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Dr. K.Nedunchelian Dr. S. Thangavelu
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Journal Office and address for communications: Dr. K.Nedunchelian, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com
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Years ago the World Health Organisation had made a fervent call to the child health providers to note the advantage of acquiring and updating knowledge in the field of child health for providing quality care to the child population in the developing world keeping with this well meaning call, this overview on recent advances in pediatric gastroenterology, will enrich their knowledge for ultimate benefit of infant, child and adolescents. The wide spectrum of topics discussed will cover “glimpses of advances in the management, diagnosis and investigatory techniques right from acute diarrhea management with various adjuncts to the current indications for liver transplantation.”

Revised guidelines for management of acute diarrhoea

The revised guidelines for management of acute diarrhoea issued by the Government of India and Indian Academy of Pediatrics recommend low osmolarity ORS, Zinc (10 mg elemental zinc for infants 2 to 6 months and 20mg /day for children > 6 months for 14 days) started soon after the onset of diarrhea and early and continued feeding of energy dense foods in addition to breast feeds. Home available foods, hand washing and other hygienic practices are emphasized. Antimicrobials are recommended only for gross blood in stools or Shigella positive culture, cholera associated septic infection or severe malnutrition.

Single dose azithromycin for childhood cholera has the clinical and bacteriological success of 81% and 84% respectively at 72 hours.

Oral ondansetron in children with vomiting and acute gastritis/gastroenteritis: In subjects with acute gastritis/acute gastroenteritis and mild to moderate dehydration who failed initial oral rehydration therapy, the proportion of children who received intravenous hydration was smaller in the ondansetron group, with lower proportion requiring admission, fewer episodes of vomiting and diarrhoea and fewer revisits than in the placebo group.

Racecadotril: IAP Task Force (2004) consensus report stated that at present there is not enough evidence on either safety or efficacy of antisecretory drugs like racecadotril for its use in treatment of diarrhoea.

Amylase resistant starch (ARS): The underlying mechanism of green banana in diarrhoea management is postulated to be mediated by its high content of amylase resistant starch (ARS). The addition of high amylase rich maize starch to ORS reduces faecal loss and shortens the duration of diarrhoea in adolescents and adult with cholera.
**Probiotics in acute diarrhoea:** In a recently published randomised controlled trial, comparison of efficacy of five different probiotic preparations viz; Lactobacillus rhamnosus strain GG, Saccharomyces boulardii, Bacillus clausii, mix of L delbrukii var bulacricalus, Streptococcus thermophylius, L acidophilus and Bifidobacterium bifidum or Enterococcus faecium SF68 suggested significantly shorter duration of diarrhoea (p < 0.001) in children who received L. rhamnosus strain GG (78.5 hours.) and the mix of four bacterial strains (70.0 hours) than in children who received oral rehydration solution alone (115.0 hours). The remaining preparations were not found effective.

Though most of the of studies were conducted in developed countries on rotavirus diarrhoea and confirmed the beneficial effects of probiotics in AWD yet studies from India do not show same benefit in acute diarrhoea. Studies are needed with the therapeutic doses of more than 5 billion CFU in both normal nutritional status and malnourished children. Therapeutic doses in the range of 5-10 billion CFU per day for bacterial strains and 250-500mg for Saccharomyces boulardii are considered appropriate for children.

**Rotavirus vaccines:** Rotarix™, the lyophilized, attenuated human rotavirus vaccine and RotaTeq™, human bovine reassortant vaccine are the available vaccines which have similar efficacy and safety profiles and are recommended by the IAP committee on immunization (IAPCOI) 2007-2008. IAPCOI recommends rotavirus vaccination after one to one discussion with parents (Category 3 vaccine).

**Celiac disease: Serology:** IgA antibody to human recombinant tissue transglutaminase (tTG) antibody (92-100% sensitivity and 91-100% specificity) and anti-endomysial antibody EMA (sensitivity 88 - 100% and specificity 91-100%) are highly sensitive and specific and are easily available tests.

Serological markers are used to identify suspected patients of celiac disease especially of post-gluten challenged group in need for intestinal biopsy, which remains mandatory for establishing the diagnosis.

**Genetics:** HLA DQ2 and HLA DQ8 are predominantly found in almost all celiac patients. Extraintestinal associates of celiac disease are diabetes mellitus, dermatitis herpetiformis, arthritis, recurrent aphthous stomatitis, psoriasis, autoimmune disorders, cryptogenic chronic hepatitis and primary sclerosing cholangitis.

Proposed criteria to diagnose celiac disease in our set up includes

1. Villous atrophy in small intestinal biopsy.
2. Positive celiac serology (EMA or tTG).
3. Unequivocal clinical response to gluten free diets in weeks.

IgA and IgG antigliadin and antireticulin antibodies have high false positivity and negativity and thus not recommended.

**Screening for celiac disease:** More than one fifth of all severe short stature are seropositive for tTG and the chances of seropositivity increases if severe anemia and bulky stool are associated.

**Cow’s milk protein allergy (CMPA):**

The diagnostic criteria includes

1) Positive modified Goldman’s criteria viz high degree of clinical suspicion of CMPA and abnormal histology (small bowel or rectal mucosal biopsy)

2) Milk and milk product elimination/challenge to the child/breast feeding mother what ever the type of presentation may be.
3) Positive skin prick test to cow’s milk antigen- reaction of more than 3mm.

4) Positive milk specific IgE antibodies by ELISA or RAST. Non- IgE (T-Cell mediated)/ mixed type appears to be a more common presentation than IgE type in our experience and most children with CMPA outgrow the disease by 4 years of age.

**Lactose intolerance:** Among the congenital, secondary and late onset types, secondary type is most common, presents at any age and often seen secondary to post viral diarrhoea, antibiotics and food allergy eg; celiac disease, Crohn’s, giardiasis and severe PEM due to villous atrophy. Diagnosis of lactose intolerance is made by

1. Suggestive clinical setting

2. Positive stool examination (liquid part) pH +ve < 6, reducing substance of >1% in a neonate and >0.5% in older child.

3. Lactose tolerance test or lactose breath hydrogen test are of academic interest only.

4. Milk / Milk products elimination and challenge testing is recommended and the disease is managed by dietary milk reduction mostly and there is only very few indication for total stoppage of milk for short duration. It is strongly recommended not to stop breast feeding without any basis.

**Inflammatory bowel disease**

Crohn’s disease and ulcerative colitis are increasingly reported. Nearly 25% of cases of Crohn’s disease are explained by NOD2 gene mutations, a gene regulating the immune response to intestinal bacteria. Serologic surrogate markers as diagnostic and prognostic tools, such as anti-neutrophil cytoplasmic antibody (ANCA) for ulcerative colitis and the anti-saccharomyces cerevisiae antibody (ASCA) for Crohn’s disease help sub- classification of patients. However tissue biopsy of both Crohn’s disease and ulcerative colitis continue to be the gold standard for diagnosis.

The management of ulcerative colitis is based on accurate diagnosis (colonic mucosal disease, no granuloma and perianal disease).

1. Corticosteroids are primary form of induction of moderate to severe disease in most of our patients.

2. For steroid refractory colitis cyclosporine, tacrolimus or infliximab are tried.

3. For maintenance therapy of mild colitis (whether pan- colonic, left- sided or proctitis) oral or topical aminosalicylates are the drug of choice.

4. For patients who do not respond to aminosalicylates, immunomodulators such as 6-mercaptopurine and azothiaprine are good options.

5. If patients do not respond to 6-mercaptopurine or azothiaprine surgery should seriously be considered. The use of infliximab has almost replaced the indication for surgery.

Options for induction therapy in Crohn’s disease include corticosteroids with 80% response in moderate to severe crohn’s disease. Increased recurrence rates after weaning of corticosteroids necessitates long term maintenance therapy. Most children with Crohn’s disease do well with either 6-mercaptopurine, azothiaprine or methotrexate as their maintenance therapy. If immune modulators fail Infliximab should be considered as the drug of choice. Complicated Crohn’s disease like intestinal strictures of terminal ileum, ileal perforations and intra-abdominal abscess and perianal fistulae are best managed with surgery and Infliximab.
Nutritional therapy especially in Crohn’s is often underutilised. Tube feeding exhibited a greater degree of mucosal healing than corticosteroid as induction therapy.\(^{21}\)

**Abdominal tuberculosis in children**

Video capsule endoscope (VCE)\(^ {22}\) Ileo-colonoscopy, Enteroscopy, Capsule endoscopy Double- Balloon enteroscopy and CECT are useful tests in a clinical context.

**Newer anthelmintics:** Ivermectin and nitazoxanide are the two newer anthelmintics.

**Ivermectin** belongs to macrolides and is a macrocyclic lactone.\(^ {23}\) It is a polyanthelminthic having broad spectrum activities against onchocerciasis, strongyloidiasis, ascariasis, trichuriasis and enterobiasis. The dose is 150 microgram/kg body weight. Ivermectin is contraindicated in children weighing less than 15 kg, who are having immediate hypersensivity to the drug, breast feeding mothers upto infants of 3 months of age. Recent evidence supports its use in the treatment of mites and scabies.

**Nitazoxanide** is a synthetic benzamide and is a new broad spectrum anti-helminthic and anti-protozoal drug.\(^ {24}\) It blocks pyruvate and enzymes essential for anaerobic metabolism. The dose is 100 mg twice daily for 3 days for children of 1 to 3 years and 200 mg twice daily for 3 days for children of 4 to 11 years old and has a good safety profile.

As part of Tamil Nadu state school health programme ratified by WHO, all school children including preschool children upto 14 years are dewormed with 6 monthly single dose of albendazole.\(^ {25}\)

**Chronic functional constipation (CFC)**

CFC can present as slow transit or normal transit or pelvic floor dysfunction (anismus).

**CFC with faecal impaction and encopresis:** The disimpaction can be done by oral route, rectal route, combination of oral and rectal routes and rarely surgical methods.\(^ {26}\)

For oral route, total bowel wash is done effectively with polyethylene glycol (PEG), an osmotic agent, in a dose of 1.5g/kg/day for 3 to 4 days and this can be dissolved in 240ml water and given orally. The dose can be adjusted accordingly. Cochrane database of systematic meta-reviews conclude that PEG was better than lactulose in managing chronic constipation by improved outcomes of stool frequency per week, form of stool and the need for additional products.\(^ {27}\)

Three hypertonic phosphate enemas 12 hourly can clear the rectum effectively in a dose of 6ml/kg/day. Soap and water enemas are not to be used in children.\(^ {28}\) Glycerine or bisacodyl suppositories are effective to evacuate rectum to certain extent in younger infants. PEG for maintenance therapy in the dose of 0.26 to 0.8g/kg/day is effective and safe.

**Biofeedback:** This is a form of habit training, based on reinforcement and it helps to enhance the rectal sensation in patients with sensory deficit, to strengthen the external and internal sphincter and to coordinate muscle contraction and adequate relaxation. This is advised after 5 years of age and is effective in 50 to 80% of patients especially suffering from pelvic floor dysfunction (anismus).\(^ {29,30}\)

Children with chronic constipation needs regular long term follow-up, counselling regarding toilet training, dietary advices (fiber and milk less diet with lot of oral fluids and to discourage voluntary withholding of faeces) and drugs for atleast 6 months to even 2 years in selected cases.
Gastroesophageal reflux (GOR)

GOR in most children presents with regurgitation and are uncomplicated and can be diagnosed clinically. Gastroesophageal reflux disease (GERD), the term is applicable when GOR is complicated by failure to thrive, erosive esophagitis, hematemesis, dysphagia or extraesophageal manifestations like respiratory symptoms, etc. 24 hour dual probe esophageal pH monitoring with simultaneous pharyngeal and esophageal sensors and impedance studies are currently the most accurate diagnostic tests for acid and non-acid gastro esophageal reflux respectively. The treatment of extra esophageal reflux manifestations needs more aggressive and prolonged anti-secretory therapy.

Newer drugs to reduce GO reflux episodes as add on to proton pump inhibitors (PPI) in refractory cases are baclofen (a GABA B receptor agonist), ondansetron (a 5HT receptor antagonist) and prucalopride (a specific 5-HT4 agonist).

Home parenteral and enteral nutrition (HPN):
HPN has become a practical option for children with intestinal failure who needs parenteral nutrition longer than 6 months where in care givers are willing to take on the responsibility of home care after adequate training, for uninterrupted HPN with adequate facility.

Protein hydrolysate formulas (PHF): PHF are recommended for infants who are intolerant to cow’s milk and soy proteins. Nearly 90% of infants tolerate PHF as well as free aminoacid – based formulas.

Liver function tests (LFT)- Clinical relevance

Serum bilirubin: Very high levels (30mg/dL) of total serum bilirubin are sometimes found when there is acute parenchymal liver cell injury associated with haemolysis such as sickle cell disease and acute hepatitis.

Transaminases: Interestingly the transaminases are found in very high levels of above thousands in conditions such as acute viral hepatitis, ischemic liver cell injury seen commonly in any ICU set up, drug induced liver disease and sometimes in autoimmune liver disorders. Incidental/ unexpected/ isolated elevation of transaminases are found in conditions such as Anicteric hepatitis, obesity/non alcoholic steato hepatitis, diabetes mellitus, some metabolic diseases eg. Wilson’s disease, glycogen storage disease, autoimmune liver disease, post-transplant allograft rejection, etc.

Prothrombin time when prolonged over 4 seconds, liver biopsy is not recommended. Liver biopsy or any invasive procedure is not recommended when the level of INR is more than 1.5 and in fulminant hepatic failure, if the INR is above 4 seconds, it is a poor prognostic marker.

Live hepatitis A vaccine: A single dose live attenuated HAV based on H2 strain of hepatitis A virus, introduced from China in preventing infection in individuals and outbreaks of Hepatitis A infection is currently found to be cheap, safe, immunogenic and effective in India.

Cholera vaccine: The new generation oral cholera vaccine (OCV) is approved by WHO. It is affordable, safe and immunogenic and confers 72% protection in all age groups.

Acute liver failure in children (ALF): Currently the management of ALF needs a multidisciplinary team work approach focussing on emergency intensive care (ICU) in a tertiary care hospital, to assess the severity and determine the etiology, to provide hepatic support, early recognition and appropriate management of complications such as fluid and metabolic disturbances, infections, cerebral edema, hepatic encephalopathy, coagulopathy, renal failure and hepatorenal syndrome and to consider prompt
referral for the definitive treatment of liver transplantation to those children with ALF with poor prognostic markers such as progressive coagulopathy (prothrombin time > 55 seconds) or progressive encephalopathy despite supportive management, rising bilirubin, falling transaminase and time of onset of hepatic encephalopathy more than 7 days after onset of clinical symptoms of ALF.\textsuperscript{36}

**Rifaximin** treatment in hepatic encephalopathy: Rifaximin, A synthetic derivative of Rifamycin and a minimally absorbed antibiotic is well documented in the treatment of ALF. Studies show a protective effect of rifaximin against episodes of hepatic encephalopathy and reduces the risk of hospitalization due to hepatic encephalopathy.\textsuperscript{37}

The drug is also indicated in conditions such as irritable bowel syndrome, small intestinal bacterial overgrowth, inflammatory bowel disease and prior to colorectal surgery.\textsuperscript{38} Generally, criteria of King’s College, London, are used to predict the outcome of ALF as well as the need for liver transplant.\textsuperscript{39}

**Hepatitis B and C in children:** Any thing new in therapies?

Chronic HBV infection needs annual monitoring and those with persistent HBV infection (replicators) characterized by persistently elevated ALT / AST more than 2 fold rise, HBeAg positivity, negative Anti- HBs antibody, raised HBV- DNA and significant liver cell damage ( liver biopsy proven) need treatment with interferon and / or lamivudine.

Chronic HCV persistent infection with high HCV viral load, genotype 1, 2 and 3 and significant liver cell damage needs treatment with interferon and ribavirin.

**Emerging new therapies** are antiviral inhibitors, nucleotides and cytokines.\textsuperscript{40}

**Liver transplantation in children- Indian scenario :** The most common indications are biliary atresia, ALF, progressive familial intrahepatic cholestasis (PFIC), Wilson’s disease, tyrosinemia, Criggler- Najjar Syndrome type-1, primary hyperoxaluria type 1, urea cycle disorders non- resectable hepatic tumors like hepatoblastoma and hepatocellular carcinoma, Budd Chiari syndrome and cryptogenic cirrhosis.\textsuperscript{41}

**Obscure gastrointestinal bleeding (OGIB):** OGIB is defined as bleeding from gastrointestinal tract (GIT) that persists or recurs without any etiology after a diagnostic esophago-gastro-duodenoscopy and colonoscopy. Most often after getting the clinical clues one should make use of radio-imaging techniques like barium meal follow-through/enteroclysis/ CT enteroclysis/ 64/128 multi slice CT/ MRI angio/virtual colonoscopy or nuclear imaging using Tc99m labelled RBC scan/ Tc 99m pertechnetate scan/ selective celiac/ superior mesenteric angiographic study during bleeding episodes or endoscopic techniques such as capsule enteroscopy, double- ballon enteroscopy (DBE) and push enteroscopy. Laporoscopic/ intraoperative enteroscopy can be utilised for locating the site of bleeding and also using the intervention radiology therapy techniques such as embolisation to arrest the bleeding.\textsuperscript{42,43}

With unending advances in the diagnostic and therapeutic aspects in the field of pediatric gastrointestinal / hepatic/ enteral and parenteral nutrition on one side it is important to consider systemic infections such as malaria, dengue, typhoid, leptospirosis, TORCH, HIV, tuberculosis, autoimmune/ connective tissue disorders (SLE) in the differential diagnosis of any patient with clinical features of hepatitis / liver failure in a tropical country like India where a combination of more than one infection in the same patient is often seen.
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**CLIPPINGS**


A prospective cohort study was done to compare the diagnostic properties of procalcitonin (PCT), C reactive protein (CRP), total white blood cells count (WBC), absolute neutrophil count (ANC) and clinical evaluation to detect serious bacterial infection (SBI) in children aged 1–36 months with fever and no identified source of infection. The study data demonstrate that CRP, PCT, WBC and ANC had almost similar diagnostic properties and were superior to clinical evaluation in predicting SBI in children aged 1 month to 3 years.
METABOLIC LIVER DISEASES

* Ashish Bavdekar
** Mita Pawar

Abstract: Metabolic liver diseases (MLDs) are large group of disorders occurring because of some inborn errors of metabolism affecting the liver primarily or secondarily. They may present anytime from neonatal period to adolescent age and cause significant morbidity and mortality in children. Due to their varied presentations, diagnosis and management of MLDs are always a challenge. The commonest MLDs are Wilson’s disease, glycogen storage diseases and galactosemia. A strong index of suspicion is the key to early diagnosis and intervention. Recent advances in genetic studies, enzyme assays and other diagnostic tools have made it possible to reach a definitive diagnosis and initiate timely therapy for some of these disorders.

Keywords: Metabolism, Liver, Diagnosis.

Liver plays a central role in innumerable metabolic processes in the body and hence is affected primarily or secondarily in many inborn errors of metabolism which are referred to as metabolic liver disorders (MLDs). MLDs are responsible for a great deal of liver related mortality and morbidity in children. They now account for upto 40% of all admissions due to chronic liver disease at large medical centres in India. Early diagnosis is the key to the outcome as specific therapies are now available in some of these disorders. A strong index of suspicion is the key to making a definitive diagnosis. The commonest MLDs seen in India are Wilson’s disease, glycogen storage diseases (GSD) and galactosemia. Some disorders like GSD usually present later in childhood and are relatively easier to diagnose due to their characteristic clinical features. However Wilson’s disease has a more varied presentation. Management of MLDs is always a challenge. Not all of them have a specific therapy but in some like Wilson’s disease, GSDs, galactosemia, etc. medical therapy or dietary manipulations are important to sustain a normal life.

The clinician should consider the possibility of a metabolic liver disease if any of the following are present.

- Family history of liver disease / consanguinity
- Unexplained hepatomegaly without jaundice
- Any unexplained chronic liver disease
- Associated rickets, failure to thrive, dysmorphism
- Associated renal, respiratory or neurological disease
- Recurrent episodes of liver disease
- Liver failure in early infancy, severe uncorrectable coagulopathy
In the order of importance to a clinician, some of the more common metabolic diseases are reviewed in this article.

**Wilson’s disease**

Wilson’s Disease (WD) is an inborn error of metabolism characterised by toxic accumulation of copper (Cu) in liver, brain, cornea and other tissues. It is an autosomal recessive disorder and occurs worldwide with an estimated prevalence of 1 in 30-50,000. It is one of the leading causes of chronic liver disease in Indian children.¹ The gene responsible has been identified as the ATP7B gene located on chromosome 13q.

**Clinical manifestations**

The clinical manifestations are a result of the deposition of copper in various organs. The age of presentation can vary from 4 to 60 years. The manifestations are more likely to be hepatic in early childhood and neurological in adolescents; however other forms of presentation are also seen. The spectrum of hepatic manifestations include all forms of chronic or acute liver disease – asymptomatic hepatomegaly, chronic hepatitis, portal hypertension, cirrhosis, acute “viral hepatitis” and sometimes in fulminant hepatic failure with high mortality. Neurological manifestations can begin even in the first decade. They can be equally varied and include clumsiness, speech difficulties, scholastic deterioration, behavior problems and occasionally convulsions as also choreo-athetoid and dystonic movements. Typically symptoms are gradual in onset and progression is slow. Neurological disease is almost always associated with the presence of Kayser – Fleischer rings (K.F.Rings). Other presentations are “osseomuscular” with bony deformities (knock knees) suggestive of resistant rickets. Renal involvement is characterised by proximal tubular dysfunction and decreased glomerular filtration rate. Hemolytic anemia can occur due to erythrocyte membrane injury from the free copper in the serum. With such diverse presenting features, the key to diagnosis is a high index of suspicion.

**Diagnostic challenges**

No single test is diagnostic by itself and a group of appropriate tests of copper metabolism needs to be done in order to make the diagnosis.

1. **Serum ceruloplasmin**: This is a copper containing alpha 2 glycoprotein, the gene for which is on chromosome 3. The level of ceruloplasmin in normal individuals is 20-40 mg/dL. Serum ceruloplasmin is reduced in most patients with WD. However 5-40% of WD may have a normal ceruloplasmin. Normal ceruloplasmin levels in WD may also be found in hepatic inflammation. On the other hand, even a low ceruloplasmin level is not diagnostic of WD as such values are also found in normal newborns, severe malnutrition and protein losing states, acute liver failure of any etiology and 20% of WD carriers.² Ceruloplasmin is a good screening test but cannot be solely relied on to make a diagnosis.

2. **24 hour urine copper**: It is normally less than 40 mg/day. In symptomatic patients with WD, the 24-hour urinary Cu excretion is more than 100mg/day. However, similar high values have also been documented in non-WD chronic hepatitis, Indian childhood cirrhosis, chronic cholestatic liver disease, acute liver failure of any etiology and Cu contaminated urine samples. Estimation of urinary Cu after a penicillamine challenge has been suggested as a test to differentiate WD from other causes of raised urinary Cu.

3. **KF ring**: A complete KF ring indicates long-standing disease and severe Cu overload. They appear as golden brown or greenish yellow
discoloration in the limbus of the cornea. A slit lamp examination is necessary for detection and it is usually first visible at the upper part of the cornea. In our series, KF ring was seen not only in neurological cases but also hepatic ones. KF rings may also be seen in chronic active hepatitis, primary biliary cirrhosis and intrahepatic cholestasis.

4. Hepatic copper: Normal values are less than 50 mg/gm of dry weight of liver. It is the single best predictive marker for WD and considered the gold standard, with values usually above 250mg/g dry weight. Disorders like Indian childhood cirrhosis, chronic cholestatic disorders also give rise to high hepatic copper but can be clinically differentiated from WD.

5. Genetic studies: Direct genetic diagnosis is difficult because of the occurrence of more than 200 mutations, each of which is rare. Gupta, et al have identified 17 mutations in eastern India including five common mutations that account for 44% of their patients. The WD mutations in different regions of India suggest high genetic heterogeneity and the absence of a single or a limited number of common founder mutations.

Diagnostic approach

In a neurological setting, diagnosis of WD is easier, as a KF ring would be positive in almost all cases and along with either a low ceruloplasmin or high urinary copper, would be diagnostic. In liver disease, diagnosis can be more complex. WD is strongly suggested by any two of the following - low ceruloplasmin, high urinary copper, presence of KF rings and confirmed by a high hepatic copper. If a liver biopsy is not possible due to coagulopathy, chelation therapy can be started immediately. Liver biopsy must then be done at the earliest opportunity, as hepatic copper may remain elevated despite years of therapy and clinical improvement.

Management

1. Diet: WD cannot be prevented or controlled by a low copper diet alone. It is advisable to avoid high copper containing foods like organ meats (liver), chocolates and nuts, dry fruits.

2. Drugs: Continuous life long drug therapy is essential in the management of WD. Treatment comprises of an “initial phase” where copper is reduced to sub toxic threshold. D-Penicillamine (DP), Trientine or Zinc are used as initial therapy, and a “maintenance phase” to maintain a slightly negative copper balance so as to prevent copper accumulation and toxicity. DP, trientine and zinc have been traditionally used for this phase. Table 1. shows detailed drug therapy of WD.

3. Liver transplant: Liver transplant is the treatment of choice in children with acute liver failure or decompensated cirrhosis unresponsive to medical therapy. One year survival ranges from 79% to 87%.

4. Management of sibs of WD: All siblings of a child with Wilson’s disease carry a 25% chance of having WD. Hence, they should undergo a detailed clinical and laboratory examination. The treatment of asymptomatic siblings is identical to that recommended for children receiving maintenance therapy viz., zinc, DP or trientine.

Glycogen storage disease

Glycogen storage diseases (GSD) are a heterogeneous group of entities classified on the basis of specific enzyme defects in various steps of glycogen synthesis or breakdown. GSDs are broadly classified depending on the main tissue involved (Table 2.).

