannot optimally metabolize all compounds safely or expediently, causing drug-induced liver injury (DILI).

Incidence
Adult incidence of DILI is 14 cases per 100,000 people annually and nearly 30% exhibit jaundice. Pediatric incidence is unknown but likely lower because children take fewer medications, are less likely to abuse alcohol or smoke cigarettes (two factors that alter drug metabolism), are less frequently prescribed medications commonly associated with DILI, and metabolize drugs differently. Prevalence of DILI is much higher in developing countries owing to malnutrition and indiscriminate drug use.

DILI accounts for almost 20% (14 % Acetaminophen; 5 % other drug and toxins) of pediatric acute liver failure cases, and is a major reason for liver transplantation in the USA.

Acetaminophen, Antibiotics including anti tuberculosis treatment (ATT) and anti epileptics are the most common drugs causing DILI.

DILI continues to be an important barrier for new drug development and marketing.

Pathogenesis:
The liver metabolizes and excretes medications using three general steps (Fig 1):
(1) (Phase 1: Activation) Cytochrome P450 (CYP450) enzymes insert an oxygen residue onto the medication, making it more watersoluble but also more toxic.
(2) (Phase 2: Detoxification) Conjugating enzymes modify the Phase 1 metabolite or original compound, increasing its water-solubility and neutralizing its toxicity.
(3) (Phase 3: Excretion) The water-soluble product is transported into the canalicular space and secreted with bile.

DILI is most often caused by accumulation of Phase 1 metabolites, following one of two patterns: intrinsic hepatotoxicity and idiosyncratic hepatotoxicity.

Drugs with intrinsic hepatotoxicity cause predictable liver damage in a dose-dependent manner when consumed in excessive amounts. Few drugs behave in this manner, but acetaminophen is the paradigm. In large amounts, acetaminophen is converted to the toxic intermediate N-acetyl-p benzoquinone imine (NAPQI) when metabolized by CYP450 monooxygenases. Normally, hepatic glutathione neutralizes NAPQI; however, excessive NAPQI depletes glutathione reserve, allowing free NAPQI to damage hepatocytes. Acetaminophen toxicity can be reversed with N-acetylcysteine (NAC), which restores glutathione production.

The majority of drugs causing DILI have idiosyncratic hepatotoxicity. Drugs with this pattern cause liver damage in susceptible individuals over variable latency periods in a less dose-dependent manner. Idiosyncratic toxicity may be caused by variations in how individuals catalyze Phase 1 and/or Phase 2 reactions. Genetic polymorphisms exist for all but one of the CYP450 enzymes, resulting in variable expression, activity, and subsequent metabolism of substrates.

Idiosyncratic toxicity may also be caused by an immunological mechanism that resembles an autoimmune or hypersensitivity insult. Drugs associated with this presentation (i.e., minocycline, methyldopa, diclofenac, nitrofurantoin) may cause a rise in serum IgG, antinuclear antibodies, and even anti-liver kidney microsomal antibodies as seen in type 2 autoimmune hepatitis.

Acetaminophen hepatotoxicity is a common and well documented example of predictable, dose-dependent injury; however, many instances of DILI are idiosyncratic, requiring a high index of suspicion to make the diagnosis and withdraw the offending agent prior to onset of lasting harm.
Host factors
Expression of drug metabolizing enzymes and transporters varies among individuals due to genetic variants, epigenetics, age, sex, hormones, nutritional status, polypharmacy, alcohol, and smoking. Known genetic polymorphisms of enzymes play an important role in clinical medication management e.g. TPMT in thiopurines.

Diagnosis:
DILI is often a diagnosis of exclusion based on careful examination of the medical history, presentation, laboratory values, and subsequent course. Exclusion of other diagnoses—ruling out viral hepatitis, pancreaticobiliary disease, nonalcoholic steatohepatitis, autoimmune hepatitis, Wilson’s disease, Alagille syndrome, primary sclerosing cholangitis, graft versus host disease, metabolic, and mitochondrial disorders is essential.

Clinical features
DILI can be subclinical with only laboratory abnormalities. However, when DILI does cause symptoms, the symptoms may reflect affected cell types in the liver. When Phase 1 metabolites damage hepatocytes, children often present with nausea, vomiting, anorexia, and elevated transaminases. When Phase 1 metabolites injure cholangiocytes, symptoms of pruritus and jaundice may be more prominent. Phase 1 metabolites also injure other liver cells, including endothelial cells, which can lead to a vaso-occlusive presentation, marked by weight gain due to ascites, hepatomegaly, and elevated bilirubin. When metabolites trigger an immunoallergic response, symptoms of fever, rash, arthralgia, and facial edema can occur. Often, DILI affects multiple cell types within the liver, resulting in a mixed hepatic-cholestatic clinical picture. If not addressed, DILI can lead to liver fibrosis, cirrhosis, liver failure, and ultimately death.

Laboratory features
Laboratory tests can be used to predict the pattern of liver injury and provide an outline to narrow the differential diagnosis and guide future evaluation. Hepatocellular injury consists of disproportionate elevation of serum transaminases [alanine and aspartate aminotransferases (ALT and AST)]. Cholestatic injury presents with predominant elevations in alkaline phosphatase (AlkP), conjugated bilirubin, and/or gamma-glutamyl transpeptidase (GGT).

Histological features
Liver histology remains the gold standard in determining whether injury is hepatocellular or cholestatic. Liver biopsy is also useful in excluding other causes of liver injury that may be difficult to distinguish from DILI, such as autoimmune hepatitis.

Treatment
The mainstay of DILI treatment is withdrawal of the injurious agent and supportive care. Few agents, aside from acetaminophen (NAC) and valproate (L-carnitine), have
antidotes. Corticosteroid use in pediatric DILI has been published, however the efficacy and safety of corticosteroids for most forms of DILI are unproven and no controlled trials have yet been performed.

Prognosis

Prognosis is variable with DILI. Some cases present with acute decompensation, accounting for as many as 20% of pediatric ALF cases in the United States. Survival in acetaminophen induced ALF is 96% (94% without transplant) while due to other drugs is 64% (36% without transplant). Other cases progress to chronic DILI despite withdrawal of the implicated agent. Chronic DILI develops in 7-20% in different series. Reported mortality after development of jaundice varies from 4-12%. Most patients eventually recover. Time to recovery can vary from days to months.