GSD Type I - Glucose 6 phosphatase deficiency is the most severe form of hepatic GSD and results in defective gluconeogenesis. Patients present in infancy with doll-like facies,
Table 1. Drug therapy of Wilson’s disease

<table>
<thead>
<tr>
<th>Drug and mechanisms of action</th>
<th>Dose</th>
<th>Common toxicity</th>
<th>Monitoring for side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. D Penicillamine (DP) acts by reductive chelation and causes cupriuresis</td>
<td>Starting 10mg/kg/day and increased to 20-30mg/kg/day in 2 to 3 divided doses on empty stomach</td>
<td>Fever, rash, Thrombocytopenia, bone marrow depression, proteinuria, worsening of neurological symptoms, autoimmune conditions</td>
<td>Complete blood counts, urine analysis before therapy, weekly during the first one month, monthly in the first year and yearly thereafter.</td>
</tr>
<tr>
<td>2. Trientine same as DP</td>
<td>25mg/kg/day in 3 divided doses on empty stomach</td>
<td>Gastritis, sideroblastic anemia, aplastic anemia</td>
<td>As above</td>
</tr>
<tr>
<td>3. Zinc acts by increasing fecal excretion of copper</td>
<td>25-50mg of elemental zinc. 3 times daily on empty stomach</td>
<td>Gastritis, biochemical pancreatitis, possible immune dysfunction</td>
<td>None</td>
</tr>
<tr>
<td>4. Ammonium tetrathiomolybdate binds to copper in the GIT and in blood rendering it unavailable for cellular uptake. (not available for routine use)</td>
<td>120mg/day in six divided doses</td>
<td>Anaemia, bone marrow depression, hepatotoxicity</td>
<td>Complete blood counts Liver function tests, BUN, creatinine, urine analysis weekly</td>
</tr>
</tbody>
</table>

Table 2. Classification of Glycogen Storage Diseases

<table>
<thead>
<tr>
<th>Primary organ involved</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>I, IIIb, IV, VI, IX.</td>
</tr>
<tr>
<td>Muscle</td>
<td>V, VII</td>
</tr>
<tr>
<td>Mixed</td>
<td>`II, III</td>
</tr>
</tbody>
</table>

trunclal obesity, massive hepatomegaly (fat and glycogen deposition), nephromegaly, failure to thrive, hypoglycemia (seizures) and lactic acidosis after short fasting intervals. Serum triglycerides, cholesterol and uric acid are moderately elevated. The kidneys are enlarged on ultrasound due to increased glycogen content. Liver biopsy shows markedly increased fat and glycogen without fibrosis. Strict dietary therapy leads to normal growth and development, but these children are at risk of developing osteoporosis, renal disease and hepatic adenomas after the second decade.4

GSD Type III: GSD III is due to abnormal activity of debrancher enzyme – amylo-1-6 glucosidase. Type IIIa is associated with progressive (cardio) myopathy while IIIb has mainly liver disease. In infancy presentation
is similar to GSD I, but milder, with hepatomegaly and hypoglycemia. Gradually hepatomegaly decreases and fasting hypoglycemia improves.

**GSD type IV**: This rare disorder occurs due to a defect in glycogen branching enzyme. Patients are normal at birth. Hepatomegaly and failure to thrive are seen in infancy. Cirrhosis and splenomegaly soon become manifest and death from liver cell failure usually occur before 3 years of age. Liver biopsy shows cirrhosis and abnormal glycogen which is diastase resistant.

**GSD types VI and IX**: These GSDs are due to defect in the hepatic phosphorylase system. The disorders are fairly benign and long term outlook for growth and liver function are good.

**Management of GSD**: Treatment of GSD I is aimed at preventing hypoglycemia by frequent daytime feeding with slowly resorbed carbohydrates (starch, glucose polymers) and continuous nocturnal feeding. Lactose, fructose and sucrose are avoided or limited. In older children uncooked cornstarch every 4-6 hours may be adequate to maintain normoglycemia. GSD III, VI and IX requires similar but less stringent dietary therapy. Liver transplant is the only available option for GSD IV but may not prevent progression of extrahepatic disease.

**Galactosemia**

It is an autosomal recessive disorder of galactose metabolism due to deficiency of enzymes galaktokinase, galactose-1-phosphate uridyl transferase (GALT) (which is the commonest) or uridine diphosphate galactose-4-epimerase. The commonest presenting feature is failure to thrive associated with vomiting or diarrhea starting within a few days of milk ingestion. Most patients manifest jaundice during the first week of life. This jaundice could be unconjugated to start with and becomes conjugated later on. Untreated these children go on to develop chronic liver disease.

**Pathogenesis** - Cataracts occur as a result of the accumulation of galactitol in the lens. The other manifestations appear to result from intracellular accumulation of gal-1-P. The most severe hepatic disturbance in galactosaemia occurs during septicemia in infants. The gene is mapped to 9p13.

**Investigations**: The laboratory findings besides those of deranged liver function include elevated blood galactose and galactose-1-phosphate, hypoglycemia, hypergalactosuria, hyperchloremic metabolic acidosis, albuminuria and hyperaminoaciduria. Urine reducing substances have been the traditional screening test, but may produce both false negatives, if the baby is not being fed and false positives in babies with other liver disorders. The recommended diagnostic method is RBC gal-1-PUT, for which the Buetler screening test is widely used. A kit method is also available at relatively low cost. RBC gal-1-PUT will be falsely normal if the baby has been transfused.

**Treatment**: Elimination of dietary galactose is the only available treatment. In neonates and small infants, the preparations used are lactose free casein hydrolysates or soya bean milks. In older children diets restricted to less than 125mg galactose are advised.

**Epimerase deficiency**: Two forms have been described. One is benign, involves only red and white blood cells without deranged metabolism in other tissues and the other form having generalised epimerase deficiency which presents with clinical features resembling transferase
deficiency and responds to restriction of dietary galactose.

**Tyrosinemia**

Tyrosinemia, a hepatorenal disease, is primarily a disease of organic acid metabolism. The defective enzyme is fumaryl acetoacetic acid hydrolase (FAH), which leads to accumulation of maleylacetoacetate (MAA), fumaryl acetoacetate (FAA) and succinyl acetone. Acute tyrosinemia, which is more common presents in infancy as acute severe liver cell dysfunction. The chronic form usually manifests as Vitamin D resistant rickets with hepatomegaly in older children. Diagnosis of tyrosinemia requires analysis of urine for succinyl acetoacetate and succinylacetone by gas liquid chromatography with mass spectrometry. Serum alpha fetoprotein is often greatly increased in tyrosinemia and is commonly used as a screening test. Treatment options available are oral NTBC [Nitisinone (2-Nitro-4-trifluoromethyl beuzoyl) -1,3-cyclohexanedione] therapy in early stages or liver transplant in advanced cases.\(^8\)

**Gauchers disease (GD)**

GD is a glycolipid storage disorder due to a deficiency in the lysosomal enzyme glucocerebrosidase. The enzyme deficiency results in accumulation of glucocerebroside (glucosylceramide), a complex lipid, in the lysosomes of tissue macrophages (reticulo endothelial cells). Three different types of Gauchers disease have been described. Gauchers disease should be suspected in any child presenting with hepatosplenomegaly and anemia. Assay of \(\beta\) glucosidase activity in the peripheral blood leukocytes is diagnostic.\(^9\) Lifelong enzyme replacement therapy, though expensive is now possible in India.

**Points to Remember**

- Metabolic liver diseases (MLD) account for 40% of chronic liver diseases in children.

**Presentation may be in early infancy or in childhood.**

- Wilson’s disease, glycogen storage diseases and galactosemia are the commonest MLDs.

**Early diagnosis is essential for appropriate treatment and favorable outcome.**

**References**

ACUTE PANCREATITIS

* Sarah Paul  
** John Matthai

Abstract: Acute pancreatitis is a potentially reversible process of inflammation of the pancreas which occurs when calcium dysregulation in the acinar cells leads to activation of trypsinogen and release of cytokines. Although much less common than in adults, incidence in children is on the rise due to better diagnostic modalities. Severe systemic illnesses, blunt trauma, drugs and structural anomalies are the most common identifiable trigger factors. Sudden severe epigastric pain with elevation of amylase or lipase to thrice normal should arouse suspicion and an ultrasound is usually diagnostic. The extent of the systemic inflammatory response syndrome determines severity and scoring systems for assessment have now been validated in children. Early diagnosis, judicious intravenous fluids, analgesia and monitoring for complications ensures a good outcome in most children.

Keywords: Pancreatitis, Amylase, Lipase, SIRS.

Acute pancreatitis is defined as acute inflammation of the pancreas, manifesting as severe abdominal pain associated with a rise in digestive enzymes in the blood and urine as well as sonographic / radiologic evidence of pancreatic inflammation. The clinical course can vary from a mild, self-limited illness to a severe fatal disease. It is now being increasingly recognized early and managed effectively in children. This is probably due to a combination of factors - better imaging techniques, safer invasive testing methods, better understanding of the pathophysiology and improved awareness of its occurrence.

Pathophysiology

The pancreas serves three primary functions namely - a) production of bicarbonate rich fluid by the ductal cells which neutralizes the gastric acid entering the duodenum, b) synthesis of digestive enzymes within the acinar cells and c) production of insulin by the islet cells. Most of the pancreas is composed of acinar cells. All digestive enzymes except amylase and lipase are synthesized and stored as proenzymes which require activation. The most abundant among these is trypsinogen (proenzyme form of trypsin) and this is normally activated only by the intestinal brush border enterokinase. Small amounts of trypsinogen normally autoactivate into trypsin, but there are intracellular protective mechanisms which keep this in constant check.

Calcium is the most important messenger signalling system in the acinar cells. With physiologic stimulation, intracellular calcium rises slowly, oscillates within a narrow range and there is a slow sustained release of proenzymes. With hyperstimulation, intracellular
calcium levels rise rapidly leading to sustained activation of trypsin followed by the other proenzymes. Calcium dysregulation has an important role in acute pancreatitis.

Acute pancreatitis is thought to occur when trypsinogen activation exceeds the capacity of the protective mechanisms. There are 3 important protective mechanisms in place. Ductal cells make up only 5% of the pancreatic mass, but produce very large volumes of bicarbonate rich pancreatic fluid. This fluid washes the digestive enzymes out of the pancreas and into the duodenum. Mutations in the CFTR (cystic fibrosis trans membrane conductance regulator) decreases the fluid secreting capacity of the pancreas. This can result in stasis of trypsin in the pancreas. The acinar cells also produce a peptide called serine protease inhibitor (SPINK1) which inhibits trypsinogen activation within the cells. Mutations in SPINK gene is associated with increased risk of pancreatitis. Normal trypsin also has a self destructive mechanism in the middle of its side chain, by which it can undergo autolysis. Patients with hereditary pancreatitis have a mutation at this site.

Pancreatitis is thought to occur when calcium dysregulation in the acinar cells leads to activation of trypsin and it cannot be counteracted due to a mutation either in CFTR, SPINK or trypsin autolysis. Trypsinogen activation results in a vigorous immune response, release of cytokines and other inflammatory mediators and systemic inflammatory response syndrome.

**Etiology**

The factors which trigger acute pancreatitis in children are very different from adults. In a review of 1276 children with pancreatitis, severe systemic illnesses and blunt trauma accounted for nearly 20% each, drugs and structural anomalies for about 10 % each; infections for 8%, while 22% were idiopathic. Among systemic illnesses, hemolytic uremic syndrome is the commonest. Among structural anomalies, pancreatic divisum and choledochal cysts predominate. Among the infectious causes, mumps, HIV and cytomegalovirus are most important. Ascaris lumbricoides is an important cause in endemic areas and is usually difficult to treat. Among drugs, valproate (idiosyncratic reaction) is most commonly implicated followed by prednisolone and L-asparaginase. Gall stones are now emerging as an important cause. Other important etiologic agents include metabolic causes (hyperlipidemia, hypercalcemia), post ERCP and familial pancreatitis.

With better diagnostic modalities, the percentage of idiopathic pancreatitis has been steadily declining.

**Clinical features**

Abdominal pain is most commonly located in the epigastrium, may radiate to the back or to the right hypochondrium. The pain is typically constant but may be intermittent and is always aggravated on eating. Knee - chest position generally relieves the pain. Epigastric tenderness is an unreliable sign. Vomiting is aggravated by eating or drinking, but vomiting does not relieve the pain. Food intolerance, when feeding is introduced in a patient recovering from a severe systemic illness is also suggestive of pancreatitis. Fever if present, is usually mild (less than 38.5°C). Hypotension or shock is unusual at presentation. Rebound abdominal tenderness with guarding and decreased / absent bowel sounds may be seen in severe disease. Upper G.I hemorrhage is thought to result from stress ulcers in the stomach. Pleural effusion and ascites may occur in severe cases.

**Diagnosis**

Diagnosis begins with a high index of suspicion, based on the sudden severe abdominal
pain in the epigastrium and elevation of serum amylase or lipase to thrice the normal. Amylase usually begins to rise within few hours of onset of symptoms, peaks within 24 hours and returns to normal within 2-5 days. The degree of elevation of amylase does not correlate with the severity of pancreatic inflammation or the clinical course. The sensitivity of serum amylase in the diagnosis of acute pancreatitis in children is low and about 40% of cases can be missed, if it is used as the sole diagnostic criterion. The urinary amylase: creatinine clearance ratio is normally 1-4% and values above 6% are considered diagnostic. It is not more useful than serum amylase in diagnosis. Serum lipase remains elevated longer than serum amylase in acute pancreatitis. The superiority of lipase in diagnosis is debatable. Both lipase and amylase can be elevated in conditions other than pancreatitis (acute cholecystitis, salivary adenitis, end-stage renal disease, salpingitis, burns). A combination of elevated amylase or lipase and serum transaminases is more predictive of pancreatitis than elevated amylase or lipase alone. Hypocalcemia and hypoglycemia may sometimes be observed. Peripheral blood counts, LDH, serum albumin and blood urea are necessary to assess the severity of pancreatitis.

CT and ultrasound are the two most commonly used imaging modalities and help to document increased pancreatic size, determine the severity and identify complications like pseudocyst as well as rule out underlying chronic pancreatitis. The two major findings on abdominal ultrasound are a) decreased echogenicity and b) increased size of the pancreas. Pancreatic pseudocysts, peripancreatic fluid collection, dilated main pancreatic duct, gall stones, biliary sludge and pancreatic calcification can also be demonstrated. Abdominal C.T scan can detect all the above findings with better precision except that abnormal attenuation is seen rather than decreased echogenicity. There is some evidence in animal experiments that CT contrast given early in the course of the disease may decrease blood flow to the ischemic areas and thus worsen the disease. It is therefore recommended that CT scan be done several days into the disease in severe pancreatitis, if the patient fails to improve, rather than in the early stages. MRCP defines the pancreatic and biliary ductal system very well and may have a role in those with unexplained recurrent pancreatitis, prolonged disease or when a structural defect is suspected. ERCP is done only when MRCP is inconclusive or intervention is required.

**Assessment of severity**

Acute pancreatitis may be mild or severe. Mild disease is defined as pancreatitis limited to peri-pancreatic fat necrosis and interstitial edema, have minimal complications, require minimal supportive treatment and recover completely. A majority of cases in children fall into this category. Presence of complications requiring prolonged treatment or specific interventions or an increased likelihood of death is indicative of severe pancreatitis. Many scoring systems [Ranson’s score, Glasgow score, the acute physiology and chronic health evaluation (APACHE)] score have been designed to help make this differentiation early in the illness. In general, the signs and symptoms in all these systems reflect the magnitude of the body’s inflammatory response to the pancreatitis, rather than quantify the amount of pancreatic injury. The most recent and most relevant scoring system in children is the one from the Midwest multicenter pancreatic study group.

The eight severity factors are as follows:

1. Age : less than 7 years
2. Weight :< 23 Kg
3. WBC count at admission : >18.5 X 10⁹
4. Admission LDH : >2,000 IU / L
5. 48 hour fluid sequestration : > 75 ml/kg/48 hr
6. 48-hour trough Ca++ : < 8.3 mg/dL
7. 48-hour trough albumin : < 2.6 g/dL
8. 48-hour rise in BUN : > 5 mg/dL

Each criterion is assigned a score of 1 point. Lower the total score, milder the disease and better the outcome. Among all the factors, young age and low weight are the major risk factors.

**Severe acute pancreatitis**

In general, death from pancreatitis is rare in children compared to adults. The extent of the systemic inflammatory response syndrome (SIRS) determines the severity of the pancreatitis. Tachycardia, hypotension, tachypnoea, hypoxemia, hemoconcentration, oliguria and encephalopathy are early indicators of severe pancreatitis. Cardiovascular collapse occurs due to fluid accumulation in the third space from vascular leak in a patient with persistent vomiting who is kept nil orally. If recognized early, this can be prevented by central venous pressure monitoring and fluid resuscitation. Acute respiratory distress syndrome, multi organ system failure and infected pancreatic necrosis have poor prognosis. Careful attention to fluid therapy, nutrition as well as judicious antibiotics may help prevent them.

**Complications**

Both local and systemic complications occur (Table 1.). Some are life threatening emergencies, while most are not. Among the local complications, pancreatic necrosis, peri-pancreatic abscess, hemorrhage and pseudocysts are important. Pancreatic necrosis is the most dangerous, but occurs in less than 1% of children. Obstruction of the pancreatic blood flow occurs due to a combination of depleted intravascular volume, high hematocrit and inflammation. Diagnosis can be made on a contrast CT. Pseudocysts are common but seldom large as in adults. Abscesses require IV antibiotics and external drainage. Hemorrhage is more common in association with blunt trauma and may require drainage after correction of the coagulopathy.

<table>
<thead>
<tr>
<th>Table 1. Complications of acute pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
</tr>
<tr>
<td>Fluid collections</td>
</tr>
<tr>
<td>Fat necrosis</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Pseudocyst</td>
</tr>
<tr>
<td>Pancreatic duct rupture</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
</tr>
<tr>
<td>Inflammation in adjacent organ</td>
</tr>
</tbody>
</table>
Among the life threatening complications shock and respiratory distress are most important. Shock occurs from a combination of vascular leak and persistent vomiting. Acute respiratory distress syndrome (ARDS) occurs from leakage of proteinaceous fluid into the alveolar spaces and hypotensive shock. Multiorgan system failure is rare but has poor prognosis in children.

**Treatment**

The emphasis today is on conservative management. Suppression of pancreatic enzyme production using somatostatin, octreotide, glucagon, etc has failed to demonstrate any beneficial effect in clinical trials. Early diagnosis and judicious fluid replacement is the key to a good outcome.

**Mild pancreatitis:** Adequate fluid replacement to maintain vital signs and good urine output is most important. The volume replacement should take into consideration, third space loss, vomiting and fever. Blood glucose, electrolytes, calcium, blood urea and packed cell volume should be monitored. Maintenance of circulatory volume is paramount, since it prevents pancreatic necrosis. Effective pain relief is achieved with pethidine or in some cases, morphine. Very little data is available on other analgesics. Continuous nasogastric drainage, proton pump inhibitors and prophylactic antibiotics are commonly used, but there is little evidence that they are useful. Most children tolerate small quantities of oral feeds by the third to fifth day. Feeding schedule is determined by absence of pain, return of bowel sounds and emergence of hunger. There is no need to wait for normalization of serum amylase / lipase to start feeds. Small frequent high carbohydrate diet is generally used, but there is no proof that a more liberal diet delays recovery. Pancreatic supplements have no role in acute pancreatitis.

**Severe pancreatitis:** About 10 – 15% of children have an unfavorable score and systemic complications. These children are best managed by a multidisciplinary team in an intensive care unit under continuous monitoring.

1. **Fluid resuscitation:** In severe pancreatitis, there is rapid loss of fluid from the vascular compartment leading to hypotension, shock, pancreatic necrosis and multi organ failure. Fluid resuscitation and subsequent maintenance of fluid balance is critical and a central venous line is very helpful. Ringer lactate or normal saline are ideal for fluid replacement. Large losses of albumin into the third space often occur, necessitating the use of FFP, albumin or dextran to maintain hemodynamic balance. The hematocrit should be maintained above 30% to ensure pancreatic micro circulation.

2. **Pain relief:** Continuous pain relief with morphine is usually necessary and contributes to improved outcome. Patient controlled anesthesia, which is liberally used in adults, is not appropriate in children.

3. **Cardiorespiratory support:** Most patients have hypoxemia due to atelectasis, pneumonia or pleural effusion. Supplemental oxygen through mask or nasal prongs is usually sufficient. ARDS characterized by increasing dyspnoea, progressive hypoxemia and pulmonary infiltrates on radiographs is rare in children. Early endotracheal intubation and ventilation is necessary for those with ARDS. Hypotension not improving with fluids and colloids can be managed with dopamine infusion. However it is best avoided, since vasoconstriction at the pancreatic microcirculation can worsen the disease.

4. **Metabolic problems:** Blood sugar levels may fluctuate in the acute stage, but insulin should be administered with caution. Hypocalcemia and hypomagnesemia require prompt correction.
5. Peritoneal lavage: There is some evidence that early peritoneal lavage and removal of the enzyme rich fluid improve outcome in severe pancreatitis. Experience in children is limited.

6. Antibiotics: Antibiotics are indicated to prevent secondary infection of the necrotic pancreas. CT guided aspiration and culture helps identify the organism. Debridement of necrotic tissue may be required if the necrotic area is extensive and the child is not improving. Surgery is best deferred for at least 2 weeks to enable proper demarcation of the necrosed area. Pancreatic abscess is a late complication.

7. Nutrition: Complete oral feeding may not be possible for several weeks. Parenteral nutrition should therefore be instituted early. Intravenous lipids can be safely used, unless there is hypertriglyceridemia. In adult patients, the tendency is towards earlier enteral feeding with elemental diets. These cause less pancreatic stimulation, are safe and well tolerated. In adults enteral feeds have been shown to be associated with lower infection rate and reduced hospital stay.

Pancreatic pseudocyst

Pseudocysts are formed from accumulation of extravasated pancreatic secretions. Recurrence of pain, vomiting and abdominal distension in a patient apparently recovering from pancreatitis, should arouse suspicion. Ultrasound is ideal for detection and should ideally be done 4 weeks after diagnosis. Cysts less than 4 cms in size, asymptomatic and non progressive require no intervention. Large cysts or thick walled cysts, especially if adherent to the stomach or intestine will require cystogastrostomy or cystojejunos- tomy. An ERCP or MRCP should be done before intervention, to rule out pancreatic duct blockage. Complete cyst resection is a better option in those with blocked pancreatic duct. Cystogastrostomy or cystoduodenostomy can be done endoscopically in older children. A stent is introduced endoscopically to drain the cyst into the hollow viscus. They can also be introduced through the ampulla of vater if the cyst communicates with the main pancreatic duct. Stents should be removed after 4 to 6 weeks.

Prognosis

Pancreatitis in children has a good prognosis. Recurrent acute pancreatitis occurs commonly with structural abnormalities, idiopathic pancreatitis or familial pancreatitis. Death in the first week is due to systemic inflammatory response syndrome, while later it occurs from multi-organ failure or pancreatic sepsis. Early diagnosis and vigorous fluid therapy is the key to a good outcome.

Points to Remember

• Pancreatitis is being increasingly recognised in children and an underlying cause can be made out in many of them. Suspect pancreatitis in children with sudden severe epigastric pain associated with vomiting.
• Ultrasound abdomen and elevated serum amylase or lipase is diagnostic. CT and MRI scans are best done later in the illness.
• Assessment of severity should be done with a pediatric scoring system consisting of clinical and biochemical parameters.
• Treatment is conservative with judicious fluid management, pain relief, pancreatic rest and monitoring for complications.
• Prognosis is good with early diagnosis and optimal care.
References


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**CLIPPINGS**

**Palivizumab for prevention of respiratory syncytial virus infection in children with cystic fibrosis**

One randomised controlled trial was identified comparing five monthly doses of palivizumab to placebo in infants up to two years old with cystic fibrosis (CF). While the overall incidence of adverse events was similar in both groups, it is not possible to draw conclusions on the safety and tolerability of RSV prophylaxis with palivizumab in infants with CF because the trial did not specify how adverse events were classified. Six months after treatment, the authors reported no clinically meaningful differences in outcomes; however no data were provided. Additional randomised studies are needed to establish the safety and efficacy of palivizumab in children with CF.

GASTROENTEROLOGY

APPROACH TO CHRONIC DIARRHEA AND MALABSORPTION SYNDROME

*Ujjal Poddar

Abstract: Chronic diarrhea is defined as diarrhea of more than 2 weeks duration. Etiology of chronic diarrhea depends on age; persistent diarrhea is the commonest cause in less than 3 years of age, whereas malabsorption syndrome (MAS) is common in 3 years of age and more. Celiac disease is the commonest cause of MAS in north India. Approach to a child with chronic diarrhea depends on the type of diarrhea (small bowel or large bowel type) and presence or absence of failure to thrive. In the absence of failure to thrive, functional diarrhea like non-specific diarrhea or irritable bowel syndrome (IBS) should be considered. In diarrhea, due to organic causes endoscopy and mucosal biopsy plays an important role in finding out the cause.

Key Words: Non-specific diarrhea, Cow’s milk protein allergy, Celiac disease.

Chronic diarrhea is defined as diarrhea (three or more stools/day) of more than two weeks duration. Etiology of chronic diarrhea depends on age. In younger age group (<3 years), persistent diarrhea is the predominant cause whereas in age group 3 years or more, malabsorption syndrome is the predominant cause of chronic diarrhea.\(^1,2\) However, in healthy children non-specific diarrhea and irritable bowel syndrome are common causes of chronic diarrhea.

Malabsorption syndrome (MAS) means failure of absorption of one or more nutrients. Commonest presentation of children with MAS is chronic diarrhea. However, almost one fifth of them present without diarrhea with signs and symptoms of nutritional deficiency like short stature, anemia, rickets and even constipation. The etiology of MAS depends on the age of the child. A study from Chandigarh\(^2\) has shown that in less than 2 years age group, persistent diarrhea is the commonest cause while in more than 2 years age group, celiac disease is the commonest cause (Table 1). Almost 20% cases of chronic diarrhea in children in north India is due to celiac disease. Though tuberculosis is a rare cause of MAS, a trial of anti-tuberculous therapy is used in the majority of cases of MAS in India. It is not only unethical but also dangerous to prescribe potentially toxic anti-tuberculous drugs without a definite proof.

**Approach to chronic diarrhea in less than 3 years age group**

Presence or absence of failure to thrive determines the approach to a child with chronic diarrhea. In an otherwise healthy child with chronic diarrhea the most common cause is non-specific or toddler’s diarrhea and needs nothing but simple stool examination and reassurance. Diagnostic clues are; healthy child with diarrhea in waking hours and positive family history of

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* Associate Professor, Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow.
irritable bowel syndrome (IBS). On the other hand if a child has failure to thrive with chronic diarrhea then investigations need to be done to find out the cause. In this setting one of the common cause is cow’s milk protein allergy (CMPA). When a persistent diarrhea child does not respond to low lactose formula or has disproportionate anemia, rectal bleeding and significant failure to thrive CMPA is a likely possibility. In this setting rectal biopsy helps to clinch the diagnosis.

**Approach to chronic diarrhea in more than 3 years age group**

In this age group, a healthy child (without failure to thrive) with chronic diarrhea is most likely due to functional diarrhea (IBS) and does not need detailed investigation. On the other hand a child with chronic diarrhea and failure to thrive is likely to be due to MAS or inflammatory bowel disease (IBD). Clinically it is important to differentiate small bowel type of diarrhea (MAS) from large bowel type of diarrhea (IBD). Usually large bowel type of diarrhea has the following features; blood, mucus, tenesmus, urgency and high frequency. However, small bowel diarrhea does not have the above mentioned features but has large volume, foul-smelling stools with undigested food particles and often associated with features of lactose intolerance like explosive diarrhea and bloating. For large bowel diarrhea colonoscopy and colonic biopsy with or without imaging (barium and CT scan) help in making a definite diagnosis.

**Approach to malabsorption syndrome**

Malabsorption syndrome can be divided into three stages. First is the clinical suspicion of MAS on the basis of history and physical examination, next the confirmation of its presence by
laboratory tests and lastly, demonstrating its cause by structural tests like endoscopy, mucosal biopsy, imaging etc.

**Clinical suspicion of MAS:** Diarrhoea is the commonest manifestation of MAS and usually of small bowel type ie, large volume stools with features of carbohydrate (lactose intolerance: explosive diarrhea, abdominal distension and flatulence), protein (offensive stools, edema) and fat (steatorrhea) malabsorption. Presence of chronic malnutrition with features of water soluble vitamin deficiencies (anemia, glossitis, angular stomatitis, etc) substantiates the clinical suspicion of MAS.

**Confirmation of MAS:** Simple laboratory tests help in finding out the presence or absence of malabsorption. Presence and type of anemia is assessed by complete hemogram. Besides anemia some specific features of MAS like lymphocytopenia (in lymphangiectasia), thrombocytosis (in celiac disease), acanthocytes in peripheral blood film (in abetalipoproteinemia) can be picked up in hemogram. Stool pH <5.5 and presence of reducing substances confirms carbohydrate malabsorption. Similarly fat malabsorption is diagnosed by fecal fat estimation (fat globules or fatty acid crystals on microscopy and quantitative fecal fat estimation). Though it is not easily available, fecal alpha-1-antitrypsin estimation is the test for protein losing enteropathy. Other tests which are commonly used in MAS are; D-xylose excretion test, lactose tolerance and lactose hydrogen breath test, Schilling test (for vitamin B12 malabsorption).

**Demonstrating the cause of MAS:** The third stage of approach to MAS is to find out the cause. Structural tests like endoscopy, small intestinal biopsy, barium meal follow through, CT scan, etc, play important role in finding out the cause of MAS. In addition to structural tests, some other specific tests like celiac serology, sweat chloride test and mutation analysis help in pin pointing a specific diagnosis. Upper gastrointestinal endoscopy and duodenal biopsy are the mainstay of all investigations for MAS. Mere presence of villous atrophy does not give a diagnosis of MAS. Mucosal biopsy is diagnostic (means always positive) in abetalipoproteinemia (fat globule within enterocytes), Whipple’s disease (finding a specific acid fast organism) and agammaglobulinemia (absence of plasma cells in the lamina propria). There are conditions where biopsy changes are diagnostic but patchy (diagnostic if found) like lymphangiectasia (dilated lacteals in lamina propria), giardiasis, strongylaidosis, lymphoma, eosinophilic gastroenteritis, Crohn’s disease etc. However, in the majority of cases of MAS the mucosal biopsy is abnormal (shows villous atrophy) but not diagnostic of a particular condition like celiac disease, tropical sprue, cow’s milk protein allergy, severe protein energy malnutrition (PEM), prolonged iron and folate deficiencies, etc. Approach to MAS is given in Fig.1.

**Celiac disease**

Celiac disease is the most common cause of MAS even in India especially in north India. Celiac disease is a result of inappropriate immune response against gluten in genetically predisposed people. It has been shown that HLA-DQ2 allele is present in more than 90% cases of celiac disease versus 30% in general population (HLA-DQA1*0501 and B1*0201 are present in 99% celiac disease cases). The frequency of HLA-DQ2 allele in north Indian children with celiac disease is similar to the West (94% from Lucknow and 100% from Delhi). Therefore, as far as genetic susceptibility is concerned there is no difference between north Indians and Europeans.

The question is why this disease is so common in North India? Probably the north Indians are genetically susceptible and wheat is the staple diet in north India.
Clinical features of celiac disease

In the West, age of onset of the disease is 6-12 months and age of diagnosis is around 18 months. Latent period between introduction of gluten and onset of symptoms is variable (months to years). In India, it has been reported that the age of onset of symptoms is 2.4-3 years and the age of diagnosis is 6.3 to 8.3 years. This delay (3 to 6 years) in diagnosis is mainly due to lack of awareness among parents and pediatricians and the delay in onset of symptoms may be due to prolonged breast feeding and delayed weaning.
Classical presentation (80%): The typical presentation of celiac disease in India is chronic diarrhea (small bowel type with features of malabsorption) with failure to thrive and anemia. However, almost one fifth of the cases of celiac disease can present with nutritional deficiency features without diarrhea and attend various specialties. In the West, almost half of the cases of celiac disease do not present with diarrhea (Table 2).

Atypical presentation (20%): Celiac disease cases may present without diarrhea but with other atypical feature of celiac disease like short stature, anemia, abdominal distension, constipation, etc. They usually present to various departments (Table 3.) and are often misdiagnosed. In a prospective study over two years at SGPGIMS, Lucknow, it has been shown that (Table 4.) 44% of all celiac disease cases are atypical.9 With increasing awareness and easy availability of serological screening tests, atypical celiac disease cases are diagnosed more often than before.

The difference in manifestations of celiac disease in India from the West is mainly due to delay in diagnosis. Short stature, under-nutrition and pallor are almost universal in India due to prolonged illness.

Diagnosis of celiac disease: Celiac disease is diagnosed by modified European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) criteria.10 According to these criteria, small intestinal biopsy should be suggestive of celiac disease (Villous atrophy) and the patient should show unequivocal clinical response to gluten free diet in weeks. However, there are many conditions other than celiac disease that can give rise to villous atrophy especially in India. Hence, if we apply these criteria in our population then we will over diagnose celiac disease. To overcome this problem we need to have some added criteria in addition to ESPGAN criteria. Best is gluten challenge but it is cumbersome, requires repeated endoscopic biopsies and needs parents and child’s co-operation. On the other hand celiac serology is simple, effective and if

Table 2. Clinical presentation of celiac disease: East versus West

<table>
<thead>
<tr>
<th>Presentation</th>
<th>George, et al18 (n= 185)</th>
<th>Mohindra, et al18 (n= 42)</th>
<th>Poddar, et al17 (n=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>3.1±3</td>
<td>8.3 (3-14)</td>
<td>6.7±3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63%</td>
<td>88%</td>
<td>84%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>55%</td>
<td>-</td>
<td>48%</td>
</tr>
<tr>
<td>Growth failure</td>
<td>50%</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>Undernutrition</td>
<td>60%</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Short stature</td>
<td>5.4%</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>Anemia</td>
<td>5%</td>
<td>90%</td>
<td>84%</td>
</tr>
</tbody>
</table>
Table 3. Atypical presentation of celiac disease

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Primary Speciality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stature</td>
<td>Endocrinology</td>
</tr>
<tr>
<td>Refractory anemia</td>
<td>Hematology</td>
</tr>
<tr>
<td>Constipation with abdominal distension</td>
<td>Pediatric surgery</td>
</tr>
<tr>
<td>Rickets with fracture and distension</td>
<td>Orthopedics</td>
</tr>
<tr>
<td>Neuropathy, ataxia</td>
<td>Neurology</td>
</tr>
<tr>
<td>Infertility, impotence, amenorrhea</td>
<td>Gynaecology</td>
</tr>
</tbody>
</table>

Table 4. Atypical manifestations of celiac disease in India

<table>
<thead>
<tr>
<th>Atypical manifestation</th>
<th>Total screened (n)</th>
<th>Celiac disease (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>17</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Short stature</td>
<td>25</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Rickets</td>
<td>6</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Recurrent abdominal pain</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent vomiting</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent aphthous ulcer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>97</strong></td>
<td><strong>18 (18.5%)</strong></td>
</tr>
</tbody>
</table>
positive at the time of diagnosis and becomes negative on follow-up on gluten free diet it confirms the diagnosis. The best antibody test is anti-endomysial antibody (EMA) with a sensitivity and specificity of 97% but it is a technically demanding test (done by indirect immunofluorescent technique). On the other hand anti-tissue transglutaminase (tTG) is as good as EMA and done by ELISA. The sensitivity and specificity of tTG is around 95%. Anti-gliadin antibody (AGA) is mainly used for population screening. In a prospective study on 180 children with celiac disease we have shown that the tTG has got 95% concordance with EMA and its sensitivity and specificity were 94% and 97% respectively. Hence, in Indian setting tTG is the best antibody to diagnose celiac disease.

Proposed criteria to diagnose celiac disease in India

1. Small intestinal biopsy should show villous atrophy.
2. Celiac serology (EMA or tTG) should be positive.
3. There should be unequivocal clinical response to gluten free diets in weeks.

Points to Remember

- **Approach to chronic diarrhea depends on age, presence or absence of failure to thrive and the type of diarrhea (small bowel or large bowel).**

- **The etiology of MAS depends on age.**

- **Persistent diarrhea is the commonest cause in first two years of life. Celiac disease is the commonest cause of MAS in more than 2 years of age group in North India.**

- **Endoscopy and mucosal biopsy play important role in the diagnosis.**

- **Increasing awareness is the key to early diagnosis of celiac disease**

- **High index of suspicion is required to diagnose atypical cases of celiac disease.**

References


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**CLIPPINGS**

*Adriano Arguedasab*  *Carolina Soley, Barbara J. Kamickerc, Daniel M. Jorgensenc.*

**Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media.** *International Journal of Infectious Disease, April 2011*

A randomized, double-blind, double-dummy, multicenter international study was conducted to assess the clinical and bacteriologic response, safety, and compliance of a single 60-mg/kg dose of azithromycin extended-release (ER) versus a 10-day regimen of amoxicillin/clavulanate 90/6.4 mg/kg per day in children with acute otitis media at high risk of persistent or recurrent middle ear infection.

Children aged 3 to 48 months were enrolled and stratified into two age groups (d”24 months and >24 months). Pretreatment tympanocentesis was performed at all sites and was repeated during treatment at selected sites.

The primary endpoint, clinical response at the test-of-cure visit in the bacteriologic eligible population, was achieved in 80.5% of children in the azithromycin ER group and 84.5% of children in the amoxicillin/clavulanate group Children who received amoxicillin/clavulanate had significantly higher rates of dermatitis and diarrhea, a greater burden of adverse events, and a lower rate of compliance to study drug compared to those who received azithromycin.

A single 60-mg/kg dose of azithromycin ER provides near equivalent effectiveness to a 10-day regimen of amoxicillin/clavulanate 90/6.4mg/kg per day in the treatment of children with acute otitis media.
IRRITABLE BOWEL SYNDROME IN CHILDREN AND ADOLESCENTS

* Ganesh R
* Suresh N
** Malathi Sathiyasekeran

Abstract: Irritable bowel syndrome (IBS) in children has a prevalence of 10-15% and poses a diagnostic and therapeutic challenge. There is paucity of data regarding IBS in Indian children and most of the data are extrapolated from adult studies. This article describes the pathogenesis, clinical features and management of IBS in children.

Keywords: Irritable bowel syndrome, Children, Constipation, Diarrhea.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal discomfort and altered pattern of defecation in the absence of specific and demonstrable pathology and has a world wide prevalence of 10-15%. Osler coined the term mucous colitis in 1892 for a similar condition seen more common in psychiatric patients presenting with mucorrhea and abdominal colic. The syndrome has been referred by various terms including spastic colon, irritable colon and nervous colon. Traditionally, irritable bowel syndrome is a clinically defined illness and a diagnosis made by exclusion since no specific motility or structural correlates has been consistently demonstrated. Initially it was referred to as irritable colon syndrome but was later changed to Irritable Bowel Syndrome since the gastrointestinal involvement was not restricted to the colon. IBS symptoms generally peak in the third and fourth decades and therefore most of the available data are from the adult population. Over the last decade this entity has been reported even in the pediatric population.

Since IBS is not associated with any definite biochemical, structural or immunological abnormalities, the diagnosis is dependent on symptom based protocols. The disturbed defecation in IBS may range from diarrhea to constipation to a combination of the two. Four bowel patterns may be seen in IBS and are IBS-D (IBS with diarrhea), IBS-C (IBS with constipation), IBS-M (IBS mixed type), and IBS-U (IBS unsubtyped). In Rome III criteria the subtypes are classified using the Bristol stool chart. The usefulness of these subtypes is debatable since within 1 year, 75% of patients may change subtypes, and 29% switch between constipation-predominant IBS and diarrhea-predominant IBS. Guidelines for positive diagnosis have been formulated based on the pattern and nature of symptoms which has negated the need for a battery of investigations. In 1978 Manning and associates established 6 criteria to distinguish irritable bowel syndrome from organic bowel disease; however the sensitivity and specificity of these criteria was not appreciable.
The Manning criteria are as follows:

- Onset of pain associated with more frequent bowel movements
- Onset of pain associated with looser bowel movements
- Pain relieved by defecation
- Visible abdominal bloating
- Subjective sensation of incomplete evacuation more than 25% of the time
- Mucorrhea more than 25% of the time

The Rome II criteria (1999) identified the various Functional gastrointestinal disorders (FGIDs) and in 2006 the Rome III criteria defined irritable bowel syndrome both in the adult (C1) as well in the pediatric age group (H2b). The criteria for IBS in adults constitutes recurrent abdominal pain or discomfort, an uncomfortable sensation not described as pain occurring at least 3 days per month during the previous 3 months that is associated with 2 or more of the following criteria with symptom onset at least 6 months before the diagnosis.

- Improvement with defecation; and/or
- Onset associated with a change in frequency of stool; and/or
- Onset associated with a change in form (appearance) of stool

In children and adolescents the Rome III criteria for IBS is similar to that outlined for adults except that it should be fulfilled at least once per week for at least 2 months prior to the diagnosis and include both the criteria:

1. Abdominal discomfort or pain associated with two or more of the following at least 25% of the time.
   a. Improvement with defecation
   b. Onset associated with a change in frequency of stool.
   c. Onset associated with a change in form (appearance) of stool

2. No evidence of any inflammatory, anatomic, metabolic or neoplastic process that explains the subject’s symptoms

**Epidemiology:** In the pediatric population IBS has been reported in 14% of high school students and 6% of middle school students. It is difficult to make the diagnosis of IBS in young children who cannot verbally express their problems. Studies from the west have reported lower prevalence in Hispanic and Asian population group compared to Caucasians. There is no sex difference in children unlike in adults where women are more affected. In the West IBS is the most common cause of functional RAP in children accounting for nearly 52% of the cases. IBS is also the most common FGID comprising of nearly 50% of a pediatric study group. A large prospective multicentric study in India including 2805 adults with IBS has revealed interesting data pertaining to our country. The mean age was 39.4 years with 68% being males. However similar data is not available for children.

**Clinical features:** The main symptom of IBS is chronic or recurrent abdominal pain or discomfort associated with altered bowel habits. The Rome III criteria mentioned above uses stool form as an indicator unlike stool frequency in Rome II. Supporting symptoms which are not part of the essential criteria include altered stool frequency, altered stool form, altered stool passage (straining and/or urgency), mucorrhea, abdominal bloating or subjective distention. The abdominal pain can be dull, colicky or sharp and is usually in the lower abdomen or periumbilical region. It has no specific pattern and can be aggravated by stress or food and partially relieved by defecation. Depending on the subtypes the stool form will vary eg in
IBS-C > 25 % of stools are hard and lumpy and < 25 % are loose or watery. A feeling of incomplete evacuation is a common complaint and is reported in 77% of Indian patients with IBS. Abdominal bloat a frequently reported symptom is less common in children than in adults. Other GI symptoms such as heart burn, dyspepsia, nausea and vomiting can be present in 25% to 50% of adults with IBS whereas 30% of pediatric patients have dyspeptic symptoms. Non GI symptoms headache (23-45%), back pain (27-81%), fatigue (36-63%), myalgia (29-36%), urinary frequency (21-61%) and dizziness (11-27%) are more common in adult patients than controls but rare in children with IBS. There is a higher prevalence of psychiatric disorders in the IBS population than in controls and somatisation disorder needs a mention. The symptoms may be triggered by some specific food or school related disturbances. An organic cause of abdominal pain should be considered when red flag signs or warning signs such as fever, weight loss, rectal bleed, arthritis, rash, family history of IBD, anemia, elevated ESR and occult blood in stools are documented.

Pathogenesis: Over the decades various theories have been presented to explain the pathogenesis of IBS including genetic factors, visceral hypersensitivity, gut dysmotility, immune mediated factors and the psyche. Recent interest has been the recognition of IBS following an episode of gastroenteritis (Post infectious IBS).

A. Genetic factors

i) Clustering within families: There are well documented studies of IBS clustering within families; however this occurrence could be partly due to familial aggregation of somatisation. Children of IBS patients have more GI complaints and the risk of developing IBS is higher in these children. The concordance rate of IBS among monozygous twins was found to be higher (range: 33.3%-22.4%) compared to dizygous twins (range: 13.3%-9.1%). Levy et al found that an affected parent was a strong predictor of IBS than a twin with IBS.

ii) Genetic-environment interaction: In the Norwegian twin study, the presence of restricted fetal growth was a significant risk factor for the development of IBS, with the onset of IBS appearing at a mean of 7.7 years earlier in low birth weight babies. In addition monozygotic twins with IBS had lower weight than those without IBS. This gene-environment interaction requires more confirmation but it may indicate that impaired maturation of the central nervous system interacts with key genes in inducing IBS like features.

iii) Candidate genes: Theoretical association between functional single nucleotide polymorphisms and IBS that may be relevant have been reviewed. Candidate genes in the serotonergic, adrenergic, ionic channels and inflammatory pathophysiological systems have been evaluated. 5HT transporter gene linked polymorphic region polymorphism has been linked with diarrhea. Mutations in sodium channel in interstitial cells of Cajal and smooth muscle cells SCN5A have been linked to abdominal pain. IBS patients have been identified to have a lower IL 10. Genetics in IBS is still in its infancy but remains potentially exciting. Till date no IBS-gene has been identified.

B. Ecology

A disturbance in the equilibrium between the gut and the ecosystem has been linked with FGIDs. Food antigens and gut flora constitute the complex intestinal ecosystem.

i) Food hypersensitivity has been implicated in the pathogenesis of IBS. Patients on a food specific IgG4 antibody guided elimination diet
are less symptomatic and also demonstrate an improvement in rectal compliance compared to those on a sham diet.\textsuperscript{11}

**ii) Gut flora:** Qualitative and quantitative changes in the gut flora have been described in patients with IBS. Patients with IBS-C have higher concentration of Veillonella sp and patients with IBS-D have lower levels of Lactobacillus sp.\textsuperscript{12} Galatola, et al\textsuperscript{13} found evidence of bacterial overgrowth in 56% of IBS-D and 28% of IBS-C type. Changes in gut flora resulting from the use of antibiotics have also been proposed as a mechanism of IBS. Perturbations in gut flora and inflammatory cell activity may modify the sensory neurotransmitter content in the colon, leading to altered visceral perception, dysmotility, increased gas production, alterations in water and electrolyte transport in the colon and changes in the bowel habits. Increased number of cells in the lamina propria, proximity of mast cells to nerves and production of substances that activate receptors in visceral sensation have been shown in patients with IBS. Small intestinal bacterial overgrowth with its associated motility abnormalities may also play a role in IBS patients.

**C. Visceral hypersensitivity**

Visceral hypersensitivity and visceral hyperalgesia are commonly associated with IBS and play a major role in causing discomfort and pain. Peripheral sensitization could be due to the action of inflammatory mediators on nerve endings in the gut wall. It has been reported that IBS patients have pain at lower volumes and pressures. When a balloon is inflated in the rectum the threshold to report pain is below the normal range in 50-70% of patients with IBS. Enhanced perception of visceral events is documented throughout the gastrointestinal tract including esophagus, duodenum, stomach, ileum. However IBS patients do not show somatic hypersensitivity to pain and may have elevated pain thresholds. Positron emission tomography (PET) and functional MRI have helped in providing insights into the brain’s response to visceral stimuli. IBS patients may show increased motor, sensory and autonomic reactivity via central modulatory pathways descending from the emotional motor cortex to the dorsal horn cells.

**D. Psychosocial factors**

Psychosocial factors have been recognized as significant triggers in predisposition, precipitation and perpetuation of IBS. These variables can alter motor function in the small bowel and colon, both in normal subjects as well as in patients with IBS. Almost 40-94% of patients with IBS have psychological abnormalities\textsuperscript{14}; depression being the commonest followed by anxiety and somatisation disorders. History of abuse in childhood (physical/sexual/or both) correlates with the severity of symptoms in patients with IBS. Anxiety, somatisation and perceived stress have been documented to be significant risk factors for the development of IBS.\textsuperscript{15} Psychological stress may induce an exaggerated response to bacterial antigens in the absence of altered baseline cytokine levels and partly explain the increased incidence of post infectious IBS in patients with psychological co morbidity. Stress can influence both innate and specific immune response via the Hypothalamic Pituitary Adrenal axis (HPA) and the sympathetic nervous system. HPA axis is dysregulated in IBS. Increased pro inflammatory cytokines such as IL-6, IL-6R and IL-8 but not IL-10 or TNF-\(\alpha\) have been documented in patients with IBS.

**E. Abnormal gut motility**

Over the past 50 years alterations in the contractility of the colon and small bowel have been described in patient with IBS. The most
common features seen in the colon are exaggerated motor response to eating. Patients with IBS-D may show a greater number of high amplitude progressive contractions (HAPC), whereas IBS -C have few HAPC and delayed colonic transit.16, 17, 18 The other nonspecific findings that have been reported in IBS include increased frequency and duration of cluster contractions, increased frequency of migrating motor complexes, retrograde duodenal and jejunal contractions, prominent high amplitude waves in terminal ileum and an exaggerated motor response to meal ingestion. The stomach may show delayed gastric emptying resulting in dyspeptic symptoms. It is not clear whether these findings relate to the pathophysiology of IBS or a mere epiphenomenon. A heightened visceral sensation may play a role in the perception of these motor events.

F. Neurotransmitter imbalance

Recent studies have reported that neurotransmitter (NT) are involved in the pathogenesis of IBS. 5% of serotonin is located in the CNS and remaining 95% in GIT, within enterochromaffin cells, neurons, mast cells and smooth cells. When released by enterochromaffin cells, serotonin stimulates the vagal afferent nerve fibres and intrinsic enteric afferent nerve fibres resulting in intestinal secretions and in peristaltic reflex resulting in nausea, vomiting, and abdominal pain and bloating. Preliminary evidence suggests that patients with IBS-D have increased serotonin levels while those with IBS-C have decreased serotonin levels in plasma and rectosigmoid colon. Other NTs that may have an important role in FGID include calcitonin gene related peptide, Ach, substance P, pituitary adenylate cyclase, nitric oxide and VIP. These NTs may provide links not only between bowel contractility and visceral sensitivity, but also between the CNS and enteric nervous system.

G. Post infectious IBS (PI-IBS)

The presence of PI-IBS refers to the development of IBS symptoms particularly abdominal pain and diarrhea shortly after an enteric infection and is based on research from prospective studies in which IBS symptoms developed in 7-32% of patients after they recovered from bacterial gastroenteritis. There is a 6-fold increased risk for developing IBS in younger subjects, those with concomitant psychological disorders (anxiety), and who have a prolonged fever during gastroenteritis. The other risk factors are female gender, bacterial toxigencity and adverse life events. The symptoms of IBS are not transient and can occur within 3 months in 12 % of those with gastroenteritis and may last even up to 9 years. Increased mucosal lymphocytes and enterochromaffin hyperplasia persists in the colonic mucosa even after the infection has settled. Increased gut motility and permeability is frequently found among patients with PI-IBS. The increased permeability allows access of bacterial products to the lamina propria which can perpetuate chronic inflammatory process.14 There is also an ongoing immune activation as evidenced by increased levels of IL-2, IFN γ and substance P. The development of IBS has recently been linked with non-GI infections invoking a role for systemic inflammatory response in the mediation of symptoms. Parasites such as Dientamoeba fragilis, Blastocystis hominis and giardiasis have been associated with chronic GI symptoms that may mimic IBS, whether they can trigger IBS per se is unknown. Viral gastroenteritis as a fore runner of IBS was reported in 24 % of subjects. It has been noted that IBS following viral illness is shorter in duration compared to its bacterial counterpart.