Conclusion

The majority of DILI is both unpredictable and idiosyncratic, with putative metabolic and immunoallergenic mechanisms gradually becoming elucidated. The diagnosis of DILI requires a high index of suspicion and methodical exclusion of other pediatric liver diseases due to its varying clinical presentation and severity. Although children are at lower risk for DILI compared with adults, it remains an important cause of pediatric acute liver failure. Antimicrobial, antiepileptic, antidepressant, and ADHD medications account for the majority of pediatric DILI cases, although the use of herbal and dietary supplements among US children is increasing. Immediate withdrawal of the injurious agent and supportive care is essential, although recovery time and normalization of liver laboratory parameters may take months.

Recommendations of American College of Gastroenterology

1. The diagnosis of DILI in patients with CLD requires a high index of suspicion and exclusion of other more common causes of acute liver injury, including a flare-up of the underlying liver disease (Strong recommendation, low level of evidence). 2. The use of potentially hepatotoxic drugs in CLD patients should be based upon the risk versus benefit of the proposed therapy on a case-by-case basis (Strong recommendation, low level of evidence). 3. There are no data to recommend a specific liver biochemistry monitoring plan when a potential hepatotoxic agent is prescribed in individuals with known CLD. Often, information contained in the package inserts is incomplete or unhelpful. Patients should be advised to promptly report any new-onset symptoms such as scleral icterus, abdominal pain / discomfort, nausea / vomiting, pruritis, or choluria. In addition, it is reasonable to monitor serum liver biochemistries at 4 – 6 week intervals, especially during the initial 6 months of treatment with a potentially hepatotoxic agent (Conditional recommendation, very low level of evidence).


Update

Alternatives to liver transplantation – Alternatives to liver transplantation that are currently being researched include liver support devices, artificial organ construction, and hepatocyte transplantation.

Liver support devices: Although the development of an artificial liver is an area of active research, no such substitute is currently available. Liver support devices, including the bioartificial liver and the extracorporeal liver-assist device, are systems that perfuse blood or plasma through a hepatocyte-containing device to remove cytotoxic elements. Both have undergone phase 1 clinical evaluation but with mixed results.

The Molecular Absorbent Recirculating System (MARS), developed in Germany, removes toxic substances from the blood, acting like an artificial liver. The device transports the patient's blood through a filter, where it is mixed with a "sticky" albumin. Albumin binds many compounds (eg, bilirubin, uremic toxins) and has many nonspecific binding sites for various toxins along with heavy metals. The toxins in the blood then attach to the albumin molecules, thus removing them.

Artificial organ construction: Tissue organ construction for the liver remains experimental at this time, with the hopes that one day it will be an alternative to available treatments.

Hepatocyte transplantation: Hepatocyte transplantation is also being studied as an adjunct treatment for acute hepatic failure. Harvested human and animal hepatocytes have shown only modest success, however. The major obstacles to xenotransplantation have been the potential spread of infection from animal to human recipient and hyperacute and vascular rejection as a result of the cross-species transplant. Although hepatocyte transplantation appears to be promising, its future role will likely be in gene transfer technology, which is still in the research phase.

The Child and Newborn, Vol 19 No 1 - 4, January – December 2015
Introduction

Biliary diseases in the pediatric population can be of congenital or acquired etiology. In neonatal period, any conjugated hyperbilirubinemia persisting beyond 14 days, should be investigated to rule out or establish any surgical condition, commonly extrahepatic biliary atresia.

In pediatric population congenital condition commonly seen is choledochal cyst or secondary to medical conditions like hemolytic diseases, hemoglobinopathies, extended administration of total parenteral nutrition (TPN), extensive bowel resection in past, dietary factors etc1.

Acquired conditions may be:

- Stones
- Stricture of common bile duct (post cholecystectomy)
- Worms in the common bile duct or even in gall bladder
  - Hydrops of the gallbladder
    - Acute hydrops has been associated with Kawasaki disease and Henoch-Schönlein purpura.
  - Acalculous cholecystitis
  - Cholestasis
  - Cholelithiasis
    - More serious complications may develop, such as acute cholecystitis, choledocholithiasis, cholangitis and pancreatitis
  - Acute and chronic cholecystitis
  - Choledocholithiasis
  - Cholangitis

Gallbladder and biliary tract disease should be in the differential diagnosis of any pediatric patient who presents with right-upper-quadrant pain, jaundice, or unremitting dyspepsia with normal endoscopic gastric findings if done. Asymptomatic gallstones and symptomatic pigment gallstones in children are common indications for surgery. Noncalcified gallstones due to long-term cholestasis or TPN may respond to medical therapy such as ursodeoxycholic acid2. As in adults, laparoscopic cholecystectomy is the most feasible option for most patients3.

Aside from gallstones, cholestasis, and biliary dyskinesia, the pediatric population can experience congenital abnormalities of the gallbladder, including gallbladder perforation, hydrops of the gallbladder, gallbladder atresia, apart from choledochal cysts.

Surgical modalities

In extra hepatic biliary atresia the gold standard of treatment is Kasai’s portoenterostomy, ideally recommended before 8 wks of age. In patients presenting later, primary split liver transplantation is the treatment of choice.

In choledochal cyst (commonly Type I), the aim is total excision of the cyst (to avoid cholangiocarcinoma in future from the lining of the cyst) along with the attached gall bladder and do a Roux-en-Y hepaticojejunostomy or hepaticoduodenostomy.

Treatment of Gallstones

The treatment of gallstones depends upon the stage of disease. Ideally, interventions in the lithogenic state could prevent gallstone formation, although, currently, this option is limited to a few special circumstances. Asymptomatic gallstones may be managed expectantly.

Once gallstones become symptomatic, definitive surgical intervention with cholecystectomy is usually indicated, although, in some cases, medical dissolution may be considered in uncomplicated cholelithiasis with biliary colic. Treatment, beyond pain control, is not initiated in the emergency department.