Diagnosis

The diagnosis of IBS is symptom-based as there are not yet any diagnostic markers. The symptom based Rome III criteria have been
noted to have a sensitivity of 0.707 and specificity of 0.878 in an adult study. Identification of IBS using either Rome II or III criteria was more or less similar being 44.0% and 45.1% respectively in a large study of children with FGID. A detailed and accurate history and complete physical examination is the key to the diagnosis of IBS. The history should include details of the presenting complaints, extra gastrointestinal symptoms, social events, school performance, extra curricular activities and family relationships. It is helpful to classify the various subtypes of IBS such as IBS-C, IBS-D, IBS-M and IBS-U based on the stool characteristics using the standard Bristol stool chart. The key point in history is to ascertain the presence of the red flag signs or warning signs to identify underlying organic disease. The physical examination is usually normal and therefore it is relevant that more time is spent in noting the child’s behaviour, body language, communication skills, eye contact and socializing abilities. The concept that IBS is a diagnosis of exclusion is not acceptable in this era. If there is a suspicion of IBS then any investigative work up will be futile since current evidence suggests that the prevalence of organic disease is not increased in the population with symptoms of IBS without alarm features and the positive predictive value of such tests is small. The presence of low Hb, elevated ESR and occult stool blood positivity may point to an organic disease. Hence basic investigations such as complete blood count, motion and urine examination are done for those who do not have any warning signals. Complete evaluation including CRP, total serum protein, albumin, creatinine, tissue transglutaminase antibody, thyroid function tests, ultra sound of abdomen, endoscopy of both upper and lower GI, anorectal manometry and contrast enhanced computerized tomography of the abdomen are planned in a phased manner if there is suggestion of an organic disease and depending on the possible diagnosis.

**Differential diagnosis**

The differential diagnosis depends upon the predominant symptom and site of pain. Lactose intolerance, Hirschsprung’s disease, inflammatory bowel disease, abdominal tuberculosis, celiac disease and solitary rectal ulcer syndrome are the common causes of lower abdominal pain with altered bowel habits and hence they should be considered in the evaluation of these children.

**Management**

**A. Patient centered care:** A good health care provider-patient relationship is the cornerstone of effective management of IBS. The elements of a good care include a non-judgemental patient-centered interview, careful and cost effective evaluation, understanding the patient’s illness, patient education and involving the patient in the management. Addressing the psychosocial factors may improve the health status and treatment response.

**B. Diet:** IBS patients usually have an inconsistent response to certain foods. Maintaining a food diary for 1-2 weeks with a record of the symptoms may be of practical value to minimize some diet related exacerbations. Common food triggers include high fat foods, raw fruits and vegetables. Food elimination based on IgG levels showed a global improvement in 28% compared to 16% on sham diet. Since IgG levels do not correlate with food intolerance it has been proposed that the effect was not due to diet alone. Wheat and milk are known to affect symptoms of IBS. Since lactose intolerance and IBS share common symptoms lactose free diet is often recommended. Restricting fructose and fructan may be beneficial if there is evidence of fructose malabsorption. There is no evidence that digestion of food or absorption of nutrients is different in persons with IBS compared to
controls. In some patients with IBS there is increase in the gastro colic response due to the heightened visceral sensitivity resulting in abdominal pain, diarrhea and/or constipation following the very act of eating or drinking.²⁰

C. Drugs based on predominant symptoms

I. Constipation

i. Bulking agents and fiber are commonly used in IBS-C. Psyllium, methylcellulose, ispaghula husk, calcium polycarbophil have been used to accelerate intestinal transit, add fluid to stool mass and create gel like matrix to the stools. However their efficacy is controversial. Soluble fibre has shown a small but significant improvement in a meta analysis.²¹ These agents can however worsen abdominal bloat and pain in those with these symptoms. The recommended dose of fibre in a child is age plus 5 gm which can be provided as food or fibre supplements.

ii. Osmotic laxatives: Polyethylene glycol or magensium containing laxatives are preferred in IBS-C. They can be titrated and used as the frequency of stools varies. Lactulose and sorbitol may increase frequency but are accompanied by abdominal bloat and cramps. Stimulant laxatives such as senna and bisacodyl can be used intermittently for refractory constipation.

iii. Serotonergic agonists: Tegaserod is a selective 5-HT4 partial agonist that stimulates gut transit. It has been used in adults with IBS-C and has been proved to alleviate symptoms and also improve outcomes related to productivity and work impairment.²² Adverse cardiovascular effects have restricted its use in men and older women.

iv. Bicyclic fatty acid derivatives: Lubiprostone acts on type 2 chloride channels located on the apical side of GI epithelial cells and increases secretion of electrolye rich fluid in the small intestine and increases motility. It is approved for treating women with IBS-C and is not approved in children or men.

II. Diarrhea

i. Loperamide has been to shown to benefit IBS-D cases without any effect on pain and can be prescribed before the stressful event.

ii. Alosetron is a 5HT3 receptor antagonist which has been approved in women with severe IBS-D. Side effects such as ischemic colitis and severe constipation have been reported.²³

iii. Tri-cyclic antidepressants such as amitryptaline, imipramine and dioxepin have been used in low doses in patients with IBS-D, though sedation is a big draw back with these drugs and is beneficial in those with insomnia.

III. Abdominal pain

The pain in IBS can be managed with antispasmodics such as hyoscamine sulphate, dicyclomine. Selective serotonin receptor inhibitors have helped in the management of pain in patients with IBS and are preferred over tricyclic antidepressants. A global improvement has been reported with maximum benefit in those with somatisation. The antispasmodics belong to the two groups namely neurotropics such as atropine which may affect other neve fibres apart from those in GIT and therefore having side effects and musculoptropics such as Mebeverine which act directly on the smooth muscles of GIT and relieve spasm without disturbing motility.

IV. Bloat and pain

Antibiotics such as the non absorbable antibiotics like rifaximin have been shown to benefit patients with abdominal bloat.

Probiotics: Disturbances in the enteric flora in patients with IBS and the ability of probiotics to
Fig. 1. Simple approach to IBS in children

History and physical exam
Rome III diagnostic criteria for IBS present. Consider IBS

Alarm features

Absent
High probability of IBS
- Parent education
- Dietary management
- Appropriate drugs
- Cognitive behavioral therapy
- Regular & diligent follow up

Present
Increased risk for organic disease
Investigate and treat the underlying cause

Not improved- Investigate further
Improved- continue treatment
exert anti-inflammatory effects have been the basis of using probiotics for the management of IBS. Bifidobacteria and Lactobacilli have been investigated with variable results. Future research will unravel the mystery of these drugs.

**Domperidone**: A dopamine receptor blocker and parasympathomimetic has been shown to reduce bloating and abdominal pain as a result of accelerated colonic transit time and reduced fecal load.

**D. Non pharmacological therapy**

Four specific psychological therapies namely cognitive –behavior therapy (CBT), gut-directed hypnosis, psychodynamic therapy and relaxation therapies have been introduced based on the principle that mind-body or brain-gut interactions play an important role in IBS. CBT has shown the greatest benefit in case controlled studies for the treatment of IBS. A survey of IBS patients has documented that the majority (60%) were interested in learning about restriction of foods, 58% in medications, 56% in coping strategies and 55% in understanding the psychological factors related to IBS. The study also indicated that 80% respondents wished to have a follow up after their visit and the majority wanted their physicians to listen to them, provide hope and support.

**E. Alternative medicine**

**Herbal remedies** such as peppermint oil and Iberogast have been used in the management of IBS. Enteric coated peppermint oil capsules have been prescribed in children with IBS with variable results.

**Yoga and acupuncture** have also been marketed in the world of IBS but most trials are not of good quality research to be recommended. The flow diagram for management of IBS is shown in Fig. 1.


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**Domiciliary oxygen for interstitial lung disease**

Oxygen therapy is used to treat patients with interstitial lung disease (ILD) with low arterial blood oxygen levels. This review evaluated the effect of domiciliary long-term oxygen therapy on survival and quality of life in patients with ILD. Only one randomized controlled trial was identified. This unpublished study reported that long-term oxygen therapy did not improve survival compared with no oxygen therapy in patients with ILD. No data on quality of life was available.


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**Methylxanthines for prolonged non-specific cough in children**

There is currently an absence of reliable evidence to support the routine use of methylxanthines for symptomatic control of non-specific cough in children. If methylxanthines were to be trialed in children with prolonged non-specific cough, cohort data (thus limited) suggest a clinical response (subjective cough severity) would be seen within two to five days (certainly within 14 days) of therapy. However methylxanthine use has to be balanced against the well known risk of toxicity and its low therapeutic range in children. Further research examining the efficacy of this intervention is needed.

GASTRO INTESTINAL BLEED

* Neelam Mohan  
** Avinal Kalra

Abstract: Upper gastro intestinal (GI) bleed is from a source in esophagus, stomach or duodenum above ampulla of Vater. Middle GI bleed is small intestinal bleed from ampulla of Vater to terminal ileum and lower GI bleed is colonic bleeding. Causes of GI bleed differs in neonates to infants to children. Portal hypertension is the commonest cause of GI bleed in children which in turn is caused by extra hepatic portal vein obstruction in 68-76% of the cases in India. The investigations are aimed at the search for the source of the bleed and include endoscopy, bleeding scan, Meckel’s scan, barium enema, CT Scan, angiography, capsule endoscopy, etc. UGI bleed is an indication for endoscopy in 5% of children annually. Bleeding can be controlled by drugs, endotherapy, interventional radiological techniques or surgery.

Keywords: Gastrointestinal Bleed, Portal Hypertension, Endotherapy, Surgery.

GI Bleed could result from bleeding from esophagus to anus due to various causes (Tables.1-3). It has been divided into upper, middle and lower depending on the site of bleeding.

“Upper GI (UGI) bleeding is defined as bleeding from a source in the esophagus, stomach or duodenum above the ampulla of Vater. Middle GI bleeding is defined as small intestinal bleeding from ampulla of Vater to terminal ileum and lower GI bleeding is colonic bleeding.”

GI Bleeding may be overt or obscure. Overt bleeding may present as hematemesis, melena or hematochezia. Obscure GI bleed is defined as bleeding from GIT that persists or recurs without any obvious etiology after a diagnostic endoscopy. It accounts for around 5% of all GI bleeds. It is of 2 types occult and overt. Occult bleeding may present as positive fecal occult blood test (e.g. guaiac testing), laboratory evidence of anemia and iron deficiency, or symptoms of anemia or blood loss (e.g. fatigue, lightheadedness, syncope, dyspnea, angina)

Hematemesia is used to describe vomiting of either bright red or coffee-ground-like material and suggests that the source of bleeding is located above the ligament of Treitz. Melena, the passing of dark black, tarry stools, occurs in patients bleeding from a site located above the ileocecal valve. The jet black color of melena stool results from the action of bacteria on hemoglobin that has been converted to hematin or other hemochromes. However an upper GI source may occasionally bleed so briskly that the blood does not remain in the GIT long enough for melena to occur. UGI and middle GI bleed should be atleast 50 ml in volume and should stay for more than 6 hours to lead to melena. Hematochezia, the passage of bright red or maroon blood from the rectum, is most commonly associated with a
Table 1. Causes of UGI bleed in children

<table>
<thead>
<tr>
<th>Newborn</th>
<th>Infant</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Swallowed maternal blood</td>
<td>• Stress ulcer / gastritis</td>
<td>• Mallory – Weiss tear</td>
</tr>
<tr>
<td>• Hemorrhagic disease of newborn</td>
<td>• Acid-peptic disease</td>
<td>• Acid-peptic disease</td>
</tr>
<tr>
<td>• Stress gastritis</td>
<td>• Mallory – Weiss tear</td>
<td>• Varices</td>
</tr>
<tr>
<td>• Acid peptic disease</td>
<td>• Vascular anomaly</td>
<td>• Stress ulcer / gastritis</td>
</tr>
<tr>
<td>• Vascular anomaly</td>
<td>• Duplication cyst</td>
<td>• Caustic injury</td>
</tr>
<tr>
<td>• Coagulopathy</td>
<td>• Varices</td>
<td>• Foreign body</td>
</tr>
<tr>
<td>• CMPI (Cow’s milk protein intolerance)</td>
<td>• Webs</td>
<td>• Vasculitis</td>
</tr>
<tr>
<td></td>
<td>• Intestinal obstruction</td>
<td>• Crohn’s disease</td>
</tr>
</tbody>
</table>

* Characterised by a large tortuos arteriole in stomach wall that erodes and bleeds

Table 2. Common causes of rectal bleeding in children

<table>
<thead>
<tr>
<th>Infant</th>
<th>Older child</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anal fissure</td>
<td>• Anal fissure</td>
</tr>
<tr>
<td>• Milk protein intolerance</td>
<td>• Intussusception</td>
</tr>
<tr>
<td>• Necrotizing enterocolitis</td>
<td>• Infectious enterocolitis, Amoebiasis</td>
</tr>
<tr>
<td>• Swallowed maternal blood</td>
<td>• Meckel's diverticulum</td>
</tr>
<tr>
<td>• Vitamin K deficiency</td>
<td>• Juvenile polyp</td>
</tr>
</tbody>
</table>

Table 3. Less common causes of rectal bleeding in children

<table>
<thead>
<tr>
<th>Infant</th>
<th>Older Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vascular lesions</td>
<td>• Inflammatory bowel disease</td>
</tr>
<tr>
<td>• Bleeding diathesis</td>
<td>• Ischemic/collagenous colitis</td>
</tr>
<tr>
<td>• Hirschprung enterocolitis</td>
<td>• Vascular malformations</td>
</tr>
<tr>
<td>• Meckel’s diverticulum</td>
<td>• Intestinal duplication</td>
</tr>
<tr>
<td>• Malrotation with volvulus</td>
<td>• Bleeding diathesis</td>
</tr>
<tr>
<td>• Intestinal duplication</td>
<td>• Henoch-Schonlein purpura</td>
</tr>
<tr>
<td>• Intussusception</td>
<td>• Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td></td>
<td>• Hemorrhoids, rectal varices</td>
</tr>
<tr>
<td></td>
<td>• Peri-anal cellulitis</td>
</tr>
<tr>
<td></td>
<td>• Rectal prolapse</td>
</tr>
<tr>
<td></td>
<td>• Solitary rectal ulcer</td>
</tr>
<tr>
<td></td>
<td>• Hereditary polyposis syndrome</td>
</tr>
<tr>
<td></td>
<td>• Sexual abuse and ano-rectal trauma</td>
</tr>
</tbody>
</table>
The annual incidence of hospitalization for upper GI bleeding is approximately 1 per 1000 adults and mortality is around 7-10%. UGI bleed is an indication for UGI endoscopy in 5% of children.

**Mimickers of gastrointestinal bleeding**

- Bleeding from the nose and oropharynx
- Bright red blood may be mimicked by red colored candies, juices, and foods
- Black colored stools may be caused by:
  - Bismuth
  - Iron preparations
  - Spinach
  - Blueberries

**Epidemiology**

Vital signs, an essential part of the evaluation should include heart rate and blood pressure in lying, sitting and if possible, in standing position which provide the most important information in the assessment of a patient with a major bleed. An increase in the pulse rate of more than 20 beats per minute or a decrease in diastolic blood pressure of more than 10mm Hg or a decrease in systolic of more than...
20mmHg within 3 minutes of standing, indicates a greater than 20% loss of intravascular volume. When the intravascular volume deficit exceeds 25%, the capillary refill is prolonged as blood is shunted from the skin to the brain and kidneys. Urine output decreases with further compromise and metabolic complications results. In short, all features of hypovolemic shock develop. Urine output and fluid intake must be carefully monitored throughout fluid resuscitation of patients in shock. Urine output in children is normally 2 to 3 ml per kg per hour, and urine output less than 1 ml per kg per hour is indicative of renal hypoperfusion. As blood loss exceeds 40%, compensation fails, pulses are lost, cerebral perfusion decreases, and the patient passes from lethargy to coma. The respiratory rate should also be carefully monitored. Hyperventilation is an early sign of a developing acidosis induced by a decrease in central nervous system pH.

To enhance the ability to anticipate shock, it is helpful if the rate of bleeding is assessed periodically. In upper gastrointestinal bleeding this is best accomplished through lavage of the stomach by means of a nasogastric tube placed in the stomach. Nasogastric aspiration that are grossly bloody confirm upper G.I. sources but a negative aspiration does not rule it out. Upto 15-18% of patients with UGI bleed have non-bloody nasogastric aspirate. The amount of blood lost in the stool should also be monitored, estimated, and recorded and any change in color from melena to bright red blood should be noted as a possible sign of increased blood loss. It is prudent that all patients with significant gastrointestinal bleeding be monitored in a pediatric intensive care unit for changes in vital signs and urine output until they are stable and bleeding has ceased.

Portal hypertension is the commonest cause of GI bleed in children. Mortality after hematemesis following variceal bleeding is 30%

In country like India, portal hypertension is caused by extra hepatic portal venous obstruction (EHPVO) (68-76%), cirrhosis (24-28%) and infrequently due to congenital hepatic fibrosis (3%), non cirrhotic portal fibrosis and Budd Chiari Syndrome.6, 7

The normal portal venous pressure is around 5-7 mmHg, a pressure more than 10-12mmHg and Hepatic Venous Pressure gradient (HVPG) of more than 5 mm of Hg is defined as portal hypertension. Unlike adults where cirrhosis is the most common cause of portal hypertension, extrahepatic portal venous obstruction (EHPVO) is the most common cause in children.

The sites for the communication of the portal and the systemic circulation are through the collaterals at the junction of protective epithelium and absorptive epithelium. In the lower end of oesophagus the oesophageal tributary of left gastric vein anastomose with oesophageal tributaries of accessory hemiazygous vein, deviation of blood flow from these vessels leads to varicosities in sub mucous layer of lower end of esophagus and upper part of stomach. Around the anal canal the superior haemorrhoidal vein of portal system anastomoses with middle and inferior haemorrhoidal vein of caval system. Deviation of blood into these channels may lead to rectal varices. At the umbilicus, left branch of portal vein anastomoses with the veins of anterior abdominal wall through paraumbilical veins obstruction of veins around the umbilicus enlarge and form caput medusa.

Investigations

Routine investigations include complete blood count, coagulation profile, liver function tests, erythrocyte sedimentation rate and electrolytes, blood grouping and typing.

Specific investigations include those that are targeted towards identifying the source /cause of bleeding.
Identifying the source of GI hemorrhage

Endoscopy: Oesphago-gastro-duodenoscopy or colonoscopy is very useful to detect the cause of GI bleed in most cases. With the availability of newer fibreoptic scopes for neonatal and pediatric procedures, it is now possible to identify the cause of bleeding in 85-90% of patients. Oesophago gastroduodenoscopy provides information like oesophagitis, Mallory Weiss tears, varices, gastritis, ulcer, vascular malformations etc.

Similarly, colonoscopy provides a lot of information in evaluating colonic causes of bleeding like colitis, polyps, inflammatory bowel disease, ulcer, vascular malformations, etc. Colonic polyps are an important cause of bleeding in children from 2-7 years. With the availability of single balloon and double balloon enteroscopy it is now possible to visualize small bowel for lesions and do interventions accordingly.

Oesophageal varices can be classified as small, medium and large (<5mm, 5-10mm and > 10mm) or can be divided into 4 grades endoscopically according to Conns classification (Table 4).

Predictors of variceal bleed include large varices and presence of red colour signs (Red wale marking, diffuse redness, hematocystic malformation).

Gastric varices are found most commonly with splenic vein thrombosis or after endoscopic sclerotherapy (EST) of oesophageal varices. They have been classified endoscopically according to location [Sarin’s classification (Fig.2)].

![Fig.2. Gastric varices (Sarin’s classification)](image)

Table 4. Conns classification of esophageal varices

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Details</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>On inspiration only</td>
<td>Can be effaced</td>
<td>Straight</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Both on inspiration and expiration</td>
<td>Cannot be effaced</td>
<td>Straight</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Projecting into lumen &lt; 50 %, wavy</td>
<td>Cannot be effaced</td>
<td>Straight</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Projecting into lumen more than 50% and coiled</td>
<td>Tense</td>
<td>Tortuous</td>
</tr>
</tbody>
</table>
• Gastro-esophageal varices (GOV) – Gastric varices continuing with esophageal varices
  - GOV1 - Extending towards lesser curvature
  - GOV2 - Extending towards fundus

• Isolated gastric varices (IGV) – Gastric varices discontinuous with esophageal varices or present in absence of esophageal varices
  - IGV1 - Fundal varices, tortuous, nodular
  - IGV2 - Ectopic varices (body, antral, pylorus)

Ectopic varices account for 5% of all variceal bleed. Duodenum is a common site.¹⁰

**Bleeding scan:** It is a noninvasive study with a low radiation exposure. Tc sulphur or Tc pertechnetate labelled red blood cell scan are used. Tc sulphur red cell scan can detect site of bleeding even when the rate of bleeding is as low as 0.1 ml/minute. However its half-life is only 2 minutes. Tc pertechnetate labeled red blood cell scan can visualize the site of bleeding when the bleeding rate is 0.5 ml/minute or higher. However, the longer half-life of the labeled red blood cells enables the images of the gastrointestinal system to continue for up to 24 hours. Tc pertechnetate-labelled blood cell scan should be considered when a small intestinal source of bleeding is suspected. In most institutions, Tc- pertechnetate labelled red blood cell scan is used to direct subsequent localized angiography. The nuclear scan can be readily repeated in patients with intermittent bleeding.

**Meckel’s scan:** Because technetium (Te) 99m pertechnetate is actively accumulated by cells in gastric mucosa, it can be used to identify the presence of ectopic gastric mucosa in a Meckel’s diverticulum or intestinal duplications. More than 90% of bleeding Meckel’s diverticula do contain gastric mucosa. A Meckel’s scan should be considered whenever significant painless lower gastrointestinal bleeding has occurred.

**Angiography:** The usefulness of angiography as a diagnostic test is usually limited to patients with active gastrointestinal bleeding and the rate of bleeding must be at least 0.5 ml/minute. When used in the appropriate situation, angiography has an accuracy of 50% to 75% but is associated with a significant complication rate of approximately 2%. The diagnostic yield of emergency arteriography is low because most hindgut lesion bleeding is intermittent and not from large calibre artery or vein. In a comparative study of emergency arteriography versus colonoscopy for diagnosis of severe ongoing hematochezia, the diagnostic yield from colonic lesion by emergency arteriography was 10% and for colonoscopy was 80%.

**UGI radiology:** Contrast studies of the upper gastrointestinal tract have taken a secondary role in the evaluation of patients since the introduction of endoscopy. Radiographic studies are particularly useful in defining anatomic deficits such as esophageal strictures, malrotation of the bowel or deep ulcerations.

**Barium enema:** Barium enema is effective in identifying the anatomic location of the large bowel and is particularly important in neonates and infants presenting with signs of obstruction associated with gastrointestinal bleeding. In these patients, malrotation with secondary intestinal volvulus must be rapidly identified. Intussusception, a common problem in infants particularly between the ages of 6 months and 24 months, can be diagnosed and in many cases treated by barium enema. The barium enema is also effective in identifying the presence of polyps.
CT Scan
- A CT Scan with contrast may also help to identify malrotation, volvulus obstruction, intussusception, duplication cysts etc as cause of GI bleed.
- CT angiography may be able to detect aneurysm A.V. fistula as cause of bleed.
- CT enteroclysis helps to identify lesions such as ulcers in Crohn’s disease.

Capsule Endoscopy: Capsule endoscopy is a way to record images of the digestive tract for use in medicine. The capsule is in the size and shape of a pill and contains a tiny camera. After a patient swallows the capsule, it takes pictures of the inside of the gastrointestinal tract. The primary use of capsule endoscopy is to examine areas of the small intestine that cannot be seen by other types of endoscopy. Capsule endoscopy is useful when disease is suspected in the small intestine and can sometimes diagnose sources of occult bleeding.

Management

Treatment goals
- Immediate assessment of severity and causes of GI bleed
- Establish and maintain the intravascular volume.
- Packed red blood cell transfusion to maintain Hb > 8gm/dl
- FFP transfusion for INR > 1.5, platelets transfusion if platelet < 50,000/mm3.
- Determine source and site of blood loss
- Stop gastrointestinal bleeding.

Resuscitation: Hemodynamic stability. Treatment of hypovolemic shock secondary to GI hemorrhage
- Oxygen is given to counter hypoxia due to acute blood loss

- Nasogastric aspiration is done to check ongoing losses
- Nasogastric lavage is done to clear the stomach for endoscopy, to define bleeding site, to check ongoing losses and to prevent blood going down the intestine. This avoids the rise in blood urea nitrogen and prevents hepatic encephalopathy particularly if there is underlying liver disease.
- Establish adequate intravenous access.
- Rapidly infuse saline, lactated Ringer. Carefully monitor pulse, blood pressure and central venous pressure
- Hematocrit should be kept at around 24 and overtransfusion should be avoided.
- Monitor urine output and skin perfusion and orthostatic changes in pulse.
- Carefully record all fluids transfused and estimate and record all recognized fluids lost

Calculating transfusion requirement
- Quantity of packed red blood cells - 
  \[ \frac{[(70 \text{ml} \times \text{weight in kg}) (\text{desired hemoglobin} - \text{present hemoglobin})]}{23 \text{ gm hemoglobin per 100 dl of packed red blood cells}} \]
- Eg. Childs weight 20ks, desired Hb 10g. Present Hb 6g
  \[ \frac{70 \times 20 \times (10-6)}{23} = 4 \]
- Rough guideline - 5 ml of packed RBC/kg will raise the Hct. 3 points and Hb. 1gm/dL (5:3:1)

Control of active bleeding (Variceal, nonvariceal)
This can be done by:
- Control of ongoing bleeding
- Prevention of 1st bleeding
- Prevention of recurrent bleeding
In acute oesophageal variceal bleeding, vasoactive drugs (either terlipressin or somatostatin) should be started as soon as possible (before diagnostic endoscopy) and maintained for 2-5 days. The efficacy of pharmacotherapy is improved with the addition of emergency endoscopic therapy. Adding endoscopic variceal ligation (EVL) improves the efficacy and safety achieved with the combination of emergency sclerotherapy and vasoactive drugs. Antibacterial prophylaxis should be an integral part of therapy in acute bleeding. To prevent rebleeding, both EVL and the combination of beta-adrenoceptor antagonists (beta-blockers) and nitroglycerin (NTG) may be a valid first-line choice. Adding beta-blockers improves the efficacy of EVL alone. Haemodynamic responders to beta-blockers with or without NTG (i.e. those with a decrease in HVPG to <12 mmHg or by >20% of baseline) have a reduction in the risk of haemorrhage to below 10% of patients and, consequently, will not need further treatment, while rescue therapies should be provided to nonresponders. Transjugular intrahepatic portosystemic shunts are the recommended rescue therapy when EVL and/or beta-blockers with or without NTG fail. Beta-blockers significantly reduce the risk of a first haemorrhage in patients with large varices and improve survival. Compared with β-blockers, EVL reduces the risk of first bleeding without any differences in mortality and should be offered to patients with large varices who have contraindications or intolerance to beta-blockers.