Medical treatments for gallstones, used alone or in combination, include the following:
• Oral bile salt therapy: In patients with established cholesterol gallstones, treatment with ursodeoxycholic acid at a dose of 8-10 mg/kg/d PO divided bid/tid may result in gradual gallstone dissolution
• Contact dissolution
• Extracorporeal shockwave lithotripsy

Medical management is more effective in patients with good gallbladder function who have small stones (< 1 cm) with a high cholesterol content. Bile salt therapy may be required for more than 6 months and has a success rate less than 50%. The recurrence rate is 50% within 5 years. Moreover, after discontinuation of treatment, most patients form new gallstones over the subsequent 5-10 years.

Surgery
The introduction of laparoscopy revolutionized the practice of surgery. By 1970, laparoscopy was commonly used by gynecologists. In 1987, the French physician Mouret performed the first human laparoscopic cholecystectomy. While performing laparoscopy for a gynecologic procedure on a woman known to have biliary colic, he tilted his camera upwards and found that he was able to remove her gallbladder without making additional incisions. This forever changed the treatment of gallbladder disease. In 1992, a National Institutes of Health (NIH) consensus conference concluded that laparoscopy was the treatment of choice for cholecystectomy.

Open cholecystectomy remains a safe and viable alternative when laparoscopy is not feasible and is commonly performed in infants and children with more uncommon diseases of the biliary tree.

Surgical intervention has evolved to single-incision laparoscopic cholecystectomy (SILC) and needle port–assisted SILC. These approaches, in adults, have been shown to have equal efficacy, with longer operating times and improved cosmesis.

Anatomic variations are common and are likely related to injury to the CBD. Care must be taken to properly identify the anatomy of each individual patient; when the anatomy is unclear, intraoperative cholangiography should be performed to avoid potential serious duct injury.

During laparoscopic cholecystectomy, a surgeon must retrieve stones that might escape through a perforated gallbladder. Conversion to an open procedure might be required in certain cases.

In patients in whom gallstones have been lost in the peritoneal cavity, the current recommendation is follow-up with ultrasonographic examinations for 12 months. Most of the complications (usually, abscess formation around the stone) occur within this time frame.

The most dreaded and morbid complication of cholecystectomy is damage to the common bile duct. Bile duct injuries increased in incidence with the advent of laparoscopic cholecystectomy, but the incidence of this complication has since declined as experience and training in minimally invasive surgery have improved.

Cholecystostomy
In patients who are critically ill with gallbladder empyema and sepsis, cholecystectomy is better avoided. In this circumstance, the surgeon may elect to perform cholecystostomy, a minimal procedure involving placement of a drainage tube in the gallbladder. This usually results in clinical improvement. Once the patient stabilizes, definitive cholecystectomy can be performed under elective circumstances.

Cholecystostomy also can be performed in some cases by interventional radiologists under CT-scan guidance. This approach eliminates the need for anesthesia and is especially appealing in a patient who is clinically unstable.

Endoscopic sphincterotomy
If surgical removal of common bile duct stones is not immediately feasible, endoscopic retrograde sphincterotomy can be used. In this procedure, the endoscopist cannulates the bile duct via the papilla of Vater. Using an electrocautery sphincterotome, the endoscopist makes an incision measuring approximately 1 cm through the sphincter of Oddi and the intraduodenal portion of the common bile duct, creating an opening through which stones can be extracted.

Endoscopic retrograde sphincterotomy is especially useful in patients who are critically ill with ascending cholangitis caused by impaction of a gallstone in the ampulla of Vater. Other indications for the procedure are as follows:

• Removal of common bile duct stones inadvertently left behind during previous cholecystectomy
• Impacted /trapped roundworm in common bile duct
• Preoperative clearing of stones from the common bile duct to eliminate the need for intraoperative common bile duct exploration, especially in situations where the surgeon’s expertise in laparoscopic bile duct exploration is limited or the patient’s anesthesia risk is high

Intraoperative endoscopic sphincterotomy (IOES) during laparoscopic cholecystectomy has been suggested as an alternative treatment to preoperative endoscopic
sphincterotomy (POES) followed by laparoscopic cholecystectomy; this is because IOES is as effective and safe as POES and results in a significantly shorter hospital stay.

**Prognosis**

It is to be noted that in successful post Kasai patients, the initial drop in serum bilirubin levels from week after the operation is quite appreciable, then it slows down and may hover around the level of 1.5 to 1.8 mg/dl even after a year of operation, without any clinical findings.

Quite a number of them may require Liver transplantation in future due to liver failure.

When pediatric gallbladder disease is treated appropriately and in a timely fashion, the prognosis is excellent. Most patients recover from a cholecystectomy and return to regular activities within a week. If left untreated, cholecystitis can lead to significant illness. Some patients have diarrhea, gastritis, esophagitis, and colicky abdominal pain after cholecystectomy, particularly after the ingestion of foods high in sugar. This is termed postcholecystectomy syndrome and may occur in as many as 30% of adult patients, but in much less patients in pediatric age group.

**Reference**


**Announcement**

**WBAP office has opened 3 renovated Air conditioned guest rooms for stay**

- Double Bed (LCD TV) available.
  - Guest Room 1 : Rs.1000/- per night
  - Guest Room 2 : Rs.1500/- per night
  - Guest Room 3 : Rs.1200/- per night
- Food available on request.

**Contact** : Smt. Bela Bhattacharya (9830866712)
Vaccination

Vaccination Before Starting Immunosuppressive Therapy

Somashekara HR
Consultant Paediatric Gastroenterologist & Hepatologist, Narayana Health City, Bommasandra, Bangalore

Solid organ transplant recipients and children with inflammatory bowel disease are at significant risk for infection. Efforts should be made to limit these risks. Vaccine-preventable diseases (VPD) continue to affect children on immunosuppression, yet vaccines remain underutilized. The reason behind the poor vaccination compliance is multifactorial and varies from one transplant center to another. Every effort should be made to ensure that children and their household members have completed the full complement of recommended vaccinations prior to initiation of immunosuppression.

Timing of vaccination:
Timing of vaccination is critical to optimize response. The response to many vaccines diminish with organ failure, thus transplant candidates should be immunized early in the course of their disease and prior to transplantation when feasible. The first 6 months after transplantation are associated with the poorest vaccine response because the patients are nearly always the most immunosuppressed

Vaccination and Inflammatory Bowel Disease (IBD)
The vaccination plan should be made after thorough study of immunocompetence at the time of diagnosis and prior to any immunomodulating treatment and/or treatment with biological agents. After immunocompetence has been assessed, a vaccine schedule is made. Serological studies for certain infections and each patient’s personal risk assessment may be needed in order to adjust the proper vaccination regimen.