### Control of acute variceal bleed

1. Pharmacotherapy
2. Balloon tamponade
3. Endotherapy
4. TIPS/surgery

---

1. **Pharmacotherapy**: The most widely used agents to stop variceal bleed are:
   
   a. Intravenous vasopressin
   b. Terlipressin
   c. Nitroglycerine
   d. Somatostatin
   e. Octreotide-synthetic analogue of somatostatin

   **a) Vasopressin (VP)**: It is a potent non-selective vasoconstrictor. It lowers the portal pressure by causing splanchnic arterial vasoconstriction and reducing the splanchnic blood flow. It is given in a bolus of 1 unit per 3 Kg of body weight diluted with 2ml/Kg of 5% dextrose given over a period of 15-20 minutes. This agent causes bleeding control in 50%, vasospastic side effects in 50% and treatment had to be discontinued in 20% of cases. Periodic ECG monitoring is recommended. In addition, since vasopressin can precipitate angina or myocardial infarction, the drug should be used with extreme caution in patients with coronary artery disease or peripheral vascular disease. To reduce this risk nitroglycerine which is a vasodilator is used with it. Vasopressin is contraindicated for use in patients with chronic nephritis accompanied by nitrogen retention.

   **b) Nitroglycerin (NTG)**: This increases the concentration of NO in the local tissue, so it produces vasodilation, decreases the venous return and thereby reducing cardiac output. It also causes arterial vasodilatation. The usual maximum rate is 5 mcg/kg/min; however, IV rates up to 20 mcg/kg/min have been used. Nitroglycerin is contraindicated in patients who have known nitrate hypersensitivity. Nitroglycerin should not be given to patients with uncorrected hypovolemia (or dehydration). Nitroglycerin should be used cautiously in
patients with hepatic disease because metabolism of the drug can be impaired, resulting in an increased risk of methemoglobinemia.

c) Terlipressin: This is a synthetic analog of VP- the triglycyl lysine vasopressin (Terlipressin) which undergoes cleavage of glycyl residues to allow a slow release of lysine- vasopressin. It acts by immediate intrinsic vasoconstriction. There is a limited experience in children of the use of this drug. However, it is found to be more effective in controlling bleeding (upto 79%) than vasopressin without any adverse side effects. It can be given as intravenous injections (2mg) every 4 hours till bleeding free interval of 24-48 hours is achieved.

d) Somatostatin: It has growth hormone inhibitory property. It acts by inhibiting release of several vasodilatory hormones such as glucagon. It induces selective splanchnic vasoconstriction. The recommended dosage is one to three bolus injections (250 microgram/ bolus) during first hour of therapy followed by infusion of 250 microgram/ hour of continuous infusion for 2-5 days. There is lower failure rate and complications in comparision to vasopressin but the disadvantage is its short half-life.

e) Octreotide: It is a synthetic analog of somatostatin with an added advantage of a long half-life of 90 minutes. In children the dose is 1 to 2 mcg/kg over 2 to 5 min, then 1 to 2 mcg/kg per hour for 5 days. The use of octreotide is often associated with mild hypoglycemia and hyperglycemia. Several cases of new onset pancreatitis have been reported in patients receiving octreotide therapy.

Effectiveness of somatostatin and octreotide for controlling acute variceal bleeding is comparable to that of vasopressin and EST.11

2. Balloon tamponade: The balloon tube tamponade may be life saving in patients with active variceal bleeding if emergency sclerotherapy or banding is unavailable or not technically possible because visibility is obscured. In patients with active bleeding, an endotracheal tube should be inserted to protect the airway before attempting to place the oesophageal balloon tube. There are three types of tubes available, The Minnesota balloon, Sengstaken Blakemore tube and the Linton tube.

- The Minnesota balloon tube has four lumens, one for gastric aspiration, two to inflate the gastric and oesophageal balloons, and one above the oesophageal balloon for suction of secretions to prevent aspiration. The tube is inserted through the mouth and correct position within the stomach is checked by auscultation while injecting air through the gastric lumen. The gastric balloon is then inflated with 200 ml of air. Once fully inflated, the gastric balloon is pulled up against the oesophagogastroduodenal junction, compressing the submucosal varices. The tension is maintained by strapping a split tennis ball to the tube at the patient's mouth.

- The oesophageal balloon is rarely required. The main complications are gastric and oesophageal ulceration, aspiration pneumonia and oesophageal perforation. Continued bleeding during balloon tamponade indicates an incorrectly positioned tube or bleeding from another source. After resuscitation, and within 12 hours, the tube is removed and endoscopic treatment repeated.

3) Endotherapy: various methods are -

- EVL( Endoscopic Variceal Ligation): Using multiband ligator
- EST(Endoscopic Sclerotherapy): Injection into (intravariceal) or around (perivascular)
varices of sclerosant. Various sclerosants used are: Absolute alcohol, Polydocanol, Sodium morrhuate and Sodium tetradeceylsulfate

• For bleeding gastric varices: Injection of Glue (N-butyl-2 Cyanoacrylate)

Sclerotherapy with sclerosant like ethanolamine olate or band ligation is used for controlling bleed from oesophageal varices. Glue injection with N-butyl-2-cyanoacrylate is used to obliterate fundal varices. Bleeding from an ulcer is controlled using injection with adrenaline and recently hemoclips are also available for clipping at the site of vessel bleed at the base of the ulcer.

Complications of endotherapy are fever, chest pain, dysphagia, superficial mucosal ulcerations (6-70%), esophageal perforation, pulmonary complications, esophageal stricture.

4) TIPS (Transjugular intrahepatic portosystemic shunt)

Transjugular intrahepatic portosystemic shunt is the best procedure for patients whose bleeding is not controlled by endoscopy. It is effective only in portal hypertension of hepatic origin. The procedure is performed via the internal jugular vein under local anaesthesia with sedation. The hepatic vein is cannulated and a tract created through the liver parenchyma from the hepatic to the portal vein, with a needle under ultrasonographic and fluoroscopic guidance. The tract is dilated and an expandable metal stent inserted to create an intrahepatic portosystemic shunt. The success rate is excellent. Haemodynamic effects are similar to those found with surgical shunts, with a lower procedural morbidity and mortality. In majority, TIPS is used as a bridge to liver transplantation.

Outcome after pharmacotherapy and other modalities of treatment is shown in Table 5.

Secondary prophylaxis: β blockers have also been compared directly with EST in 10 RCT in adults, EST was associated with a lower rate of rebleeding but no survival advantage. The actual probability of rebleeding at 1 year was 33 % in the EST group and 53% in propranolol. The benefits of EST in preventing rebleeding may be balanced by an increased rate of complications. No such data is available in pediatric age.

Primary prophylaxis (Fig.3): Non-selective β-blockers (propranolol and nadolol) are used for the primary prophylaxis. By β 1 blockage they reduce the cardiac output and thereby lower the portal pressure and by β 2 blocking action they

---

Table 5. Mechanism of action of pharmaco and endotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Portal flow</th>
<th>Portal resistance</th>
<th>Portal pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstrictor (β₁ Blockers)</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Splanchnic vasoconstrictor</td>
<td>↓↓</td>
<td>-</td>
<td>↓↓</td>
</tr>
<tr>
<td>Venodilator</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Endotherapy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TIPS / Shunt</td>
<td>↑</td>
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produce splanchnic vasoconstriction due to unopposed adrenergic activity and reduce portal pressure and variceal flow. With β blocker therapy 25 % reduction of sleeping pulse rate from baseline is often used as a surrogate marker of efficacy.\textsuperscript{14}

**Control of non variceal bleeding**

Treatment depends on the cause of the bleeding. Various treatment modalities are:

- H\textsubscript{2} receptor antagonists/PPIs
- Vasoactive agents
- Endotherapy - Injection of Sclerosants, Adrenaline, Alcohol, Thrombin/ Fibrin glue
- Mechanical measures using clips or suturing
- Electro - thermal methods are electro - thermal cautery, laser photo coagulation, bipolar coagulation and argon plasma coagulation

**Endotherapy for non variceal bleeding**:
Polypectomy using snare polypectomy with coagulation current is now a routinely used endotherapeutic procedure to remove colonic polyps. This should be preferably carried out with flexible scopes and one must evaluate the entire colon because of the possibility of more than one polyps in a patient and polyps higher up in the colon. Disadvantage with rigid scopes is that they can evaluate only the rectum and sigmoid. Colonoscopy also allows access for direct coagulation of bleeding lesions using electrocoagulation, thermocoagulation, laser therapy or argon plasma coagulation, clips.

Interventional radiology - It is useful for conditions like aneurysm and A.V. fistulas. Procedures done are stenting and TIPS of IVC / hepatic vein in budd Chiari syndrome.

Approach to children with upper and lower GI bleeds who are hemodynamically stable are summarised in Figs. 4 and 5.

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**Fig.3. Primary prophylaxis**
Fig. 4. Approach to a case of upper GI bleed/massive lower GI bleed

**Surgery**

It’s indicated in a number of conditions causing GI bleed such as – shunt surgery (for extrahepatic portal vein obstruction, budd Chiari syndrome), oesophageal transection for refractory variceal bleed, surgery of meckel’s diverticulum, duplications of small bowel, malrotation, volvulus, intussusception, Hirschsprung’s disease, refractory bleed in IBD, vascular lesions etc. In lower GI hemorrhage, hemicolecction or subtotal colectomy is occasionally required.

**Points to Remember**

- *Extrahepatic portal venous thrombosis (EHPVO) is the most common cause GI Bleed in children in India.*
Fig. 5. Approach to a case of lower GI bleed

- **UGI bleeding** is massive and recurrent in EHPVO but risk of rebleeding after major episode is less.
- **UGI Endoscopic therapy** is recommended in any patient presenting with documented UGI bleed & esophageal varices.
- **Hematocrit** should be kept at around 24 and overtransfusion should be avoided.
- **Effectiveness of somatostatin and octreotide** for controlling acute variceal bleeding is comparable to that of vasopressin and Endoscopic Sclerotherapy (EST).
- The balloon tube tamponade may be life saving in patients with active variceal bleeding if emergency sclerotherapy or banding is unavailable.
Endoscopic variceal ligation (EVL) is recommended modality of choice, although EST may be used if EVL is technically difficult as in small babies. Choice may depend on local expertise and technical considerations.

For secondary prophylaxis, EVL is effective in children & may be superior to EST when feasible.

Transjugular intrahepatic portosystemic shunt (TIPS) is the best procedure for patients whose bleeding is not controlled by endoscopy.

References


CHRONIC ABDOMINAL PAIN

* Bhaskar Raju B  
** Sumathi B

Abstract: Chronic or recurrent abdominal pain (CAP) is a primarily functional disorder that affects 10–15% of school-age children and accounts for a large number of referrals to pediatric healthcare professionals. Though the term chronic is used, each episode of pain is usually discrete with a pain free interval. In the developed world, most cases of CAP in pediatric age group are functional with no organic cause made out in spite of extensive investigations. In developing nations and in third world countries, parasitic infections and infestations do contribute significantly to CAP. Still the majority of cases of CAP here too are functional in origin. However, when confronted with a case of CAP, the treating physician has to go all out to rule out treatable organic causes of pain in children. A good and detailed history followed by a thorough physical examination is a crucial step in assessing children presenting with chronic abdominal pain. Investigations are to be ordered in a stepwise logical manner. While organic causes are handled with specific therapy for the identified cause, for functional abdominal pain, medicine has very little to offer as therapy, beyond plenty of reassurance.

Keywords: Chronic abdominal pain, Functional, Organic, Recurrent abdominal pain, Children.

Chronic or recurrent abdominal pain is the commonest gastroenterological complaint the physician or pediatrician is confronted with, in his out patient clinic. The term recurrent abdominal pain was defined by Apley, as abdominal pain of severity, significant enough to disturb daily activities, occurring at least 3 times over a 3-month period. The definition has stood the test of time, though the term chronic abdominal pain is now preferred and the original definition requiring demonstration of distinct pain free intervals is no longer mandatory for a diagnosis of chronic abdominal pain. Chronic abdominal pain is defined by American Academy of Pediatrics (AAP) subcommittee simply as any long lasting, intermittent or constant abdominal pain that may be functional or organic, without any other caveats. 12 weeks of pain is accepted by consensus as duration criteria, though the AAP’s definition of CAP did not specify duration. CAP is mostly functional though a significant, but small number of them will have an organic disease as reason for abdominal pain. In smaller number, pain may be part of some psychosomatic illness.

Childhood chronic abdominal pain is often periumbilical pain, occasionally associated with autonomic and functional symptoms like nausea, vomiting, pallor and sometimes with other painful conditions like headache and limb pains.1-3 Such pain is usually described as functional CAP when no evidence of anatomical,
biochemical, metabolic, inflammatory, immunological or neoplastic disorder can be identified to explain the pain. The Rome III committee on functional abdominal disorders defined and codified all GI functional disorders as in Table 1.

Epidemiology

In general, population based studies suggest that CAP is experienced by 10–12% of school-age children and almost 20% of middle-school and high-school students. As children grow older, the incidence of CAP appears to rapidly decrease in boys but not so rapidly in girls. Apley found an incidence of 10 to 15% among school going children and various studies after him have also confirmed the high incidence of CAP in pediatric school going population. The marked differences in data on CAP in different studies (0.3% to 20%) are due to choice of populations studied-hospitalized patients, out patient clinics or school-based studies. The prevalence of CAP in community-based studies ranges from 0.5% to 19%. Boey and his colleagues studied CAP among school children in Malaysia and found a prevalence of 10.2% (urban 8.2-9.6%, rural 12.4%).

Symptoms remit spontaneously in 30%–50% of children and in about 50% can persist to adulthood as abdominal pain, migraine or irritable bowel syndrome (IBS). A decade ago, cohort studies from India documented a high prevalence (74%) of non-organic CAP. IBS is probably the commonest cause (52%) of functional CAP among older children in the West.

Classification

In early 70s recurrent abdominal pain (as this problem was called then) was classified as organic (10%) and psychogenic (90%). However in 80s, a revised classification was adopted. RAP was classified as organic (20%), dysfunctional (75%) and of psychiatric pathology (5%). To clear the existing confusion in defining all functional GI disorders (FGIDs), experts in the field met in Rome in 1999 and again in 2006 to publish what is now known as Rome criteria II and III for all functional abdominal disorders. Rome III 2006 (Table 1) divides FGIDs in pediatrics into Type G for neonates and toddlers and Type H for older children and adolescents. It reduced time duration to 2 months and also introduced many new functional disorders like postprandial distress syndrome, functional dyspepsia, etc.

The validity and reliability of Rome III criteria in diagnosing pediatric FGID, however is yet to be fully validated, though it is clinically sound. One recent Sri Lankan study attempted that. They studied 55 children with RAP diagnosed as per Apley’s original criteria. Of them, thirteen (23.6%) had organic RAP. According to Rome II, 33 (60%), and according to Rome III, 39 (71%) (functional abdominal pain 19, irritable bowel syndrome nine, functional dyspepsia nine, abdominal migraine one, aerophagia one) of those RAP children had FGD; thereby validating the new Rome III criteria to some extent.

Pathogenesis of functional abdominal pain:
The origin of abdominal pain in CAP is complex and does not lend itself to a single model of causation. The gut and the brain are highly integrated and communicate in a bi-directional fashion. Emotion, behavior, gut function and abdominal pain are closely interrelated. Children with CAP tend to have more anxiety disorders, depressive symptoms, and other somatic complaints and may have experienced more negative life events than unaffected children. Parents of children with CAP do have more gastrointestinal anxiety and depressive symptoms than control parents. There are only few studies, which looked into prognosticating factors in
Table 1. ROME III Abdominal pain related functional GI disorders in children
(Other functional GI disorders described in Table III)

H2a. Diagnostic criteria* for functional dyspepsia
Must include all of the following:
1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus).
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome).
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.

H2b. Diagnostic criteria* for irritable bowel syndrome
Must include all of the following:
1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with
   2 or more of the following at least 25% of the time:
   (a) Improved with defecation
   (b) Onset associated with a change in frequency of stool; and
   (c) Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.

H2c. Diagnostic criteria† for abdominal migraine
Must include all of the following:
1. Paroxysmal episodes of intense acute periumbilical pain that lasts for 1 hour or more.
2. Intervening periods of usual health lasting weeks to months.
3. The pain interferes with normal activities.
4. The pain is associated with 2 or more of the following: anorexia, nausea, vomiting, headache, photophobia, pallor.
5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.

H2d. Diagnostic criteria* for childhood functional abdominal pain
Must include all of the following:
1. Episodic or continuous abdominal pain.
2. Insufficient criteria for other functional gastrointestinal disorders.
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.

H2d1. Diagnostic criteria* for childhood functional abdominal pain syndrome
Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following:
1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain, or difficulty in sleeping

H1c. Diagnostic criteria* for aerophagia
Must include at least 2 of the following:
1. Air swallowing
2. Abdominal distension due to intraluminal air
3. Repetitive belching and/or increased flatus

* Criteria fulfilled at least once per week for at least 2 months before diagnosis; †Criteria fulfilled 2 or more times in the preceding 12 months.
pediatric CAP. One such recent study showed moderate evidence that having one parent with functional GI symptoms, predicted the persistence of CAP in children. It also showed weak evidence, that parental perception of illness predicted the persistence of CAP. There was, however, strong evidence in that study that female sex had no predictive value for the persistence of CAP.14

Levine, et al in 1984 proposed a model where the presence or absence of pain was explained by an interplay of several environmental factors such as lifestyle and habits, temperament and learned responses, somatic predisposition and critical events in the child’s life. All of the above could trigger cortical stimulation of increased gut activity and pain. Many factors early in life shape one’s response to stress and capability to cope with negative events in life. They include genetics, parental attitudes, factors such as family influences on illness expression, abuse, major losses, or exposure to multiple GI infections. These early influences may induce gut dysfunction, abnormal motility, altered mucosal immunity and even visceral hypersensitivity. Hence, FGIDs are viewed as the clinical product of this brain-gut axis interaction of psychosocial factors and altered gut physiology.14 The appearance in medicine of many effective new pharmacological agents influencing this brain-gut axis, like serotonin agonists and antagonists, and centrally acting agents for stress induced effects on GIT are testimony to this concept of disordered brain-gut axis in FCAP.15-20 While genetics do play a role in FGIDs, the aggregation of FGIDs in families21 is not entirely genetic. What children learn from parents may contribute to the risk of developing an FGID. In fact, children of adult patients with IBS make more health care visits (and incur more health care costs) than the children of non-IBS parents.22, 23

Functional chronic abdominal pain (FCAP) wherein no organic cause can be identified is genuine pain. While in a few cases the motivation for pain complaint may be to avoid unpleasant experience or modeling of parental pain, in the vast majority it is genuine pain whose etiology is still poorly understood. Two factors have been described as of primary importance in the perception of pain in functional CAP. They are:

1. Visceral hypersensitivity
2. Altered intestinal motility24

Visceral hypersensitivity, otherwise known as augmented visceral perception refers to the ability of FCAP children to feel events in the gut that are generally imperceptible to normal children. Afferent impulses from gut processed through Meissner’s plexuses are filtered to a variable extent at the level of the hypothalamus (hypothalamic gate) and only limited impulses go up to cortex for perception. This is how most routine impulses generated in the gut are not felt as events, painful or otherwise. Physiological events like peristaltic and non-propulsive contractions of the small and large bowel, postprandial gastric and intestinal distension/contractions, intestinal gas are often felt by FCAP children as dyspepsia or pain. Quasi-pathological problems like lactose intolerance,25 simple constipation and aerophagia can also initiate sensation of pain through distension of bowel in FCAP children.26-28

Evidence for such augmented visceral perception comes from enhanced awareness of balloon distension of rectum and demonstrable pain associated with intestinal migrating motor complexes.29, 30 Involvement of the autonomic nervous system in FCAP is indicated by the presence of headaches, vomiting, pallor, dizziness, motion sickness and temperature intolerance in almost a third of patients with FCAP, confirms further the concept of disordered
enteric nervous system playing a major role in perception of pain in FCAP. Autonomic tests too are often abnormal in many of FCAP patients. Along with augmented visceral perception, FCAP children have significantly increased contractions of the gut—both peristaltic and non-peristaltic. The increased contractile activity seen both in amplitude and length are attributed to impulses from the brain often triggered by environmental factors. Levine’s hypothesis tries to understand this phenomenon of increased cortical stimulation of the gut musculature through his conceptual model, which attributes several environmental factors triggering cortical stimulation of increased gut activity. More recent studies have reported impaired gastric myoelectrical activity, hypomotility of proximal and distal stomach and delayed gastric emptying in children with functional CAP.\textsuperscript{31, 32} There is growing evidence to suggest that FCAP may be associated with visceral hyperalgesia, a decreased threshold for pain in response to changes in intraluminal pressure.\textsuperscript{24, 25} Multiple mucosal inflammatory processes attributable to infections, allergies or primary inflammatory diseases may cause sensitization of afferent nerves and have been associated with the onset of visceral hyperalgesia. The site of hyperalgesia may vary with the predominant symptom such as rectal hyperalgesia in patients with IBS and gastric hypersensitivity in children with CAP.

**Lifestyle and habits** refer to the role of active lifestyle and regular habits especially eating and toilet habits significantly reducing incidence of FCAP. Sedentary lifestyle and irregular eating and bowel habits, substance abuse and addictions predispose to FCAP.

**Temperament and learned responses**: Children who are petted and pampered and have grown up with little disciplining, handle discomfort and disappointment poorly. Secondary gain can make such children exaggerate discomfort to pain.

**Somatic predisposition** refers to the frequent finding of “pain families”. While some of the pain in such families can be modeling, there seems to be definite predisposition for FCAP to show a familial occurrence.

**Milieu and critical events**: Many events in a child’s life could be of intense stress besides exams. Loss of a friend, change of school, family tragedies can heighten the child’s perception of discomfort and induce painful contractions of the bowel.

Summarizing, the presently accepted concept of functional CAP suggests that environmental and lifestyle factors cause abdominal pain in a susceptible population. The susceptible population is characterized by a heightened sensitivity to afferent stimuli originating from gut.

**Typical pain pattern in functional pain** is paroxysmal, with variable severity and clustering of pain, gradual in onset, usually peri-umbilical, occasionally epigastric with poor relationship to food, defecation. Children are often unable to clearly describe nature or location of the pain. Pain may be associated with other symptoms like pallor, nausea, fatigue, and anxiety in about 10-25% of the cases.

Typical pain pattern in organic CAP is a clearly localized pain (away from the umbilicus), radiating pain, well-defined pain (burning, stabbing etc), and pain awakening the child at night. One should meticulously look for presence of red flag signs of organic cause which include unexplained weight loss, pain with fever, tenderness, organomegaly, blood in stools (occult and obvious), altered bowel movements, family history of IBD, anemia, urinary symptoms, Elevated ESR / CRP, arthralgia, rash and purpura.

Major causes of organic pain are illustrated as in Table 2. Major differences between functional and organic abdominal pain are tabulated as in Table 3.
### Functional GI disorders other than CAP as per Rome III

#### Functional gastrointestinal disorders

<table>
<thead>
<tr>
<th>Infants/toddlers&lt;sup&gt;33&lt;/sup&gt;</th>
<th>Child/adolescent&lt;sup&gt;34&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1. Infant regurgitation</td>
<td>H1. Vomiting and aerophagia</td>
</tr>
<tr>
<td>G2. Infant rumination syndrome</td>
<td>H1a. Adolescent rumination syndrome</td>
</tr>
<tr>
<td>G3. Cyclic vomiting syndrome</td>
<td>H1b. Cyclic vomiting syndrome</td>
</tr>
<tr>
<td>G4. Infant colic</td>
<td>H1c. Aerophagia</td>
</tr>
<tr>
<td>G5. Functional diarrhea</td>
<td>H2. Abdominal pain-related FGIDs</td>
</tr>
<tr>
<td>G6. Infant dyschezia</td>
<td>(Described above)</td>
</tr>
<tr>
<td>G7. Functional constipation</td>
<td>H3. Constipation and incontinence</td>
</tr>
<tr>
<td></td>
<td>H3a. Functional constipation</td>
</tr>
<tr>
<td></td>
<td>H3b. Nonretentive fecal incontinence.</td>
</tr>
</tbody>
</table>

#### Organic diseases as cause of CAP

**Gastrointestinal**

- Oesophageal: Gastro-oesophageal reflux disease, oesophagitis (viral, pill, candida)
- Stomach: Peptic ulcer, H. pylori gastritis, bezoar
- Intestinal: Giardiasis, amoebiasis, helminthiasis, tuberculosis, inflammatory bowel disease (ulcerative colitis, Crohn disease), lactose intolerance, coeliac disease
- Surgical: Malrotation with or without volvulus, intussusception, postsurgical adhesions, small bowel lymphoma
- Hepatobiliary: Choledochal cyst, choledolithiasis, choledocholithiasis, space-occupying lesions
- Pancreas: Pancreatitis

**Non-gastrointestinal**

- Renal: Urinary tract infection, obstructive uropathy
- Pelvic: Pelvic inflammatory disease, ovarian pathology
- Haematological: Leukemia
- Vascular: Henoch–Schonlein purpura, polyarteritis nodosa
- Metabolic: Diabetic ketoacidosis, porphyria, lead poisoning

### Approach to a case of CAP:

Given the myriad causes of CAP, it helps to slot children presenting with CAP into one of the following, to narrow down diagnostic possibilities and the investigations ordered:

- Isolated paroxysmal abdominal pain (usually peri-umbilical)
- Abdominal pain with dyspepsia
- Abdominal pain with altered bowel habits

Functional CAP can present with any of the above presentations and whatever the presentation, it is still the commonest cause of CAP. Organic causes of CAP however will differ with the type of presentation and such
Table 3. Differences between functional and organic abdominal pain

<table>
<thead>
<tr>
<th>Organic pain</th>
<th>Functional pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized pain (usually away from umbilicus)</td>
<td>Paroxysmal: Periumbilical, epigastric or lower abdomen</td>
</tr>
<tr>
<td>Consistent</td>
<td>Intermittent, occurs in clusters</td>
</tr>
<tr>
<td>Radiation present</td>
<td>No radiation</td>
</tr>
<tr>
<td>Longer lasting pain</td>
<td>Short duration pain or dull aching pain</td>
</tr>
<tr>
<td>Nocturnal pain. Can disturb sleep</td>
<td>Pain does not wake up a sleeping child</td>
</tr>
<tr>
<td>Definable pain like burning/stabbing pain</td>
<td>Vague pain. May also present with nausea, vomiting and anxiety</td>
</tr>
</tbody>
</table>

Table 4. Practical classification of chronic abdominal pain

I. Paroxysmal abdominal pain (periumbilical)
   - **Functional (>85%)**
     - Isolated paroxysmal periumbilical pain (FCAP)
     - Abdominal migraine
   - **Organic (5%-10%)**
     - Tuberculosis abdomen
     - Inflammatory bowel disease
     - Malrotation, adhesions
     - Lymphoma
     - Renal colic, biliary colic

II. CAP with dyspepsia (epigastric)
   - **Functional FCAP (75%)**
     - Functional dyspepsia
       - Ø Motility type
       - Ø Ulcer type
       - Ø Reflux type
     - Aerophagia
   - **Organic (25%)**
     - Gastro-oesophageal reflux disease
     - Peptic ulcer disease, H. pylori related gastritis
     - Cholecystitis
     - Pancreatitis
     - Biliary disease
     - Parasitic infestation
     - Henoch–Schonlein purpura
     - NSAID ulcer
     - Chronic hepatitis

III. CAP with altered bowel habits (left lower quadrant)
   - **Functional (75%)**
     - Irritable bowel syndrome
     - Habitual constipation
   - **Organic (25%)**
     - Inflammatory bowel disease
     - Tuberculosis abdomen
     - Food allergies
     - Short bowel syndrome
     - Malabsorption, lactose intolerance.
classification will help narrow our search for organic causes. Practical classification of chronic abdominal pain is illustrated in Table 4.

**Stepwise approach to CAP (Fig.1)**

**Step I**

**History and physical examination:** When a child presents with symptom of abdominal pain, a structured approach to identify the etiology should be adopted. It includes a detailed history that includes all details of pain especially its relationship to food and defecation, presence of nocturnal pain, radiation and localization if any. Also one should enquire for and record details of dysphagia, heartburn, bowel movements, dyspepsia, bloating, early satiety, headaches, photophobia, giddiness, weight loss, fever, fatigue, muscle pains, disturbance of daily activities, history of drug intake and psycho social factors, menstrual history, sexual activity (in older children) in all cases of CAP.

General examination in a child with CAP should include thorough physical examination which consists of nutritional status, right iliac fossa or epigastric tenderness any organomegaly, loaded colon, spastic sigmoid, visible peristalsis, rashes/purpura, bone tenderness, and any spinal lesions. Besides detailed history and physical examination case of CAP requires evaluation of the child’s interpersonal relationship with the rest of family especially parents, sibs, grand parents and friends, child’s immediate emotional environment in school and home, child’s personality, child’s response to discomfort and pain, sociability, school performance, etc.

Detailed history and a diligent physical examination should normally be sufficient to make a diagnosis of functional CAP and many experienced pediatricians do not insist on any investigations to confirm it. However, much of treatment of functional CAP depends on the rapport one establishes with the child and family and much of that rapport depends on the seriousness with which the physician approaches the problem. Investigations are one way of reassuring the family and the child that his complaint is being taken seriously. Further, it is not unusual for some common (GERD) and uncommon (HSP/Porphyrias) causes of RAP to be missed on clinical exam. Hence a structured investigatory approach is needed in all cases wherein CAP is diagnosed and is disturbing enough to be brought to the physician for relief.

**Step II**

**Investigations:** This consists of ordering investigations based on clinical assessment. For practical purpose investigations are classified into three levels as below:

**Level 1 investigations:** All cases of CAP must go through the following investigations:

- Complete hemogram, S Amylase/ S Lipase/ Liver and renal function tests, stool, urine analysis screening for TB, skiagrams of chest and abdomen (Optional), USG abdomen.

The above panel will pick up most cases of organic abdominal pain and if these investigations are negative, and if the child fits clinically into one of functional CAP, one stops investigations at this point and starts appropriate therapy for FCAP. In our experience the above would be adequate for >80% of cases that report to out patient department with complaints of CAP. In small number of selected cases one may need to resort to further investigations (Level II).

**Level 2 investigations:**

- **Indications:**

  a) Presence of red flag signs/symptoms with strong clinical suspicion of organic cause for pain.
b) Persistence of significant pain in clinically suspected FCAP, in spite of adequate therapy.

Investigations should include contrast studies on the entire GI tract. upper GI scopy with biopsies of cardia, antrum and duodenum and where required, colonoscopy also. Persistent dyspepsia, vomiting, epigastric pain and tenderness would merit UGI evaluation. Diarrheas especially with mucus and or blood, occult evidence of gastrointestinal bleeding, involuntary weight loss or growth deceleration, iron deficiency anemia, elevated acute-phase reactants (sedimentation rate, C-reactive protein), extraintestinal symptoms suggestive of inflammatory bowel disease (fever, rash, joint pains, recurrent aphthous ulceration) would justify additional colonoscopic evaluation and/ or a barium enema.

Level 3 investigations:

In a small percentage of cases wherein there is persistence of troublesome pain and or other red flag signs, with no organic cause made with the above protocol, one may have to resort to further investigations like EEG to rule out abdominal epilepsy, cyclical vomiting syndrome. Also, selected cases will benefit from screening for porphyria, collagen vascular disorders, lead poisoning, lactose intolerance, food allergy and motility disorders.

Generally speaking such extensive work up should pick up most if not all organic causes of CAP in pediatric practice. Still experience tells us some causes if not looked for diligently and with strong suspicion, can still be missed and the child be misdiagnosed as FCAP even though it has an organic cause for the pain. Such easily missed causes include GERD, H pylori gastritis / duodenitis, chronic constipation, chronic appendicitis/appendicular colic, giardiasis, pin worms, leukemias (bone pain), hernias (Linea alba), spinal lesions (Discitis). Every attempt must be made to rule out these before a diagnosis of FCAP is made.

**Management of chronic abdominal pain**

Conventional interventions for CAP include reassurance and general advice, symptom-based pharmacological therapies, and psychological and behavioral treatments. Standard pediatric care typically consists of reassurance that there is no serious organic disease and general advice about learning to manage and cope with pain. Wherever a recognizable organic cause for the abdominal pain is identified it will need appropriate treatment for the same. As much as possible, unnecessary investigations and hospitalizations have to be avoided since it is likely to reinforce pain behavior.

**Management includes:**

- Make a positive diagnosis
- Explain the suspected pathophysiology and the cause of pain
- Establish goals of therapy and explain complete relief of pain is not one of them
- Identify and modify triggers- physical/ psychological stress factors/diet
- Drug therapy in selected cases
- Active psychological support

Making a positive diagnosis of FCAP even though all investigations are normal and explaining the pathophysiology to parents and to the extent possible to the child, is a major part of management of functional CAP and often the only part. The other point to be emphasized to parents is that once the child is made to understand and accept this, the pain relief is earlier and more complete since the stress contribution by the pain itself is reduced.
Chronic abdominal pain

Step I

History & Physical Examination

Alarm signs & symptoms

No (FAP) → Level 1

CBC, Peripheral smear, urine and stool routine

Reassurance
Involved doctor care
Parent education
Diet modification
Appropriate drugs
Cognitive behavioural therapy
Close and diligent follow up

Step II

Level 1a
In addition to level 1 + USG abdomen, Blood sugar, renal function tests, LFT, S. amylase, lipase, mantoux, chest & abdominal X-ray, celiac tests

Level 2
GI endoscopy. Barium contrast studies, CECT abdomen, Laparoscopy, MRCP, motility studies, breath test

Level 3
EEG, S.lead level, screening for porphyria

Treat the cause

Yes (Organic) → Step III

MRCP magnetic resonance cholangiopancreatography
EEG electroencephalogram

Fig.1. Step wise approach to chronic abdominal pain
**Goals of therapy:** The major and only goal of therapy is to normalize lifestyle and not allow the pain to curtail either the daily activities or achievement expectations from the child. Attainable goals would include, 1) Normal school attendance, 2) Scholastic and extracurricular performances to the child’s potential, 3) Normal growth pattern and 4) Normal sleep pattern.

**Identify and assuage stress and trigger factors:** Many of the known factors that trigger and sustain pain in FCAP were discussed earlier and they need to be addressed and some can be removed and others modified enough to reduce its impact on the child’s gut. Greater success would be obtained from abolishing secondary gain from pain by preventing the child from using the pain to avoid unpleasant but essential responsibilities. A talk with teachers and school authorities not to panic over the pain but to respond to it with reasonable care and attention is a big part of treatment. The child may be allowed to rest at school till the pain abates and not be sent home every time he/she complains of pain. Similarly the family and immediate society around the child must be encouraged to be supportive and sympathetic to the child’s complaints but not go overboard with undue over-reactions, which may make the child believe he/she has a major disease and/or lead to secondary gain behavior.

**Diet:** It has very little role in modifying pain though, avoiding/reducing carbonated and sweetened drinks, high carbohydrate diets, milk and milk products and diet containing complex carbohydrates that may escape digestion and generate gas in the colon, may help. Timely meals and a balanced diet would translate to better lifestyle and general sense of well being that would help the pain and the capacity of the child to handle it.

**Drug therapy:** True FCAP does not need any drugs and drug therapy is often useless. Antispasmodics may be judiciously used to relieve severe pain, remembering that they may predispose to constipation—another major cause of CAP. Documented acid peptic disease will benefit from anti-acid therapy. H. pylori, if identified will create a dilemma with reports suggesting good response to therapy and with equal reports refuting its benefits.35 High incidence of H pylori positivity in the third world and the high incidence of re-infection make decision regarding benefits of therapy for H. pylori difficult to take. High incidence of giardiasis in many Indian studies would make the use of a course of metronidazole in all cases of CAP a worthwhile idea.36-38 Other drugs/treatment modalities that may have a role in FCAP include, moderate fiber diet (child’s age in years + 5gms per day) prokinetics, mineral oil, polyethylene glycol (PEG), lactulose when bowel movements are hard or irregular. Antimotility agents are generally not advised unless there is disturbing diarrhoea with FCAP. Enteric-coated peppermint oil has found anecdotal benefit in some cases of FCAP.39 Abdominal migraine, if suspected will benefit from cyproheptadine and propranalol.40,41 Drugs like 5HT receptor antagonists, which have been found useful in adults with, pain predominant IBS have not been tried in FCAP in children. They include alosetron (5HT3 antagonist) in diarrhoea predominant IBS42 and tegaserod (5HT4 agonists) in constipation predominant IBS.43

**Psychiatric help:** As a rule FCAP responds badly to psychiatric consults and children with FCAP and parents react badly to suggestion that psychiatric pathology may be responsible for the pain. However some situations do need psychiatric help and they are best obtained from a psychiatrist with pediatric experience. Such situations include conversion reaction,
anxiety, depression, low self-esteem, maladaptive family, modeling / imitating family pain behavior, and poor response to conservative therapy. Whenever psychiatric help is needed, it is ideally done as a part of a multidisciplinary approach. At the same time, not all children with CAP benefit from conventional treatments, and interest in alternative therapies, such as biofeedback therapy, hypnotherapy, and peppermint oil, is growing. For severely affected patients with functional disability, an interdisciplinary rehabilitation approach may be warranted. Following a comprehensive medical evaluation, consideration of these various options is important. Other modalities of psychological therapy include cognitive behavioral therapy, which aims to help the child accept his pain as not indicative of impending or existing disease and to lead socially active lives. Some reports of success with this approach are available. While short-term success wasn’t different from conservative management, long-term pain relief was attained in a higher (56% vs. 24% at 6 months and 59% vs. 37% at 12 month follow up) percentage of children who underwent cognitive behavioral therapy.

Prognosis: A significant section of children with FCAP have complete relief of pain within 6 to 8 weeks of diagnosis indicating the role of a positive diagnosis of FCAP. Many do get recurrences of pain but handle it better without affecting their daily activities. In 30 to 50% of children the pain follows them into adult life, though 70% of such adults do not allow the pain to affect their daily life activities. A third of them may develop other chronic complaints like headaches, back pains, and menstrual abnormalities.

Points to Remember

1. **CAP is a common problem in school going children.**

2. **Majority of pain in children is functional in origin.**

3. **All children with CAP need structured work up to rule out possible organic cause.**

4. **Re-assurance and confidence building are key to success in therapy of CAP in children.**

5. **Normalization of life pattern rather than pain relief should be the primary goal of therapy.**

References


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**NEWS & NOTES**

**MAHAPEDICON 2011**

**Nashik, Date: 2-4 December, 2011**

**Contact**

Dr.Kedar Malwatkar,
Mobile: 9822502295, E-mail: ksmalwatkar@yahoo.co.in
GASTROENTEROLOGY

APPROACH TO A CHILD WITH JAUNDICE

* Seema Alam
** Shaad Abqari

Abstract: This article describes the approach to jaundice of the infant with conjugated bilirubinemia or neonatal cholestasis as well as the older child with conjugated bilirubinemia and liver disease has been discussed in detail. The definition, common causes and cost-effective clinic-investigative approach to these patients has been discussed in detail.

Keywords: Jaundice, Children, Investigations.

Jaundice is a symptom characterized by yellowish discoloration of sclera, skin and mucous membranes due to increased circulating bilirubin. Clinically apparent jaundice in children occurs when serum concentration of bilirubin reaches 2-3 mg/dL however neonates may not appear icteric until the bilirubin levels reaches >5mg/dL. Depending on pathophysiology, there are 3 types of jaundice (a) hemolytic (prehepatic), (b) hepatocellular and (c) cholestatic.

Prehepatic or hemolytic jaundice: This is caused by hemolytic anemias or by a familial disturbance of bilirubin metabolism like Gilbert syndrome.

Hepatocellular jaundice: Primarily involvement of the liver, the major cause of hepatocellular jaundice is viral hepatitis.

Cholestatic jaundice: Both intra as well as extrahepatic cholestasis which includes syndromes like biliary atresia, Alagille, Zellwegers and cholodochal cysts.

Depending upon the duration, jaundice can occur as a part of acute liver disease, acute on chronic liver disease and chronic liver disease.

Acute liver disease

Acute liver disease is when the jaundice settles down within 4-6 weeks. The commonest etiology of acute liver disease in children is infection due to hepatitis viruses, systemic infections (like malaria and enteric fever), drugs, Wilsons disease and autoimmune hepatitis (Table1). The clinical spectrum of acute liver disease varies from a mild illness requiring no treatment; to fulminant liver failure requiring liver transplantation. A consensus of the members of the Pediatric Acute Liver Failure (PALF) Study Group, a multicenter and multinational consortium, resulted in a working definition for acute liver failure (ALF) that is the summation of clinical and biochemical parameters, as follows:

- The acute onset of liver disease with no known evidence of chronic liver disease as evident by firm to hard liver, splenomegaly or portal hypertension.
### Table 1. Causes of acute liver disease according to age

<table>
<thead>
<tr>
<th>Neonates</th>
<th>Infectious</th>
<th>Metabolic</th>
<th>Ischaemia</th>
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<tbody>
<tr>
<td></td>
<td>Sepsis, HBV, herpesviruses, Ebstein Barr Virus, cytomegalovirus, echovirus, adenovirus</td>
<td>Galactosemia, tyrosinemia, neonatal hemochromatosis, mitochondrial disease</td>
<td>severe asphyxia, congenital heart disease, cardiac surgery, myocarditis,</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Older children</td>
<td>Infections</td>
<td>Drugs</td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>HAV, HBV, NA–G, herpesviruses, sepsis, parvovirus B19</td>
<td>Acetaminophen, Valproate, Isoniazid, carbamazepine, Halothane</td>
<td>Wilson’s disease, tyrosinemia, hereditary fructose Intolerance, α 1 antitrypsin deficiency, Nieman Picks disease, Indian childhood cirrhosis</td>
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<td></td>
<td></td>
<td></td>
<td>Immune</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Autoimmune hepatitis</td>
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<td></td>
<td></td>
<td></td>
<td>Ischaemia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Congenital heart disease, cardiac surgery, myocarditis, severe asphyxia, Budd Chiari syndrome</td>
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<td>Toxins</td>
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<td></td>
<td></td>
<td></td>
<td>Amanita phalloides, carbon tetrachloride, phosphorus</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Tumors</td>
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<td></td>
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<td>HCA,hepatoma</td>
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- Biochemical and/or clinical evidence of severe liver dysfunction: international normalized ratio (INR) < 2.0 and hepatic encephalopathy with INR >1.5.

### Chronic liver disease

A common disorder in the pediatric population in India. Liver diseases are often reflected by abnormalities of hepatocytes (hepatocellular dysfunction), the biliary excretory apparatus (cholestasis) and the vascular system (portal hypertension) (Table 2). Irrespective of the initial insult, most chronic liver diseases (CLD) of childhood result in cirrhosis. CLD should be considered if:

- Ongoing involvement of liver has the potential to progress to more severe or end stage liver disease.
- Etiological conditions which are potentially chronic in nature, although duration may be less than 6 months (except HBV infection which should be more than 6 months duration).
- Children with histological features of hepatic fibrosis / cirrhosis.

### Neonatal jaundice

Jaundice is an important problem in the first week of life. Nearly 60% of term newborn becomes visibly jaundiced in the first week of life with 5-10% needing intervention for the management of hyperbilirubinemia. The cause of neonatal jaundice is not well understood but increased bilirubin load due to a shortened red blood cell lifespan, increased activity of the enterohepatic circulation, and inefficient uptake of bilirubin by hepatocytes due to relatively immature expression of ligandin, which mediates the uptake of organic anions, in addition to immaturity of hepatic bilirubin glucuronosyl transferase are the most likely reasons.
**Table 2. Causes of chronic liver disease**

1) **Hepatocellular**
   - Metabolic
     - b) α 1 Antitrypsin deficiency
     - c) Carbohydrate defect: Fructose intolerance, glycogen storage Ia, Ib, Ic, Id, III & IV
     - d) Lipid storage: Niemann- Pick, Gauchers’s disease,
   - e) Tyrosinemia type 1
   - f) Cystic fibrosis
   - g) Peroxiosomal disorder: Zellweger syndrome
   - h) Nonalcoholic fatty liver disease

2) **Viral**
   - a) Hepatitis B± delta
   - b) Hepatitis C
   - Autoimmune Hepatitis
     - a) Type I
     - b) Type II
   - Drug / toxins

3) **Biliary**
   - a) Choledochal cysts, stones
   - b) Sclerosing cholangitis
   - c) Alagille syndrome, non syndromic biliary hypoplasia
   - d) Progressive intrahepatic cholestasis
   - e) Drugs

4) **Vascular**
   - a) Hepatic vein thrombosis: Budd Chiari syndrome
   - b) Chronic congestive heart failure
   - Hemangioma liver

* Treatable causes are in **bold letters.**

**Physiological jaundice** - Jaundice attributable to physiological immaturity usually appears between 24-72 hours of age, peaks by 4-5 days in term and seventh day in preterm neonates and disappears by 10-14 days of life. It is predominantly unconjugated and levels usually do not exceed 15 mg/dL.

**Pathological jaundice** : Bilirubin levels that deviate from the normal range and requiring intervention would be defined as pathological jaundice. Appearance of jaundice within 24 hours, increase in serum bilirubin beyond 5 mg/dL/day, peak levels above the expected normal range would be categorized under pathological jaundice. The common causes include Rh or ABO incompatibility, prematurity, extravasated blood (cephalhematoma), ongoing hemolytic disease, exaggerated perinatal weight loss (>7% of birth weight), glucose-6-phosphatase dehydrogenase (G-6PD) deficiency, breast milk jaundice, Criggler Najar and hypothyroidism. Approximately half of term babies are jaundiced; more severe jaundice (serum bilirubin >15 mg/dL) occurs in 8–20% in the first week of life. Some maternal factors associated with severe jaundice include maternal diabetes mellitus and induction of labor with oxytocin. Infants who have abnormalities in bilirubin glucurono syltransferase, which cause Gilbert syndrome alone or in addition to G6PD deficiency are at greater risk for severe physiological jaundice and breast-milk jaundice.

**Neonatal cholestasis**

Neonatal jaundice should be differentiated from neonatal cholestasis which is conjugated hyperbilirubinemia ( >1mg/dL if total bilirubin <5mg/dL and >20% if total bilirubin is >5 mg/dL) beyond 2 weeks or 14 days of age. Presence of dark urine (staining the clothes) or pale colored stools would suggest cholestatic jaundice. The commonest causes of neonatal cholestasis are biliary atresia and neonatal
hepatitis syndrome (Table3). Among TORCH infections cytomegalovirus (CMV) is the commonest infection and herpes simplex virus (HSV) infection has a more fulminant course.

**Clinical assessment**

**Jaundiced baby and infant**

In the antenatal history it would be prudent to know if during the pregnancy there was history of drug intake, alcoholism, smoking, intercurrent illnesses, pruritus of pregnancy, hepatitis B virus or CMV infection in the mother. Family history and history of consanguinity would be important in hereditary and metabolic liver disease. Neonatal hepatitis may occur more often in male infants, low birthweight, premature with a family history of neonatal hepatitis. Whereas biliary atresia may be more common in term good weight female infants with no family history. Congenital malformations like polysplenia, situs inversus with cardiac anomalies maybe present in a third of the biliary atresia patients. Infants may be small for gestational age, especially those with intrauterine infections, Alagille’s syndrome, progressive familial intrahepatic cholestasis and metabolic liver disease. Dysmorphic features are present in trisomy 18, trisomy 21, Alagille’s syndrome, Zellweger syndrome and with certain congenital infections. Allagille syndrome have intrahepatic cholestasis with dysmorphic facies and butterfly vertebrae. Some non syndromic intrahepatic cholestasis can also present in this age group. Hypogonadism (in males) if present in a jaundiced baby should suggest hypopituitarism especially if associated with hypoglycaemia and optic dysplasia. The history of the present illness should include: Date of jaundice, color of stools and urine, drug history, parenteral nutrition, bleeding, petechiae, or bruising, feeding history and weight gain. Clinical features suggesting liver disease include: Pale stools and dark urine, suggesting cholestasis or obstruction. Acholic stool is a cardinal feature of biliary atresia but even intrahepatic cholestasis and neonatal hepatitis cases will have acholic stools and early biliary atresia may have pigmented stools. Irritability, poor feeding, vomiting and lethargy are indicators of metabolic disease like galactosemia and tyrosinemia. Babies born with acute liver failure are mostly due to neonatal hemochromatosis.

Bruising, petechiae, or bleeding, suggest coagulopathy which could be due to ALF. Hepatomegaly and failure to thrive also suggest liver disease. A mass in the right upper quadrant may be felt in approximately 50% of patients with a choledochal cyst. Splenomegaly suggests an intrauterine infection, metabolic liver disease, or advanced liver disease with hepatic fibrosis and early portal hypertension. The spleen may also be palpated in healthy babies 1-2 cm below the left costal margin. An impalpable spleen in an infant with severe cholestatic jaundice may suggest extrahepatic biliary atresia with

<table>
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<th>Table 3. Common causes of neonatal cholestasis</th>
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<tr>
<td>Neonatal hepatitis syndrome</td>
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<tr>
<td>Obstructive</td>
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<td>Metabolic</td>
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polysplenia. Ascites suggests an intrauterine infection, inborn error of metabolism or advanced liver disease. If the infant is acutely ill, then sepsis or acute liver failure should be considered. Tyrosinemia type 1 presents with CLD, renal failure, resistant rickets, muscle weakness and self-mutilation. Galactosemia and congenital rubella can present with cataract in newborn and early infancy.

**Older child with jaundice**

History of neonatal jaundice (Wilson’s disease, α1-antitrypsin deficiency, cystic fibrosis and Niemann–Pick C disease may be associated with transient jaundice), drug history, transfusions, ear piercing, tattooing, previous surgery, Hepatitis A or B immunizations are the important information required. Family history of neuropsychiatric disorders are present in Wilson’s disease. Family history of HBV positivity (especially HBV positive mother) would be important information.