An IBD patient is considered to be immunocompromised when they meet any of the following criteria:
- Treatment with glucocorticoids (> prednisolone 20 mg / day equivalent, or 2 mg / kg / day if < 10 kg, for 2 weeks or more, and within 3 months of cessation)
- Ongoing treatment with 6-Mercaptopurine / azathioprine or recent discontinuation within the previous 3 months
- Treatment with methotrexate or recent discontinuation within the previous 3 months
- Treatment with infliximab or recent discontinuation within the previous 3 months
- Significant protein-calorie malnutrition

The best time to vaccinate IBD patient is at the time of initial diagnosis, i.e., before the institution of any immunosuppressive medications. Patients receiving immunosuppressive medications should not receive any of the live vaccines listed in Table 1. Immunosuppression should not be initiated until 4 to 6 weeks after vaccinations as the immune response may be blunted.

A practical approach for immunization before stating immunosuppression is outlined below (Fig).

Vaccination and Liver transplantation (LT)
Solid organ transplant (SOT) recipients are at increased risk for infectious complications due to their chronic disease and due to iatrogenic reasons.

Table 1. Live, Attenuated Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
</tr>
<tr>
<td>Bacillus Calmette-Guerin (BCG) vaccine</td>
</tr>
<tr>
<td>Live Attenuated Influenza Vaccine (LAIV) - nasal spray/mist</td>
</tr>
<tr>
<td>Measles-Mumps-Rubella (MMR)</td>
</tr>
<tr>
<td>Oral Polio live vaccine (OPV)</td>
</tr>
<tr>
<td>Smallpox vaccine</td>
</tr>
<tr>
<td>Typhoid live oral vaccine</td>
</tr>
<tr>
<td>Varicella Zoster Virus (VZV)</td>
</tr>
<tr>
<td>Yellow fever (YF)</td>
</tr>
</tbody>
</table>
Immunosuppressive therapy required to prevent rejection of the allograft. They also have higher risks of not having been optimally immunized because of delays of routine vaccinations even before they become SOT candidates.

With respect to vaccine-preventable diseases (VPD) this risk includes:

- A higher attack rate and higher risks for severe and complicated illness, as documented e.g. for varicella, measles, influenza, and invasive pneumococcal disease (IPD),

- Limited efficacy and duration of vaccine-induced protection in patients due to chronic organ failure and post-transplant immunosuppressive treatments.

Evaluation of vaccine-induced immunity in the pre-transplant period

Evaluation and documentation of the immunization status and the estimate of protection against VPD is very important as the incidence and the risk for severe VPD increases with progressing organ disease (eventually requiring SOT), and persists thereafter. This evaluation is essential to define which

```
Initial office visit: obtain vaccination history—when did you receive the tetanus, diptheria, pertussis, human papilloma virus (HPV), influenza, pneumococcal, hepatitis A, hepatitis B, meningococcal, MMR, varicella.

Completed vaccination series or up to date on vaccine?

Not sure

If no prior history of infection, check titers for MMR, varicella, hepatitis A and B

Not immune to MMR/ varicella

Not immune to hepatitis A or B

If no plans to start immunosuppressive therapy within 4–12 weeks or if not currently on immunosuppressive therapy

Recommend*: MMR varicella or herpes zoster

Regardless of immunosuppressive therapy

Recommend*: tdap (tetanus, diptheria, pertussis)

HPV

influenza

pneumococcal

hepatitis A

hepatitis B

meningococcal

Evidence of protective antibodies to hepatitis A and B in past 5 years?

No?

Check titers

Not immune
```
vaccinations are to be completed, before SOT. It relies on the documentation of

- Review of immunization records
- Serology (Vaccine-induced immunity)

**Serology:**

Documentation of the vaccination status in children awaiting transplant should be done by the determination of specific antibody titers, because it may not be possible to assume protective immune responses even from a complete vaccination history as in healthy persons.

Determination of antibody levels as a surrogate marker for protection may be helpful when:

- It is unclear whether there is immunity (after disease or by immunization) against particular vaccine preventable disease
- The need for a booster immunization (e.g. tetanus, hepatitis B) must be assessed
- The response after completed primary or a booster immunization needs to be evaluated
- It is desirable to assess the likely (long term) protection.

The antibody levels are best measured 1–3 months after completion of a primary immunization series or a booster dose.

**Immunizations in the pre-transplant period**

Every effort should be made to ensure that transplant candidates and their household members have completed the full complement of recommended vaccinations prior to transplantation. Since the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their disease. The need for

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication for determination of specific antibody titres</th>
<th>Specific antibody (IgG) and unit</th>
<th>Interpretation of serological analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During end-stage organ disease</td>
<td>At pre-transplant (listing)</td>
<td>After catch-up immunization (pre- or post-transplant)</td>
</tr>
<tr>
<td><strong>Tetanus</strong></td>
<td>Yes, if history unclear ($)</td>
<td>If unknown serology</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae type b</strong></td>
<td>Yes (children &lt;5 years) ($)</td>
<td>Yes, (If unknown serology in children &lt;5 years)</td>
<td>Yes (children &lt;5 years)</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Yes (#, &amp;</td>
<td>)</td>
<td>Yes, if unknown serology</td>
</tr>
<tr>
<td><strong>Measles</strong></td>
<td>Yes</td>
<td>Yes, if unknown serology</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Rubella</strong></td>
<td>Yes</td>
<td>Yes, if unknown serology</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>Yes</td>
<td>Yes, if unknown serology</td>
<td>Yes</td>
</tr>
</tbody>
</table>

---

individual catch-up vaccinations pre-transplant will be based on results vaccination record review and determination of specific vaccine antibody levels. Evaluation of the immunization records should lead to:

- Catch-up basic vaccinations, including DPT, Polio, MMR, and HIB plus PCV (children < 5 years)
- Identify and immunize patients who are not immune against varicella and hepatitis B
- Identify females > 9 years of age not yet immunized against HPV. Vaccination of boys against HPV may be considered given the enhanced risks of cancer in immunosuppressed patients.
- Administer or catchup vaccines recommended to high-risk patients (including vaccines against influenza, pneumococcal disease, hepatitis A)

Table 3 shows the recommended accelerated schedule for vaccination of SOT candidates. This schedule gives the minimal age for each particular vaccine and the scheme with the shortest possible immunization series.

Live vaccines (MMR, VZV, YF) should no longer be administered after the patient is included on an emergency transplantation list and when SOT is considered likely within 4 weeks. Specific antibody levels have to be checked after specific vaccination. If protective levels are not reached, additional immunizations are recommended.

**Conclusions**

Vaccinations offer immunity against preventable diseases. A diligent effort should be made to vaccinate all patients before immunosuppressive therapy is initiated. Immunosuppressed patients are at a higher risk of infection with vaccine preventable diseases. Live vaccines are contraindicated in patient on immunosuppressant medications due to risks of vaccine associated infection. Despite the concerns for impaired immune response in immunosuppressed patients, most of these patients develop adequate response after vaccination.

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**Table 3**

**Recommended accelerated vaccination schedule in the pre-transplant period**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum age</th>
<th># doses</th>
<th>Schedule (minimal Interval in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTPw IPV</td>
<td>6 weeks (&gt;7 years dTPw)</td>
<td>first dose &lt; age 1 year; 4 doses ≥ 1 year; 3 doses</td>
<td>0, 1, 2, + 1x 12 months $^{1,2}$ 0, 1, 6 $^{1,2}$</td>
</tr>
<tr>
<td>dT(p) booster</td>
<td>8 years</td>
<td>1 dose every 10 years</td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>6 weeks</td>
<td>first dose &lt; 1 year: 4 doses 12–59 months: 2 doses</td>
<td>0, 1, 2, + 1x 12 months $^{1}$ 0, 2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>3 (hexavalent vaccines or rapid schedule: 4 doses; 11–15 years: 2 adult doses)</td>
<td>0, 1, 4 (1-3 primary doses + booster after ≥4 months)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>6 months (off label &lt;1 years)</td>
<td>2</td>
<td>0, 4</td>
</tr>
<tr>
<td>PCV13</td>
<td>6 weeks (off label &gt;5 years)</td>
<td>first dose &lt; 1 year: 3-4 doses 1 year: 2 doses &gt;1 year: 1 dose</td>
<td>0, 1, 2 + 1x 12 months $^{1}$</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 months</td>
<td>children &lt;9 years: 2 doses in first season</td>
<td>if 2 doses: 4 weeks interval.</td>
</tr>
<tr>
<td>MMR</td>
<td>6 months</td>
<td>2 doses</td>
<td>0,1 $^{3,4}$</td>
</tr>
<tr>
<td>Varicella</td>
<td>6 months</td>
<td>2 doses</td>
<td>0,1 $^{3,4}$</td>
</tr>
<tr>
<td>HPV (women)</td>
<td>9 years</td>
<td>2 doses if first dose &lt; 15 years; 3 doses if first dose &gt; 15 years</td>
<td>0, (1), 4</td>
</tr>
<tr>
<td>MenACWY conjugate$^e$</td>
<td>1 year (off label &lt;11 years)</td>
<td>2 doses (+ booster to be considered every 5 years)</td>
<td>0, 2</td>
</tr>
</tbody>
</table>

$^{1}$ 3 doses in the first year of life: 4, dose a) >6 months after dose 3 and b) after 12 months of age.
$^{2}$ further DTPw IPV at age 4 (~7) years, see SIP.
$^{3}$ not recommended if emergency listing with likelihood of SOT within 4 weeks (live attenuated vaccine).
$^{4}$ if first dose <12 months of age, give 2nd dose after 12 months of age or include a 3rd dose after 12 months of age.
$^{5}$ prefer MenACWY conjugate vaccine to polysaccharide vaccine [31].
Reference


Forthcoming WBAP programmes

October 2016
2 Oct : CME on Primary Immunodeficiency at Science Congress Association Hall

November 2016
12,13 Nov: XXIII East Zone Pedicon and 35 W.B. Pedicon
Venue : The Park, Park Street

December 2016
11 Dec : Howrah Pedicon
18 Dec : Neonatology CME

Clinical Meetings

Sept 29 : Medical College, Kolkata

October 27 : B R Singh Hospital

Nov 24 : IPGME&R and SSKM Hospital

Dec 22 : Calcutta Medical Research Institute (CMRI)
HIV disease progresses very rapidly in young children, often leading to death. Without care and treatment, 1/3rd of infants will die in the first year & 50% of children by second year of life. HIV exposed is defined by any infants and children born to mothers infected with HIV, until HIV infection can be reliably excluded or confirmed in them. Asymptomatic infants and children <18 months are often missed out on prevention, care, support and treatment. The new guidelines on ‘Early Infant Diagnosis’ have come out to ensure that HIV exposed and infected infants and children <18 months of age receive the required national essential package of care and support.

Tests of Choice for Infants & Children <18 Months of Age

Test Recommendation: No HIV antibody because of false +ve due to persistent maternal antibodies. HIV p 24 Antigen can be done, but lower sensitivity than PCR (27% at 6 weeks) HIV viral culture is costly, result takes 2-4 wks, and also not readily available. HIV DNA PCR is preferred investigation of choice with 98% sensitive from 6 weeks of age.

Positive HIV antibody (Ab) alone indicates there has been exposure to HIV but it does not mean that child is infected, it can be due to circulating maternal antibodies. Test to diagnose HIV in this population is HIV DNA PCR (Qualitative). First positive virological test (HIV DNA PCR) should be confirmed by a repeat positive test on a separate Dry blood Spot (DBS) specimen.

For discordance among the EID results and rapid tests at 18 months, continue ART irrespective of antibody test results at 18 months, if ART had been initiated on the basis positive DNA-PCR result any time between 6 weeks and 18 months. This discordance needs further evaluation if negative at 18 months, repeat 3 antibody tests at the same testing site after 1 month. If Positive, continue ART, if still negative, continue ART and refer to NACEP (national AIDS clinical expert panel) for further advice.