A prodrome of malaise, lethargy and anorexia nausea, vomiting, or weight loss may suggest viral hepatitis and absence of prodromal symptoms is seen in drug induced hepatitis. Abdominal discomfort or tender hepatomegaly suggest acute hepatitis. Presence of anemia and deteriorating school performance suggest Wilson disease. Pancytopenia in the setting of ALF suggests infection with parvovirus. Presence of joints pains, skin rashes and chronic diarrhea may indicate autoimmune hepatitis and associated celiac disease. A metabolic cause of CLD should be suspected if there is consanguineous marriage, multiple miscarriages, neonatal deaths in the family or a positive family history. Evidences of precocious puberty may suggest endocrinal involvement in Wilson’s disease or severe liver disease. Ascites is commonly present in chronic liver disease and Budd-Chiari syndrome. Hematemesis, ascites and splenomegaly suggest portal hypertension and also indicate chronic liver disease. Presence of hepatosplenomegaly

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Ophthalmological Features</th>
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<tbody>
<tr>
<td>Wilson’s disease</td>
<td>Kayser Fleischer ring: in peripheral descemnet membrane 2-3 mm inside the limbus&lt;sup&gt;7,9&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Sunflower cataract: green frond like petals at posterior pole of lens.</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>Pinguecula, cherry red spot on the macula, strabismus, nystagmus, conjunctival deposits,</td>
</tr>
<tr>
<td></td>
<td>corneal opacities, retinal hemorrhages and retinitis pigmentosa</td>
</tr>
<tr>
<td>Neimann Pick</td>
<td>Cherry red spot on the macula, optic atrophy, retinal ganglion ballooning and increased</td>
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<tr>
<td></td>
<td>scleral translucency.</td>
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<tr>
<td>Tyrosinemia</td>
<td>Pseudoherpetic keratitis, long eyelashes, discreet conjunctival plaques with papillary</td>
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<tr>
<td></td>
<td>hypertrophy, hazy cornea leading to corneal ulcer.</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>Uplanting palpebral features, epicanthal folds, hypoplastic supra orbital ridges, cataract,</td>
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<tr>
<td></td>
<td>glaucoma, corneal clouding, brushfield spots, optic nerve dysplasia.</td>
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<tr>
<td>Alagille syndrome</td>
<td>Posterior embryotoxon</td>
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is more likely seen in Gaucher’s and Neumann Pick disease. Wilson’s disease and cystic fibrosis more often present with associated portal hypertension. Aversion to sweets is seen in hereditary fructose intolerance. Obesity with asymptomatic hepatomegaly and acanthosis nigricans may suggest non-alcoholic fatty liver disease. Presence of Keyser Fleischer ring, hemolytic anemia, tremors, psychiatric problems, bony deformities with resistant rickets, endocrine manifestations, and family history would suggest the diagnosis of Wilson disease. Ophthalmological features which suggest specific liver diseases have been listed in Table 4.

**Investigative approach to neonatal cholestasis**

It is important to remember that the investigative work up should be for the treatable
causes of neonatal cholestasis and also should be done rapidly or else it would be late to correct biliary atresia which is one of the commonest treatable causes. The Kasai’s portoenterostomy done for biliary atresia should be done with 6-8 weeks of age for optimum results. Hence the centres which are not regularly doing the surgery should refer the baby to a centre where at least 6 such surgeries are done annually. So to ensure that the patient is referred early we should let the neonatal cholestasis be evaluated in a centre well equipped to manage biliary atresia. There are different school of thoughts about doing scintigraphy in the evaluation of the cholestatic infant, some suggest we should do the liver biopsy and if the diagnosis is not clear then we may do MRCP or ERCP and decide. If still the doubt persists then a peroperative cholangiogram will settle matters at laparotomy (Fig.1).

**Investigative approach to older child with jaundice**

If the presentation is acute liver disease or ALF then the investigative work up should be keeping in mind the complications and the etiology. So, we need to look at the hepatic functions (transaminases, bilirubin, serum albumin, prothrombin time with INR and gamma glutamyl transferase), blood sugar, USG abdomen, serum electrolytes, renal functions, liver biopsy, Hepatitis A antibodies, Hepatitis B surface antigen (with HBV e antigen as well as core antigen and respective antibodies), Hepatitis C antibodies (as well as polymerase chain reaction) and serum ceruloplasmin with total urinary copper should be done. For ALF serum ammonia and blood gas analysis would also be required.

If the presentation is chronic liver disease then we need to do hepatic functions (transaminases, bilirubin, serum albumin, prothrombin time with INR and Gamma glutamyl transferase), blood sugar, USG abdomen, serum electrolytes, renal functions, liver biopsy, Hepatitis B surface antigen (with HBV e antigen as well as core antigen and respective antibodies), Hepatitis C antibodies (as well as polymerase chain reaction) and serum ceruloplasmin with total urinary copper should be done. Moreover we need to do the upper GI endoscopy to look for esophageal varices and portal hypertension. If there is cholestasis then we need to do the MRCP or ERCP to decide biliary/pancreatic stones or strictures. Since autoimmune hepatitis is not commonly seen in Indian population we can look for it if the other etiologies have been ruled out in both acute and chronic presentations of the jaundiced older child.

**Points to Remember**

- **Types of jaundice are** hemolytic, hepatocellular and cholestatic.
- **Jaundice can be due to** acute, acute on chronic, chronic liver disorders.
- **Etiology of liver disease vary depending on age of onset and duration**
- **A systemic approach to jaundice, both in neonatal and later age groups will lead on to appropriate diagnosis and treatment.**

**References**


CLIPPINGS

Adjustable versus non-adjustable sutures for the eye muscles in strabismus surgery

No reliable conclusions could be reached regarding which technique (adjustable or non-adjustable sutures) produces a more accurate long-term ocular alignment following strabismus surgery or in which specific situations one technique is of greater benefit than the other. High quality RCTs are needed to obtain clinically valid results and to clarify these issues. Such trials should ideally a) recruit participants with any type of strabismus or specify the subgroup of participants to be studied, for example, thyroid, paralytic, non-paralytic, paediatric; b) randomise all consenting participants to have either adjustable or non-adjustable surgery prospectively; c) have at least six months of follow-up data and d) include re-operation rates as a primary outcome measure.

Haridas A, Sundaram V. Adjustable versus non-adjustable sutures for strabismus. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD004240. DOI: 10.1002/14651858.CD004240.pub2. This version first published online: January 24. 2005. Last assessed as up-to-date: September 27. 2010

Emma Flavel, Malcolm Boyle. Which is more effective for ventilation in the prehospital setting during cardiopulmonary resuscitation, the laryngeal mask airway or the bag-valve-mask? - A review of the literature. Journal of Emergency Primary Health Care, Nov 2010

The findings from this review suggest that the laryngeal mask airway is more effective at ventilations over time during cardiopulmonary resuscitation in adults, as there is less risk of gastric regurgitation and pulmonary aspiration. The bag-valve-mask (BVM) is quicker at performing the first ventilation but there is a loss of effectiveness over time. BVM is considered the best method for ventilating children and neonates.
APPROACH TO A CHILD WITH FEVER AND ALTERED SENSORIUM

* Dipangkar Hazarika

Abstract: Fever with altered sensorium is a common presenting complaint in pediatric emergency department, causes varying according to geographic area. A thorough history, general, neurological examination and judicious use of investigations like CSF analysis, peripheral blood smear examination and neuroradiological evaluations helps in diagnosis. Child presenting with features suggestive of viral encephalitis, post-infectious or post-immunization encephalitis (e.g. ADEM) should be excluded as treatment is different for these two conditions.

Keywords: Fever, Altered sensorium, CSF, ADEM.

A child presenting with fever with altered sensorium which ranges from lethargy to coma, (Table 1) is a common presentation in pediatric age group. This article focuses on approach to diagnosis of such a child.

Causes: There are many causes which may vary according to the geographic area. The common causes are:

All causes of febrile encephalopathy can be grouped into four categories.


Prior to categorising, one should exclude transient causes such as hypoxia or hypoglycemia septic shock, electrolyte disturbances, post ictal, state etc.

Approach to diagnosis: The initial evaluation should include a careful history and physical examination. The history should focus on the following key elements.

i. Duration, type, degree of fever, diurnal variation and associated symptoms with fever. The associated symptoms may indicate the focus of infection.

ii. Place of residence and/or recent visit to an endemic /hyper endemic area for malaria, VE.

iii. Duration of illness- fever, seizures, unconsciousness and any other symptoms.

iv. Presence of convulsion before the onset of unconsciousness.

v. Onset of illness and presence of non-specific febrile illness like viral prodrome, anorexia, poor feeding, symptoms of upper respiratory tract infection, skin eruptions.

vi. History of similar cases in the same locality and or family.
Physical examination

It should include both general and neurological examination.

Neurological: A complete neurological examination is necessary with particular attention to 5 physiological variables in a child with altered sensorium. Objective of this is to look for brain stem signs, keeping in mind the signs of herniation syndrome. Level of consciousness, pattern of respiration, size and reactivity of the pupils, spontaneous and induced eye movement and motor response. In addition, the signs of meningeal irritation, cranial nerve palsy and signs of increased intracranial pressure should be looked for.

Level of consciousness: It should be assessed by modified Glasgow Coma Scale (GCS), which is frequently used in infant and young children. An alternative method is the AVPU score. Like GCS it is also useful for the serial observation of the trends in the level of coma. A – Alert, V- Responds to voice, P-Response to pain and U- Unresponsive.

Respiratory pattern: Respiratory pattern abnormalities signify either metabolic derangement or neurological insult. Types of respiratory pattern are:

Cheyne- Stokes respiration: A pattern of periodic breathing where hyperpnea alternates with apnea. The depth of breathing alters from breath to breath with a smooth rise to a peak and a smooth fall. It results from deep hemispheric or diencephalic dysfunction and seen in children with metabolic abnormalities.
Central neurogenic hyperventilation: This is sustained regular, rapid and deep respiration, which may be seen in children with brainstem dysfunction.

Abnormalities within the medulla and pons cause 3 different patterns of respiration:

1. Apneustic breathing: Characterized by inspiratory pauses lasting 2-3 seconds often alternating with end-expiratory pauses. It is seen in pontine infarction and anoxic encephalopathy.

2. Ataxic breathing: Haphazard breaths and pauses without predictable pattern.

Pupillary size and reaction: The presence or absence of the pupillary reaction to light is one of the most important differentiating features to distinguish between structural and metabolic disorders as metabolic disturbances affect the papillary pathways late.

Usually in metabolic disorders leading to altered level of consciousness pupils remain reactive in the initial stages. But in structural disorders with increased ICP, signs of termination syndrome will appear. Depending on which part of brain is affected, pupillary signs vary. In uncal herniation, features of III nerve palsy i.e. unilatral dilated fixed pupil will be seen. In diencephalic stage of herniation pupils are small and reactive. If pons are affected in herniation, pupils are pin point and reactive when medulla is involved pupils are dilated and fixed.

Induced eye movements: Two tests are helpful in a comatose child.

1. Oculucephalic or Doll’s eye movement: It is performed by holding the eyelids open and rotating the head from side to side. The normal or positive response is conjugate deviation of the eyes in the opposite direction to which the head is turned.

2. Oculovestibular or Caloric test: Elevate the patient’s head to 30°C and slowly injecting 50 ml of ice water (approximately 0°C) with a syringe. 3 types of reactions can occur:

   a. Normal awake patients with intact brainstem: Nystagmus with the slow components towards the irrigated ear and fast component towards midline.

   b. Unconscious patient with intact brainstem: Fast component abolished, eyes move towards stimulus and remain tonically deviated for more than 1 minute.

   c. Unconscious patient with brainstem dysfunction/brain dead: No responses to stimuli, i.e. eyes remain in the midline.

Motor examination: Assessment of muscle strength, tone and tendon reflexes should be done for normality and symmetry. The ability of the patient to localize stimuli as well as presence or absence of abnormal posturing helps in the assessment of severity of neurological dysfunction. Spontaneous movement of all limbs indicates a mild depression of hemispheric function without structural damage. Various motor deficits are:

Decorticate posturing: Flexion of upper limbs and extension of the lower limbs. It suggests involvement of cerebral cortex and preservation of brainstem function.

Decerebrate posturing: Rigid extension of both arms and legs indicative of cortical and brainstem dysfunction.

   The flaccid patient with no response to painful stimuli indicates deep brainstem dysfunction.

   Monoplegia or hemiplegia, except when in post-ictal phase, suggests a structural disturbance of the contra lateral hemisphere.
Opisthotonous: Neck is hyper extended and the teeth are clenched; the arms are adducted, hyper extended; and the legs are extended with feet plantar flexed. It indicates severe brainstem dysfunction.

**Signs of meningeal irritation:** They include nuchal rigidity, back pain, **Kernig** sign: Flexion of the hip 90° with subsequent pain on extension of the leg, **Brudzinski** sign: Involuntary flexion of the knees and hips after passive flexion of the neck while supine.²

In some children, particularly those between 12-18 months, Kernig and Brudzinski signs are not consistently present.² So, whenever there is suspicion of acute CNS infection, lumber puncture (LP) should be done.

Cranial neuropathies of the ocular, oculomotor, abducens, facial and auditory nerve should be looked for.

**Signs of increased intracranial tension** in children range from headache, vomiting to herniation (Tables 2 and 3).⁴

**B) General examination:** Look for i) Cutaneous manifestations: Petechiae, purpura, erythematous macular rash: Acute bacterial meningitis, ii) Pallor, icterus: Complicated malaria, typhoid fever, iii) Hepato-splenomegaly: Malaria, typhoid fever, iv) Skin vesicles and shallow ulcers: Hallmark of HSV infection, v) Anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucination: In HSV encephalitis.

**Differential diagnosis**

**Cerebral malaria**

It is the commonest form of severe malaria in children, more likely in children with parasitemia more than 5%. It is defined strictly as unarousable coma (i.e. there is a non-purposeful response or no response to a painful stimulus) which is not attributable to any other cause in a patient with falciparum malaria. Coma should persist for at least 1 hour after a generalized convulsion.⁶ It is characterized by two types of onset: a) Sudden following a generalized seizure. b) Gradual with initial drowsiness, confusion, disorientation, delirium or agitation followed by loss of consciousness. Length of prodromal history can be as short as 6-12 hours in children.

A history of generalized or focal seizure is common. There may be some passive resistance to head flexion but board like rigidity of meningitis and other signs of meningeal irritation are not found. Severe anemia, hypoglycemia are commonly associated but, jaundice is unusual. It may be associated with very high fever but presence of fever is not a must for diagnosis. Localizing neurological signs are found infrequently. In severe cases there may be increased muscle tone, contracted or unequal pupils, hemiplegia, absent or exaggerated deep tendon reflexes, positive Babinski sign, opisthotonus and decerebrate rigidity.⁶

**Viral encephalitis**

JapaneseB encephalitis is the most common cause, but we should consider other viruses like herpes simplex, mumps, measles and enterovirus while evaluating such a case (Table 4). In areas where the disease is endemic JE is seen mainly in children below 15 years.⁷ The onset of illness can be abrupt, acute, subacute or gradual. The course of the disease is characterized by:

**Prodromal stage:** High grade fever with or without rigors, headache (frontal or generalized), malaise, nausea and vomiting. Adolescents complain of retrobulbar pain, photophobia, pain in the legs, neck, back and respiratory symptoms, while infant may present with irritability and lethargy.⁷
Table 2. Signs of increased ICT in children

<table>
<thead>
<tr>
<th>Headache, vomiting.</th>
<th>Hypertension with bradycardia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulging fontanel or diastasis (widening of sutures).</td>
<td>Apnea or hyperventilation.</td>
</tr>
<tr>
<td>Oculomotor (anisocoria, ptosis) or abducens nerve paralysis.</td>
<td>Decorticate or decerebrate posturing, stupor, coma.</td>
</tr>
<tr>
<td>Signs of herniation (Table 3).</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Signs of incipient downward herniation

<table>
<thead>
<tr>
<th>Arousal</th>
<th>Breathing</th>
<th>Pupils</th>
<th>Oculocephalic responses</th>
<th>Motor signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired early, before other signs</td>
<td>Sighs, yawns, sometimes Cheyne- Stokes respirations</td>
<td>First small reactive (hypothalamus), then one or both approach mid-position</td>
<td>Initially sluggish, later tonic conjugate.</td>
<td>Early hemiparesis opposite to hemispheric lesion followed late by ipsilateral motor paresis and extensor plantar response.</td>
</tr>
<tr>
<td>Uncal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired late, usually with other signs</td>
<td>No early change</td>
<td>Ipsilateral pupil dilates, followed by somatic third nerve paralysis</td>
<td>Unilateral 3rd nerve paralysis</td>
<td>Motor signs late, sometimes ipsilateral to the lesion</td>
</tr>
</tbody>
</table>

**Encephalitic stage:** Marked by CNS symptoms from 3rd to 5th day, which manifests with altered sensorium, convulsion, neck stiffness, muscle rigidity, mask like face and abnormal movements.

Features of raised ICP are frequently present. Focal neurological signs may be stationary, progressive or fluctuating. Seizure is a prominent feature of encephalitis. JE characterized by rapidly changing CNS signs e.g. hyperreflexia followed by hyporeflexia or changing plantar response.

Some children may appear to be mildly affected initially only to lapse into coma and die suddenly. In others high fever, violent convulsions interspersed with bizarre movement, hallucinations alternating with brief periods of clarity followed by complete recovery. Death usually occurs in the first week.
### Table 4. Characteristics of common viruses causing encephalitis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Peak Groups</th>
<th>Peak Season</th>
<th>Clues in Presentation</th>
<th>Epidemiological Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>Infants, young Children</td>
<td>Summer, Fall</td>
<td>Exanthem, myopericarditis, conjunctivitis, pleurodynia, Hand-foot mouth disease, herpangina</td>
<td>Known epidemic</td>
</tr>
<tr>
<td>Mumps</td>
<td>5-9 yrs, M&gt;F</td>
<td>Late winter, early spring</td>
<td>Parotitis, orchitis, oophoritis, pancreatitis, hyperamylasemia It most commonly presents 5 days after parotitis.</td>
<td>Known exposure to mumps, recent vaccination</td>
</tr>
<tr>
<td>JE virus</td>
<td>Children&lt;15 yrs</td>
<td>In northern India may-oct, Southern India July-December</td>
<td>3 stages, seizures and parkinsonian features common, polio like flaccid paralysis</td>
<td>Known epidemic</td>
</tr>
<tr>
<td>HSV-1,2</td>
<td>All age group, 1 more common in adult, 2 more common in neonate</td>
<td>All season</td>
<td>Fever, hemi cranial headache, Language and behavioral, memory impairment, seizure.</td>
<td></td>
</tr>
</tbody>
</table>

**Late stage:** About 1/3rd recover normal neurological function. Residual neurological impairment includes speech defects, aphasia, paresis and intellectual deficit. Localized paresis is more common and upper limb is commonly involved.\(^7\)

**Atypical presentation of JE:** Presents with only brief period of altered sensorium and may be diagnosed as atypical febrile seizures. Some present with a short duration of altered behavior and few present with acute flaccid paralysis like illness as initial presentation.

**Herpes simplex encephalitis:** Due to injury to frontal or temporal cortex or limbic system HSV encephalitis is characterized by anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations and focal seizures.

**Measles encephalitis:** Symptoms of encephalitis begin 1-8 days after the appearance of rash but can be delayed for 3 weeks. Onset is abrupt with lethargy or obtundation that rapidly progress to coma. 50% develop GTCS. Usually associated with hemiplegia, ataxia and involuntary
Table 5. Stages of TBM (British medical Council, staging of TBM)\textsuperscript{10}

**Stage I (Prodromal stage):** No definite neurological symptoms at admission or in the history before admission. The symptoms are nonspecific with few or no clinical signs of meningitis. The patient remains fully conscious and alert. It usually spans 2-3 weeks. Recent history of whooping cough or measles usually present.

**Stage II (Stage of meningeal irritation):** Signs of meningitis, drowsiness or lethargy, cranial nerve palsies, focal neurological deficit, focal or generalized convulsions.

**Stage III (Stage of local or diffuse cerebral involvement):** Severe clouding of consciousness, stupor or coma, convulsions, gross paresis or paralysis. Sign and symptoms of raised ICT become more obvious. Multiple cranial nerve palsies (usually II, III, IV, VI, and VII) are present. Untreated, the disease usually lasts for about 4 weeks.

Table 6. Diagnosis of TBM (AIIMS, Dept. Of Pediatrics)\textsuperscript{10}

Demonstration of acid fast bacilli in the CSF or fulfillment of the following criteria:

**Essential:** CSF showing predominant lymphocyte pleocytosis $> 50/mm^3$, protein $> 60$ mg\%, sugar $< 2/3^{rd}$ of blood sugar.

**Supportive:** Along with the essential ones, two or more of the following clinicoinvestigational criteria:

- History of fever of two weeks or more.
- Generalized lymphadenopathy.
- Positive radiological evidence of tuberculosis elsewhere in the body.
- Isolation of AFB from gastric lavage or other sites.

- Positive family history of TB.
- Mantoux test (5TU $> 10$ mm).
- CT scan evidence of basal exudates or CNS tuberculosis.
- Histologically proven tubercular adenitis.

Movement disorder. There is a chronic form named sub acute sclerosing panencephalitis.$^1$

In children presenting with features of encephalitis, always rule out post-infectious or post- immunization encephalitis or encephalomyelitis (e.g. acute disseminated encephalitis [ADEM]), and encephalopathy (e.g. secondary to metabolic disturbance, anoxia, ischemia, organ dysfunction), which is defined by a disruption of brain function in the absence of a direct inflammatory process in the brain parenchyma. ADEM is a monophasic illness, a febrile illness or immunization often precedes the neurological syndrome and varies according to the precipitant (e.g. 1-14 days after vaccination and $< 1$ week after the appearance of rash of exanthematous illness). Fever is usually absent
at the onset of neurological illness and patient presents with multifocal neurological signs affecting the optic nerves, brain and spinal cord. 

**Acute bacterial meningitis:** The onset has two prominent patterns

i. Sudden onset with rapidly progressive manifestations of shock, purpura, DIC, reduced level of consciousness progressing to coma or death within 24 hours ii. More often, meningitis is preceded by several days of fever accompanied by non-specific findings like fever, anorexia, poor feeding, headache, symptoms of URTI, myalgia, arthalgia and various cutaneous signs like petechiae, purpura or erythematous macular rash followed by non-specific signs of CNS infection such as lethargy and irritability.

Manifestations of bacterial meningitis depend on the age of the patient. Infants typically have non-specific findings and may be subtle, they usually present with vomiting, diarrhea, poor appetite, a bulging fontanel (30% cases), an altered level of consciousness (usually lethargy, irritability) and hyperactive or hypoactive deep tendon reflexes.

Older children complain of headache that is described as being severe, generalized, deep seated and constant, accompanied by nausea, vomiting, anorexia and photophobia. On examination they exhibit signs of meningeal irritation more reliably.

Focal neurological signs are common and more frequently associated with cranial neuropathies. They include hemiparesis, quadripareisis, visual field defects, cortical blindness, ataxia, deafness, vestibular nerve dysfunction.

Focal or generalized seizures are present in 20-30% cases. Seizures are more common in children with meningitis caused by S.pneumoniae and H.influenze compared with children with meningococcal meningitis. Petechiae and purpura or a diffuse nonspecific maculopapular rash are more common in patients with meningococcal meningitis. Papilledema can be present in all ages; its absence must not be taken as proof that the ICP is normal because of the acuity of the meningitis process.

**Partially treated bacterial meningitis:** Occasionally during the early phase of the illness, before symptoms suggest meningitis, a child receives oral or rarely parenteral antibiotics for a presumed or identified focus of infection outside the CNS. After the antibiotics have been started, the child exhibits meningeal signs or other symptoms suggestive of CNS infection. This can be differentiated with the help of CSF analysis.

**Tuberculous meningitis:** Typically TBM is characterized by global encephalopathy with focal deficit. Diagnosis is based on clinical, CSF analysis and other bacteriological results (Table 5).

TBM is most common in children between 6 months to 6 years of age. The most common age group is 9 months to 3 years. Risk factors for TBM include age < 5 years, contact with an adult suffering from TB, PEM grade III and IV and HIV infection. Classically TBM evolves through three stages (Table 6) and spans a period of 3-4 weeks after the onset of meningeal symptoms.

TBM may have some atypical presentation such as asymptomatic onset, other resembling enteric fever and yet another onset with severe convulsions, paralysis, tumour type, spinal type onset and bronchopneumonia, abdominal pain, or hydrocephalus as presenting features.

**Complicated enteric fever:** It is common in multi drug resistant salmonella typhi and usually
occurs in children who remain untreated for 2 weeks or more. Neurological complications occur in two forms. Typhoid state (Typhoid encephalopathy): It is an acute toxic confusional state characterized by disorientation, delirium and restlessness progressing to coma. Delirium is the earliest neurological symptom observed. Typhoid meningitis: Usually seen in children less than 5 years of age. It mimics pyogenic meningitis. Convulsions are unusual in enteric fever but cerebral ataxia is one of the commonest neurological manifestations.11

**Brain abscess:** Presence of focal neurological signs in such cases, along with risks factors brain abscess should always be ruled out. The early stages of cerebritis and abscess formation are associated with nonspecific symptoms. The significance of these symptoms is generally not recognized and an oral antibiotic is often prescribed with resultant transient relief. With progression of disease vomiting, severe headache, seizures, papilledema, focal neurological signs and coma may develop.2

A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting and headache. If it ruptures into the ventricular system, overwhelming shock and death usually ensure.

**Laboratory investigations**

**For etiologic diagnosis**

1. **Peripheral blood smear** for diagnosis of malaria, its species and percentage of parasitemia (% of RBC infected). Light microscopy of well stained thick and thin films by a skilled microscopist has remained the gold standard for malaria diagnosis. Once negative, sample should be examined for at least 3 consecutive days where clinical suspicion of malaria persists.12

2. **Rapid diagnostic tests (RDT) for malaria:** They detect plasmodia specific antigens (HRP-II and pLDH) in blood. If blood smear is positive for malaria parasite there is no need to do RDTs. They are indicated in far away communities where patient have poor access to health care facilities and microscopic examination is not possible, for early and rapid diagnosis of malaria where the risk of serious disease is more if there is delay in diagnosis and treatment, in severe and complicated malaria peripheral parasitemia may be negative due to sequestration.12

3. **Lumbar puncture and CSF analysis:** This is the most important investigation in such cases, unless there is contraindication.4 Contra indications of LP are elevated ICP owing to a suspected mass lesion of the brain or spinal cord, symptoms and signs of pending cerebral herniation, critical illness and platelet count less than 20,000/mm.3

   Look for CSF pressure, glucose, protein, cell count and differentiation, gram staining, LDH, ADA and culture and sensitivity (Table 7). If history and physical examination indicate, a portion of CSF should be sent for viral (PCR or antibody) studies (HSV1 and 2, enterovirus).