Infant Feeding

Counseling for infant feeding should begin in the antenatal period. All HIV infected pregnant women should be informed about infant feeding options, viz. exclusive breast feeding or exclusive replacement feeding. Breast feeding is the preferred choice in developing countries as it maximizes the chances of survival of the infant. Breast-feeding provides the infant with all required nutrients and immunological factors that help to protect against common infections.

Breast feeding is generally begun within an hour in a normal vaginal delivery and within first 4 hours in a LSCS delivery. Mixed feeding i.e. breast milk and replacement feeds combined increases the risk of transmission of HIV and should be avoided at all cost. The health care providers and counselors should be trained to help the pregnant women in reaching the right decision and to support them in implementing breast feeding.

10 principles of infant feeding for HIV-infected women

1. All HIV positive pregnant women should have PPTCT interventions provided early in pregnancy as far as possible. The interventions include maternal ART and infant ARV prophylaxis.

2. Exclusive breast feeding is the recommended infant feeding choice in the first 6 months.

3. Only in situations where breastfeeding cannot be done or on individual parents’ informed decision, then replacement feeding may be considered only if all the 6 criteria for replacement feeding are met.

4. Mixed feeding should not be practiced for the first six months at any cost, as it enhances the risk of transmission of HIV to the infant.

5. Exclusive breast feeding should be done for first 6 months, after which complementary feeding should be introduced.

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gradually, irrespective of whether the infant is diagnosed with HIV infection or is uninfected by early infant diagnosis.

6. Mother should be adherent to ART not only for the whole duration of breast feeding but for the entire duration of her life.

7. Breast feeding should be stopped once a nutritionally adequate and safe diet without breast milk can be provided.

8. For breast feeding infants who are diagnosed HIV uninfected, breast feeding should be continued till 12 months of age ONLY.

9. For breast feeding infants diagnosed HIV infected, ART should be started and breast feeding should be continued till 2 years of age.

10. Abrupt stopping of breast feeding should NOT be done. Mothers who decide to stop breast feeding should stop gradually taking comfort level of mother and infant into consideration.

**Safer Infant Feeding : NACO Recommendations**

*Found HIV positive through EID algorithm* – For these infants, exclusive breast feeding is to be done till 6 months. Breast feeding should be continued up to 24 months.

*Found HIV Negative through EID algorithm* – Exclusive breast feeding is to be done till 6 months and start complimentary feeding at 6 months of age. Breastfeeding should continue up till 12 months ONLY. Mothers who decide to stop breast feeding should stop gradually taking comfort level of mother and infant into consideration HIV testing needs to be done again 6 weeks after cessation of breastfeeding according to the EID protocol.

**Criteria for replacement feeding**

1. Safe water and sanitation are assured at the household level and in the community.

2. The mother or other caregiver can reliably afford to provide sufficient replacement feeding (milk), to support normal growth and development of the infant.

3. The mother or caregiver can prepare replacement feeding frequently enough in a clean manner, so that it is safe and carries a low risk of diarrhea and malnutrition.

4. The mother or caregiver can, in the first six months exclusively give replacement feeding.

5. The family is supportive of this practice.

6. The mother or caregiver can access health care that offers comprehensive child health services.

**Infant Daily Nevirapin (NVP) Prophylaxis**

All infants born to HIV positive mother will get daily nevirapin upto minimum 6 weeks regardless of exclusively breast fed or exclusive replacement fed. Extended to 12 weeks, if the duration of ART of mother is less than 24 weeks and she is breast feeding. Daily dose of nevirapin are Infants with birth weight <2000 gm(2 mg/kg ie, 0.2 ml/kg once daily), Birth weight 2000 – 2500 gm (10 mg ie, 1 ml once daily) and Birth weight >2500 gm(15 mg ie, 1.5 ml once daily).

**Indications for starting cotrimoxazole prophylaxis**

(i) All HIV-exposed infants /children; from 6 weeks of age (or at first contact with health services).

(ii) All HIV-infected infants and children up to 5 year of age regardless of WHO stage or CD4 counts or CD 4%.

(iii) All HIV-infected children >5 years of age with WHO Stage 3 and 4 regardless of CD4 or CD4 <250 cells/mm3 regardless of WHO staging.

(iv) As secondary prophylaxis after completion of treatment for PCP.

**Indications for stopping Cotrimoxazole prophylaxis**

(i) All HIV-exposed infants /children where HIV infection has been reliably excluded by a negative antibody test at 18 months, regardless of ARV initiation.

(ii) All HIV-infected infants & children at 5 years of age, when clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e. in a child >5 years of age with a WHO T-stage 1 or 2 and CD4 count of >250 cell/mm3 on two occasions not less than 6 months apart.

(iii) All HIV-infected children >5 years of age if CD4 count >250 cell/mm3 for at least 6 months and if patient is on ART for at least 6 months and patient is asymptomatic and well are the indications for stopping cotrimoxazole.

**Assessment and management after confirmed HIV infection in the child**

Assess growth, development and nutritional status using standard techniques and scales, and assess the intervention needs. WHO growth charts should be used for assessment of growth.

Assess immunization status and provide appropriate immunization as per the National Immunization Schedule. All UIP and additional IAP recommended immunization can given as per schedule. Assess for signs and symptoms of opportunistic infections including tuberculosis (TB). If Opportunistic Infections (OI) are suspected, then diagnosis and treatment of OIs take priority over ART initiation. Screening
for TB is strongly recommended in all HIV infected children, as it is an important aspect of pre-ART care. Assign WHO clinical stage of HIV.

Assessment and management after confirmed HIV infection in the child

A baseline and annual fundoscopic examination for evidence of CMV retinitis is recommended.

Ensure that the child is on cotrimoxazole prophylaxis as per guidelines. Identify any concomitant medication use that may have drug interactions with ART. Perform baseline and six monthly follow up CD4 count or CD4%. CD4 counts should be also done, if clinically indicated and advised, by the expert even if done within the last 6 months. Screen the family members for HIV and other OIs. Psychosocial and family background assessment by the counselor to identify primary caregiver for the child and his/her ability and willingness to adhere to follow up and administer medications, especially ART. Assess family members’ understanding of HIV disease and treatment and family’s financial status including ability to pay for transportation to clinic, ability to afford adequate food / nutritional supplements for the child and ability to pay for any treatment needed. Assess disclosure of HIV status within the family (whether the child knows his/her status and whether anyone else knows, and also if the child knows the parent/s' HIV status).

Developmental Assessment

Abnormal development raises concerns of HIV encephalopathy. Developmental assessment at each visit includes assessment of: Motor / Fine motor, language and social skills. Make sure that child sees, hears and listens. Use developmental charts for plotting. If milestones are delayed – refer to expert.

Deciding which ART regimen for HIV-infected

Infants and children <18 months of age with HIV DNA PCR detected ART indicated regardless of any CD4 count or CD4%. Assess history for previous exposure to single dose NVP or PPTCT regimens containing NVP or EFV and hemoglobin level. Regimen will be if Hb is >9G% AZT+3TC+LPV/r (Zidovudine+Lamivudine+Lopenavir/Ritonavir) and if Hb is <9 G% ABC+3TC+LPV/r (Abacavir+Lamivudine+Lopenavir/Ritonavir).

Conclusions

Diagnosis of HIV exposed Infants & Children <18 months of age depends on testing infant’s blood through Dried Blood Spot (DBS) and confirmed by repeating the test on a Whole Blood Specimen by performing DNA PCR. Breast feeding modifies the diagnostic algorithm; however, exclusive breast feeding for the first 6 months should be advocated in all infants. HIV infection has to be confirmed by antibody tests at the age of 18 months. However, in discordant cases, further evaluation and referral to NACEP have to be done. All the HIV confirmed infants and children (<5 years) shall be initiated on ART as per NACO guidelines and those less than three years of age need to be on LPV/r based ART regardless of prior NVP (Nevirapin)/NNRTI (Non nucleoside reverse transcriptase inhibitors) exposure in mother or not. Abnormal development raises concerns of HIV encephalopathy. Assess immunization status and provide appropriate immunization as per the National Immunization Schedule. All HIV-infected infants and children up to 5 year of age regardless of WHO stage or CD4 counts or CD4% should get co-trimoxazole prophylaxis.

Source: WHO and NACO guideline 2015.
Case Report on Ullrich Muscular Dystrophy –Type Collagen 6 Defect

Tarun Choudhuri

Abstract
Congenital Muscular Dystrophy (CMD) is a heterogeneous condition. Ullrich CMD is due to defect in extracellular matrix protein-Collagen Type 6. It is mostly autosomal (COL6A1,COL6A2,COL6A3). Clinical features include slow progressive muscle weakness, distal laxity (hands, feet, fingers), contracture of proximal joints & early respiratory failure. We report a 5yrs.old girl with the above features, diagnosed to have Ullrich CMD. This case is being reported for its rarity and to highlight the importance of diagnosis.

Keywords
Congenital Muscular Dystrophy, Collagen type 6, Ullrich Muscular Dystrophy.

Introduction
CMD is a group of conditions, which share early presentation and a common muscle pathology varies according to aetiology, severity, associated symptoms & outcomes. Clinical features are distinctive & classical in Ullrich CMD as it is due to defect in extracellular matrix protein-collagen type 6. It can be confirmed by muscle biopsy & subtype by Molecular Genetics.

Ullrich CMD was first described by Otto Ullrich in 1930, as Congenital Atonic Sclerotic Muscular Dystrophy, or CMD with distal laxity. Since then only 30 patients have been reported worldwide. Diagnosis is suspected from history and clinical examination, and confirmed by Muscle Biopsy.

Case Report
This 5 yrs. old girl, born of nonconsanguinous marriage presented with history of weakness of upper and lower limbs since the child was 8 months old. The child learnt to roll over & sit but did not stand or walk. She had no convulsion or difficulty in respiration. Her mental development and speech was normal. There is no family history of similar complaint. She was one of the twin, the other twin boy is absolutely normal. Her antenatal, natal, postnatal history are uneventful.

On Examination
The child’s weight and length were less than 3rd percentile. Vitals were normal. The girl had low set ears (fig.1), prominent calcaneum of both feet, and contracture of both knees and elbows.(fig.2). On CNS examination- Higher functions, cranial nerves, sensory and cerebellar system were normal. Motor system showed symmetrical decrease in bulk and hypotonic upper and lower limbs. She had extremely hyperextensible fingers and toes. (fig.3) There were no fasciculation or hypertrophy of any group of muscles. Proximal group of muscles had power 3/5 and distal 2/5. Her reflexes were normal. Examination of other systems were normal.

On Investigation
CPK was 995u/l (normal range 15-171). EMG showed slow nerve velocity. Muscle Biopsy (fig.4) –showed effaced fascicular structure, rounding of myofibres with variation in diameter and atrophied nuclei and angulated fibres. Infiltration of Endomysial collagen was present. There was no necrosis, myophagocytosis and regeneration.

Based on clinical presence of hyperextensible limb, distal wasting, low set ears, prominent calcaneum and characteristic muscle biopsy report, a diagnosis of Congenital Muscular Dystrophy –Type 6 Collagen defect –Ullrich Muscular Dystrophy was made.

(For Mol. Genetics & Special histopathology –took the help of NIMHANS/Bengaluru.)

Fig. 1 (Typical facies, Low set ears)

Fig. 2 (Contractures both knee)

Fig. 3 (Hyperextensibility of finger)

Fig. 4 (Classical Muscle Biopsy Pic)

Reference
Non nutritive sucking for GERD in preterm LBW infants
Cochrane Database Syst Rev. 2014 Oct 15;(10)
Psaila K, Foster JP, Richards R, Jeffery HE

Abstract

Background:
Gastro-oesophageal reflux (GOR) is commonly diagnosed in the neonatal population (DiPietro 1994), and generally causes few or no symptoms (Vandenplas 2009). Conversely, gastro-oesophageal reflux disease (GORD) refers to GOR that causes troublesome symptoms with or without complications such as damage to the oesophagus (Vandenplas 2009). Currently there is no evidence to support the range of measures recommended to help alleviate acid reflux experienced by infants. Non-nutritive sucking (NNS) has been used as an intervention to modulate neonatal state behaviours through its pacifying effects such as decrease infant fussiness and crying during feeds (Boiron 2007; Pickler 2004).

Objectives:
To determine if NNS reduces GORD in preterm infants (less than 37 weeks' gestation) and low birth weight (less than 2500 g) infants three months of age and less, with signs or symptoms suggestive of GORD, or infants with a diagnosis of GORD.

Search Methods:
Computerised searches of the electronic databases of the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2013), MEDLINE (1966 to September 2013), CINAHL (1982 to September 2013), and EMBASE (1988 to September 2013) were performed. No language restrictions were applied.

Selection Criteria:
Controlled trials using random or quasi-random allocation of preterm infants (less than 37 weeks' gestation) and low birth weight (less than 2500 g) infants three months of age and less with signs or symptoms suggestive of GORD, or infants with a diagnosis of GORD. Studies reported only by abstracts, and cluster and cross-over randomised trials were included.

Main Results:
Thus no studies examining the effects of NNS for GORD in preterm and low birth weight infants could be identified.

Authors' Conclusions:
There was insufficient evidence to determine the effectiveness of NNS for GORD. Adequately powered RCTs on the effect of NNS in preterm and low birth weight infants diagnosed with GORD are required.

Does the Use of pacifier affect GER in Preterm infants
J Pediatrics 2016 May, 172:205-208
Corvaglia L, Martini S, Corrado MF, Mariani E, Legnani E, Bosi I, Faldella G, Aceti A
This crossover study showed that non-nutritive sucking, provided with a pacifier in 30 preterm infants, had no effect on acid and nonacid gastro-esophageal reflux evaluated by esophageal pH-impedance, and thus may be reasonably used in preterm neonates with symptoms of gastro-esophageal reflux.

Pharyngeal pH monitoring in Gastrectomy patients
United European Gastroenterology Journal 2016: 4(4) 541-545
Wilhelm D, Jell A, Feussner H, Schmid RM, Bajbouj M, Becker V
For diagnosis of GER a newly designed pharyngeal probe (Dx-pH) was used. In this study this probe was used in Total
Gastrectomy patients with complete extinction of gastric acid production. Methods: Pharyngeal pH monitoring was performed in 10 consecutive totally asymptomatic patients with h/o total gastrectomy. All the patients were off PPI therapy and on non-acid diet during the complete measurement period. Results: Six of the ten asymptomatic had pathological results derived from the validated reference values (Ryan Score) in pharyngeal pH monitoring. Conclusion: Pathological pH values as assessed by the Dx-pH device, (usually interpreted as pathological aerosolized acidic gastroesophageal or laryngeopharyngeal reflux) are dissociated from gastric acid production. Pharyngeal pH monitoring systems seem currently not to be useful to guide diagnostic or therapeutic decisions.

Prevalence of celiac disease among first-degree relatives of Indian Celiac Disease patients

Dig Liver dis. 2016 Mar; 48(3):255-259
Mishra A, Prakash S, Kaur G, Sreenivas V, Ahuja V, Gupta SD, Makharia GK.

Background:
Celiac disease, once thought to be uncommon in Asia, is now recognized in Asian nations as well. The prevalence of celiac disease in first-degree relatives of celiac disease patients was investigated in this study.

Methods:
First-degree relatives were screened prospectively for celiac disease using questionnaire-based interview and anti-tissue transglutaminase antibody. Serology positive first-degree relatives underwent duodenal biopsies. Diagnosis of celiac disease was made based on positive serology and villous abnormality Marsh grade 2 or higher. Human leucocyte antigen DQ2/-DQ8 was also assessed in 127 first-degree relatives.

Results:
434 first-degree relatives of 176 celiac disease patients were prospectively recruited; 282 were symptomatic (64.9%), 58 were positive for serology (13.3%). Seroprevalence was higher in female than in males (19% vs 8.5%; p=0.001) and highest in siblings (16.9%) than parents (13.6%) and children (5.9%) of celiac patients (p=0.055); 87.4% first-degree relatives were human leucocyte antigen-DQ2/-DQ8 positive. Overall prevalence of celiac disease was 10.9% amongst first-degree relatives.

Conclusions:
All first-degree relatives of celiac disease patients should be screened for celiac disease even if asymptomatic or with atypical manifestations.

Coeliac disease in patients with short stature: A tertiary care centre experience.
Singh P, Sharma PK, Agnihotri A, Jyotsna VP, Das P, Gupta SD, Makharia GK, Khadgawat R.

Background:
The aim of this study was to determine the prevalence of coeliac disease among children with short stature at a tertiary care centre and to define the predictors for coeliac disease, if any, in them.

Methods:
In this retrospective study, the case records of children and adolescents with growth retardation attending the Paediatric Endocrinology Clinic from January 2008 to June 2011 were reviewed. All patients underwent the multi-tier stratified diagnostic protocol for complete evaluation of short stature. Coeliac disease was screened using IgA-anti-tissue transglutaminase antibody. The diagnosis of coeliac disease was made on the basis of the modified European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria.

Results:
Of 432 patients (238 boys) who presented with short stature, 72 (16.7%) had physiological, while 360 (83.3%) had pathological causes. Endocrine causes were growth hormone deficiency (86 patients, 19.9%), hypopituitarism (31, 7.2%), hypothyroidism (22, 5.1%) and others (7, 1.6%). The systemic causes were: coeliac disease (47, 10.9%), haematological diseases (14, 3.2%), renal diseases (11, 2.5%) and others (24, 5.6%). Chronic diarrhoea (OR 15.7, 95% CI 7.8-31.5) and anaemia (OR 4.9, 95% CI 1.9-12.7) were significant predictors for coeliac disease in patients with short stature. There was a definite response to gluten-free diet in them and the mean (SD) growth velocity measured over at least 6 months of gluten-free diet was 8.1 (3.0) cm/year.

Conclusion:
Nearly 11% of patients presenting with short stature have coeliac disease. In these patients chronic diarrhoea and anaemia were significant predictors of coeliac disease. So best to screen all short stature patients for Celiac Disease too.
Protect every child with the
No. 1 Hepatitis A vaccine, approved by WHO and IAP
Choose BIOVAC
Live Attenuated H2-strain Hepatitis A Vaccine
Longer and better immunity against Hepatitis A

Please remember,
1st dose at 15th month
2nd dose 3 months apart 18th month
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Live Attenuated Varicella Vaccine (0.544 lg PFU)
MORE PFU, MORE TITRES

1. IMS MAT January 2016 data 2. WHO position paper 2014