**Important points regarding CSF analysis**

1. Normally CSF contains no RBC and its presence indicate traumatic tap or subarachnoid hemorrhage. Centrifuged immediately, supernatant of a bloody tap is clear, but it is xanthrochromic in subarachnoid hemorrhage.4

2. CSF protein is increased after a bloody tap by 1mg/dL for every 1,000 RBC/mm³. Traumatic tap affects the leukocytes and protein level, although Gram stain, culture, glucose level may not be influenced.4

3. Two biochemical markers are important. First is CSF adenosine deaminase (ADA); sensitivity is 60-100% and specificity is
Table 7. CSF findings in various CNS disorders associated with fever\textsuperscript{8}

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pressure (mm H\textsubscript{2}O)</th>
<th>Leukocytes/mm\textsuperscript{3}</th>
<th>Protein (mg/dl)</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>50-80</td>
<td>&lt;5; 75% lymph</td>
<td>20-45</td>
<td>&gt;50 mg/dl or 60% of blood glucose</td>
</tr>
<tr>
<td>Acute Bacterial Meningitis</td>
<td>Elevated</td>
<td>&gt;1000, 75-95% PMN; in 20% it is &lt;250\textsuperscript{2}</td>
<td>100-500</td>
<td>Depressed, usually&lt;40 mg/dl</td>
</tr>
<tr>
<td>Partially treated Bacterial Meningitis</td>
<td>Normal or ↑</td>
<td>↑; PMN usual but mononuclear predominate if pretreated for extended period</td>
<td>100+</td>
<td>Depressed or normal</td>
</tr>
<tr>
<td>Tubercular Meningitis</td>
<td>Usually ↑; May be low due to block in advanced stages</td>
<td>10-500; PMN early but lymphocytes predominate through most of course</td>
<td>100-500; may be higher in presence of block</td>
<td>&lt;50 mg/dl usual in most cases; ↓ with time if treatment is delayed</td>
</tr>
<tr>
<td>Fungal Meningitis</td>
<td>Usually ↑</td>
<td>25-500; mononuclear cells predominate except PMN early.</td>
<td>25-500</td>
<td>&lt;50 mg/dl usual in most cases; ↓ with time if treatment is delayed.</td>
</tr>
<tr>
<td>Viral meningitis Or Meningoencephalitis</td>
<td>Normal or slightly ↑</td>
<td>PMN early; rarely &gt;1000; mononuclear cells predominate during most of course</td>
<td>50-200</td>
<td>Generally normal; may be ↓ to&lt;40 mg/dl in various viral diseases, particularly mumps(15-20%)</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>Usually ↑</td>
<td>10-200; fluid rarely acellular; lymphocyte predominant; if abscess ruptures into ventricles PMNs predominant and cell count may &gt;100,000\textsuperscript{2}</td>
<td>75-500</td>
<td>Normal unless abscess ruptures into ventricles</td>
</tr>
<tr>
<td>Cerebral malaria\textsuperscript{6}</td>
<td>↑</td>
<td>Minimal or no pleocytosis</td>
<td>↑</td>
<td>Normal</td>
</tr>
</tbody>
</table>
84-99%. Its level is usually higher compared to other forms of meningitis. Various studies have a cut-off point between 7-11.3 IU/L. It provides supportive evidence in favor of TBM but should not be taken in isolation.\(^9\)

2nd is CSF-lactate dehydrogenase (LDH). Total LDH level > 100U/L is strongly suggestive of bacterial meningitis, level between 30-100U/L is suggestive of TBM, Level below 30U/L suggests either viral or tubercular meningitis and LDH isoenzymes help to distinguish the two. LDH3 and 4 are increased in TBM.\(^10\)

4. Gram staining is important, positive in 70-90% untreated cases and it depends upon the CSF concentration of bacteria. When the bacterial concentration is 10\(^3\) CFU/ml the chance of positivity is 25%, 60% when between 10\(^3\) to 10\(^5\) CFU/ml; it is 97% when level is >10\(^5\) CFU/ml.\(^13\)

5. PMNs are not normally found in the CSF of infants and children; more than one PMN/µl should be considered abnormal.\(^2\)

6. The CSF picture of TBM mimicked by partially treated bacterial meningitis. In such situation CSF can be repeated after 48-72 hours of treatment with a fresh set of broad spectrum potent antibiotics to evaluate changes in clinical status as well as in CSF. During this time effort should be made to establish the diagnosis by collecting evidence using PPD, chest X-ray, bacteriological diagnosis.\(^9\)

4. Radiological evaluation: CT scan prior to lumbar puncture should be reserved for children who show signs suggesting herniation or who may have an intracranial mass causing signs and symptoms similar to meningitis.\(^8\) MRI being more sensitive and specific but in its absence CT scan brain with or without contrast is useful (Table 8).

5. EEG: It indicates cerebral dysfunction in early stage of encephalitis. It helps in etiological diagnosis. In > 80% of patients with herpes simplex encephalitis, there is temporal focus showing periodic lateralizing epileptiform discharge. These stereotypical sharp and slow wave complexes occur at intervals of 2-3 and typically seen on days 2-14 after symptom onset.\(^14\)

Frontal triphasic sharp waves are seen in patients with hepatic, uremic and other metabolic encephalopathies. In JE EEG changes are non-specific and include diffuse theta and delta waves, burst suppression, epileptiform activity and alpha coma. The generalized changes in an EEG help in differentiating JE from herpes encephalitis.\(^7\)

It has a role in identifying patient with non-convulsive seizure activity who is confused, obtunded or comatose\(^7\). The severity of abnormal EEG findings does not usually correlate with the extent of disease in the acute phase, but rapidly improving EEG findings often indicate a good prognosis.

6. Immunological tests

JE: i. Detection of JE virus, antigen or genome in tissues, blood or other body fluid by immunofluresence or by PCR. ii. JE virus specific IgM in CSF and blood by IgM capture Elisa. iii. Four fold or greater rise in JE virus specific antibody in paired sera through IgM/IgG by ELISA.\(^7\)

Herpes simplex virus: i. isolation of virus or antigen or viral DNA by PCR is more specific and sensitive. ii. HSV IgM is unreliable. iii. Four fold or greater increase in HSV IgG titers between acute and convalescent serum is only useful in retrospect. iv. An initially negative CSF PCR may be repeated if clinical and or radiological features suggest herpes simplex encephalitis after 3-7 days later on a second
### Table 8. CT/ MRI scan findings in various conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>CT scan/ MRI Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBM</td>
<td>Reveals basal enhancement; hydrocephalous with or without peri-ventricular ooze; tuberculoma (s); or infarcts especially in basal ganglia, thalamus and internal capsule(^9).</td>
</tr>
</tbody>
</table>
| ABM                | Not routinely indicated in proven cases, done when there is focal neurological deficit or when brain abscess or subdural effusion is suspected. Two pattern of meningeal enhancement is seen\(^15\)  
1. A pattern of patchy meningitis appears as diffuse linear thickening of the normal dural lining.  
2. Leptomeningeal pattern of enhancement, where there is enhancement seen along the pia-arachnoid membranes, following the sulcal groove.  
Subdural effusion is crescentic collections which are isodense to CSF on CT scan and isointense to CSF on MRI.  
Subdural abscess can be crescentic or lentiform when large and slightly denser than CSF on CT. A rim of enhancement of variable thickness is better detected on MRI. |
| JE                 | Involvement of thalamus, basal ganglia, mid brain, pons and medulla. MRI shows extensive hyper intense lesions of the thalamus, cerebrum, and cerebellum. MRI is more sensitive than CT in detection of these lesions\(^7\). |
| Herpes simplex     | Mainly fronto-temporal areas are involved beyond neonatal period, in neonates there is global involvement. Bilateral temporal lobe involvement is nearly pathognomonic but a late development\(^14\). |
| ADEM               | Multiple focal or confluent areas signal abnormality in subcortical white matter, sometime subcortical gray matter. Lesions are enhancing and display similar stages of evolution\(^14\). |
| Brain abscess      | Parenchymal low- density lesion in the stage of cerebritis. Abscess cavity shows a ring-enhancing lesion by contrast CT. MRI is more diagnostic, reveals abscess capsule\(^15\). |

**Note:** Normal CT scan does not rule out TBM and in case of strong clinical suspicion, a repeat follow-up CT scan few days may show newly developing lesions\(^9\).
CSF specimen. In this instance, a negative CSF PCR result may allow discontinuation of acyclovir therapy. Presence of < 10 WBCs/mm³ in the CSF has been associated with a higher likelihood of a negative CSF PCR.¹⁴

**Other viral causes:** PCR can detect varicella zoster virus DNA, although a negative test does not exclude the diagnosis. PCR is also of value for detection of cytomegalovirus, with a high sensitivity and specificity for CNS infection. Epstein-Barr virus can be detected by PCR, although a positive result does not necessarily denote CNS infection, because latently infected mononuclear cell can cause a false positive result¹⁴.

7. **For suspected complicated typhoid fever:** Widal test, blood culture (positive in 40-60%) can be done. Complete hemogram also provides information, usually there is pancytopenia. But in some cases total count may be as high as 20,000-25,000/mm³. Thrombocytopenia may be a marker of severe illness.

8. **Blood culture:** It is useful in acute bacterial meningitis and typhoid fever. It is positive in two-third cases of ABM and should be done in all cases, particularly when LP cannot be done or is traumatic. Rates of positivity for clinically diagnosed cases of TBM range from 25-70%, but take 6-8 weeks for growth. Recently introduced BACTEC system detects the growth within 8-14 days.¹⁰

**Other investigations**

1. Hb%, TCS, DLC, Platelet count: Typhoid fever and cerebral malaria may be associated with severe anemia and thrombocytopenia.

2. Random blood sugar, Serum Na+, K+, and Ca++: RBS is needed to be interpreted with CSF glucose. Hypoglycemia and electrolyte imbalance are usually associated with central nervous system infection and they may contribute to altered sensorium.

3. Serum creatinine, blood urea to assess the renal function.

4. Serum bilirubin and fraction, SGPT, SGOT and Prothrombin time if jaundice is present.

To conclude, every effort must be made to find out the cause as most of the conditions are treatable and early intervention affects the long term prognosis.

**Points to Remember**

- **Causes of fever with altered sensorium may vary according to geographic area.**
- **Acute bacterial meningitis Cerebral malaria, viral encephalitis, TBM and complicated typhoid fever are common causes.**
- **Light microscopy of thick and thin film remains the gold standard for the diagnosis of malaria.**
- **Every effort must be made for diagnosis as most of the conditions are treatable and early intervention affects the long term prognosis.**
- **Child presenting with features of viral meningitis or meningoencephalitis, ADEM must be rule out as management is different for these two conditions.**
- **CSF ADA is highly specific for TBM, but should not be taken in isolation.**
- **MRI is superior to CT scan with or without contrast in such cases.**
- **CT scan brain is not routinely indicated in a proven case of acute bacterial meningitis, but done when complications are suspected.**
References


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**CLIPPINGS**

*Sublingual immunotherapy for allergic rhinitis (including hay fever)*

In reviewing 60 trials, we found a significant reduction in symptom and medication scores in patients treated with sublingual immunotherapy compared to placebo. There were no serious adverse reactions reported in the included trials and no patient needed the use of adrenaline. This updated Cochrane Review therefore reinforces the conclusions of the earlier review in confirming the efficacy and safety of sublingual immunotherapy.

GLYCOPEPTIDES IN PEDIATRIC PRACTICE

* Jeeson C Unni

Abstract: The glycopeptides, notably vancomycin, have traditionally been the mainstay of treatment of MRSA but overuse has led to the emergence of vancomycin-intermediate and vancomycin-resistant MRSA (VISA and VRSA, respectively). Although the mechanisms underlying vancomycin resistance are not yet fully understood, changes to the bacterial cell wall-the site of action of the glycopeptides, are believed to be the key. Recent evidence also supports the transfer of genetic material among bacteria as contributing to the development of VRSA. Teicoplanin is equally effective and has a better safety profile.

Keywords: Glycopeptides, Vancomycin, Teicoplanin, VRSA, VISA, GRE.

Glycopeptide antibiotics are a class of antibiotic drugs. The class is composed of glycosylated cyclic or polycyclic nonribosomal peptides. Significant glycopeptide antibiotics include vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin and decaplanin. Vancomycin and teicoplanin are the two glycopeptides that have been used clinically for the treatment of multidrug-resistant infections that are caused by gram-positive organisms. Vancomycin, isolated in 1956 from the actinomycete Streptomyces orientalis is the more widely used glycopeptide in pediatrics.¹ Teicoplanin, extracted from Actinoplanes teichomyceticus, was discovered in the early 1990s, is widely used in Europe but not approved in the United States.²

Vancomycin’s molecular structure is made up of a seven-membered peptide chain and two sugar moieties, vancosamine and glucose.³ As penicillinase-producing staphylococci emerged in 1958 vancomycin use increased. However, when methicillin became available 2 years later, clinicians began using this drug instead of vancomycin. This was partly due to the cost factor and mainly due to toxicity of fermentation byproducts of early vancomycin preparations. With the emergence of methicillin-resistant Staphylococcus aureus (MRSA) led to a resurgence of interest in vancomycin therapy.⁴ However, several newer classes of antibiotics, including linezolid of the oxazolidinone class and daptomycin of the lipopeptide class have proven to have activity against MRSA.⁵

Teicoplanin is more lipophilic than vancomycin,⁶ as it has more fatty acid chains. It is considered to be 50 to 100 times more lipophilic than vancomycin. Teicoplanin has an increased half life compared to vancomycin, as well as having better tissue penetration. It can be two to four times more active than vancomycin, but it does depend upon the organism. Teicoplanin is more acidic, forming water soluble salts, so it can be given intramuscularly. Teicoplanin is much better at penetrating into leucocytes and phagocytes than vancomycin.
Teicoplanin has a longer half-life than vancomycin, it can be given once daily as an intravenous bolus or by intramuscular injection.7

**Mechanism of action**

Vancomycin and teicoplanin exhibit concentration-independent bactericidal activity by the inhibition of bacterial cell wall synthesis. They inhibit the synthesis of peptidoglycan, the major component of the cell wall of gram-positive bacteria. This mechanism of action is unusual in that it acts by binding precursors of peptidoglycan, rather than by interacting with an enzyme. The binding interaction involves the peptide portion of vancomycin and the terminal D-alanine-D-alanyl peptide portion of the peptidoglycan precursor.8 This mechanism of action does not readily permit mutation to resistance. Because â-lactams inhibit cell wall biosynthesis in the third phase, there is no cross-resistance between the drugs and no competition for binding sites. Vancomycin requires actively growing bacteria to exert its effect and is capable of injuring protoplasts by altering the permeability of their cytoplasmic membrane and selectively inhibiting RNA synthesis.9 Vancomycin exhibits minimal concentration-dependent killing action, but a moderately long in vitro postantibiotic effect.10

**Antimicrobial spectrum and clinical indications**

Vancomycin and teicoplanin are the glycopeptides of clinical use in pediatrics. They are active against an extremely broad range of gram positive organisms but afford no gram negative cover. They are used to treat staphylococci, including MRSA, coagulase negative staphylococci, streptococci, enterococci and clostridia. Glycopeptide resistant coagulase negative staphylococci (especially teicoplanin resistant) and enterococci are becoming important pathogens in hospital acquired infections. MRSA with reduced susceptibility are also being reported.

Vancomycin should be reserved for the treatment of multi-antibiotic resistant staphylococci 2,11 and coagulase negative staphylo coccal septicaemia12, and as prophylaxis against endocarditis.13 Oral vancomycin is the second line agent for treating pseudomembranous colitis.14 Metronidazole is, however, as effective for treating pseudomembranous colitis. It is cheaper and does not risk promoting emergence of glycopeptide resistant enterococci. Vancomycin or teicoplanin have become important agents used in combination with other antibiotics when initiating therapy for infections caused by various access devices (eg, central venous catheters, ventriculoperitoneal shunts) because of its activity against coagulase-negative staphylococci.15 It is also used in bacterial meningitis because of its activity against penicillin-nonsusceptible S pneumoniae, and in selected episodes of febrile neutropenia because of the possibility of resistant viridans streptococci.16

**Vancomycin in comparison to teicoplanin**

A meta-analysis of trials comparing the efficacy and safety of teicoplanin and vancomycin suggested that teicoplanin is as effective as vancomycin for treating MRSA infections. Side effects were less in the teicoplanin-treated group.17 Systematic reviews have shown that teicoplanin is not inferior to vancomycin with regard to efficacy for the treatment of suspected or proven infections and is associated with a lower adverse event rate than vancomycin.18,19

Study of the distribution of teicoplanin and vancomycin resistant strains among coagulase negative staphylococci (CONS) have shown that teicoplanin is less effective than vancomycin
against CONS and the most resistant strain is S. hemolyticus.\textsuperscript{20,21} However a recent study found teicoplanin was more effective against CONS.\textsuperscript{22}

Teicoplanin is very effective in preventing experimental streptococcal, enterococcal, and staphylococcal endocarditis and may be an attractive alternative antibiotic in patients allergic to β-lactams, especially in the outpatient setting.\textsuperscript{23,24}

Teicoplanin appears to be the best choice for treatment of Clostridium difficile-associated diarrhea because the available evidence suggests that it is better than vancomycin for bacteriologic cure and has borderline superior effectiveness in terms of symptomatic cure.\textsuperscript{25}

**Pharmacokinetics**

In general, vancomycin is only administered intravenously although oral administration is important in the treatment of some GI infections such as pseudomembranous colitis. Oral bioavailability of vancomycin is too low to treat systemic infections; serum concentrations are often undetectable even when inflammatory lesions are present. Vancomycin is not administered intramuscularly due to severe pain at the injection site. Systemically administered vancomycin is distributed into most body tissues and fluids including pericardial fluid, pleural fluid, ascitic fluid, synovial fluid, urine, peritoneal dialysis fluid, and atrial appendage tissue. Concentrations obtained in tissues and fluids are variable and somewhat dependent on the degree of inflammation present. Thus vancomycin penetrates only inflamed meninges.\textsuperscript{26} There is no apparent metabolism of vancomycin. Excretion is mainly by glomerular filtration, with about 80% of the drug excreted in 24 hours in the urine and only small amounts excreted in the feces. In patients with normal renal function, vancomycin has a serum half-life of about 4-6 hours. The 24-hour area under the curve (AUC)-MIC ratio is probably the most important pharmacokinetic-pharmacodynamic parameter correlating with the efficacy of vancomycin.\textsuperscript{27} Blood level monitoring is required - approximate time to steady state is 1-2 days. Suggested sampling times for levels at fourth dose is the trough immediately prior to next dose and post dose (peak) 1 hour after completion of infusion. Therapeutic levels are trough 5-10mg/L and peak 18-26mg/L. For CSF level monitoring trough sample immediately prior to next dose needs to be taken. However, wide variability and poor consensus was noted with regard to post-dose vancomycin assay sampling times, target ranges and what constituted a toxic level.\textsuperscript{28}

Teicoplanin is not absorbed orally, but intravenous and intramuscular administration are well tolerated. Teicoplanin is eliminated predominantly by the kidneys and only 2 to 3% of an intravenously administered dose is metabolised. Total clearance is 11 ml/h/kg. Steady state is reached only slowly, 93% after 14 days of repeated administration. Elimination is triexponential, with half-lives of 0.4 to 1.0, 9.7 to 15.4 and 83 to 168 hours. Volumes of distribution are 0.07 to 0.11 (initial phase), 1.3 to 1.5 (distribution phase) and 0.9 to 1.6 (steady state) L/kg.\textsuperscript{29} Following bolus administration of single 400mg intravenous doses, concentrations likely to be inhibitory to susceptible bacterial strains have been reported in blister fluid, gall bladder wall, bile, tonsils, cartilage, mucosa, liver, pancreas and bone; lower concentrations were achieved in fat, skin and cerebrospinal fluid.

**Dosage**

Vancomycin\textsuperscript{30} - Newborn - IV 15mg/kg/dose <28 wk once daily, 29-35 wk twice daily and > 35 wk 3 times daily. Intrathecal all newborn 2.5-5mg once daily.
Child IV 15mg/kg loading dose followed by 10mg/kg/dose 4 times daily. (max 2gm/day). Intrathecal 1month-4yr 5mg, 4-15yr 10mg and > 15yr 20mg once daily. Children with enlarged ventricles need higher doses. Adjust dose according to CSF levels aiming for a trough level of < 10mg/L.

Teicoplanin - High loading doses reduce the delay to attaining therapeutic concentrations. Newborn - loading 16mg/kg and 24hr later start maintenance 8mg/kg/day as single dose; children 10mg/kg/dose 12 hourly x 3 doses and then once daily in same dose for severe infection and 6mg/kg/day once for moderate infection.

Orally for pseudomembranous colitis 10mg/kg/dose 2 times daily.

It may be given intra-ventricular and intra-peritoneal route also.

Administration

Vancomycin - IV: intermittent infusion is the preferred method of administration though continuous infusion has been used when intermittent infusion is not feasible. Vancomycin on reconstitution 500mg powder displaces 0.3ml; for IV administration add 9.7mL Water for injections to give a 50mg in 1 ml solution. No displacement volume for non-proprietary products; for IV administration add 10mL Water for injections to give a 50mg in 1mL solution. Further dilute with NaCl 0.9% or glucose 5% to give 5mg in 1mL, which is infused over at least 1 hour. In fluid restricted patients maximum concentration is 10mg in 1mL, infused centrally over at least 1 hour.

The powder should be stored below 25°C. After reconstitution it may be stored in the fridge for 24 hours. Inspect for particulate matter and discolouration prior to administration.

Oral: The injection may be given orally. Common flavoring syrups may be added to the solution at the time of administration. Solutions of the parenteral powder intended for oral use may be stored in a fridge (2-8°C) for 96 hours.

Teicoplanin: Teicoplanin may be given either IV or IM. The injection vial should be reconstituted with 3.2ml of water for injections from the ampoule supplied. This will provide a solution of 400mg or 200mg in 3ml as excess is included in the vial. Roll the vial gently until the powder is completely dissolved. Excessive agitation may lead to foaming. If this occurs, allow to stand for 15 minutes. Give as an IM, slow IV injection or by IV infusion over 30 minutes. Further dilute if required in 0.9% NaCl, 5% glucose or 0.18% NaCl/4% glucose.

Drug interactions

Concurrent use of other potentially nephrotoxic drugs, such as aminoglycosides and amphotericin B requires careful monitoring. Concurrent administration of vancomycin and anesthetic agents has been associated with erythema, histamine-like flushing and anaphylactoid reactions. No specific interactions are known for teicoplanin and there is no evidence of synergistic toxicity with other neurotoxic or nephrotoxic agents. However, monitoring of renal and auditory function is advised when such combinations are used.

There is continued research on whether glycopeptides and β-lactam antibiotics have a synergistic effect or not in the treatment of glycopeptide resistant bacteria.

Resistance

The first clinical isolate of S. aureus with reduced susceptibility to vancomycin was reported in 1996 from Japan. The vancomycin minimum inhibitory concentration (MIC) result reported for this isolate was in the intermediate range (vancomycin MIC=8 μg/mL). By 2002,
eight patients with clinical infections caused by vancomycin-intermediate S.aureus (VISA) were confirmed in the United States. The same year, the first documented case of infection caused by vancomycin-resistant S.aureus (VRSA) (vancomycin MIC >32 μg/mL) was reported there. Vancomycin-resistant enterococci (VRE) is another disturbing development. There have been reports to the CDC of a 25 fold increase in glycopeptide-resistant enterococci (GRE) in the US over the 4 years from 1989 to 1993. Though true and intermediate resistance are being reported, the more common phenomenon is probably that of heteroresistance, where there exists a variability of vancomycin susceptibilities among subpopulations of a single isolate; a scenario where the majority of the population are susceptible to vancomycin (<4 µg/mL) and a minority are resistant. Fortunately, as with penicillin resistant S pneumoniae, VISA and VRSA are rare thus far in India.

Five genotypes of acquired glycopeptide resistance have been documented in enterococci, with vanA and vanB being the most globally widespread and prevalent. The VanA (vancomycin and teicoplanin resistant) and VanB (vancomycin resistant; teicoplanin susceptible) phenotypes are encoded by a gene that is easily transferable between enterococci by conjugation. The transfer and expression of these genes from enterococci to S aureus achieved experimentally is cause for concern as this portends the possibility of multi-resistant staphylococcal strains becoming a major public health problem.

The factors associated with emergence of glycopeptide-resistance include current or recent vancomycin use, gastrointestinal tract colonization by GRE, duration of hospital stay, proximity to patients who are infected by GRE, intrahospital transfer of patients between wards or floors, prior use of certain broad spectrum antimicrobials (antianaerobes), location in an intensive care unit, hemodialysis, ventilator, catheter and other invasive device use, large hospital size and intra-abdominal surgery.

Effective screening directed at those patients considered to be most at risk should therefore be a priority. The treatment options available for these infections are now severely compromised and thus new classes of antimicrobial agents effective against MRSA, VISA and VRSA are urgently required.

**Adverse reactions**

The “red man” syndrome is a nonimmunologically mediated histamine release associated with rapid infusion of vancomycin. Clinical signs and symptoms include pruritis, erythema and flushing of the upper torso, angioedema and occasionally, hypotension. Slow administration (for at least 1 hour) and the administration of prophylactic antihistamines given two hours prior to infusion can protect against the development of this side effect. It has been reported even with oral vancomycin supposedly due to significant absorption of vancomycin that may occur in neutropenic patients with normal renal function.

A rapid bolus of vancomycin can also result in painful muscle spasms. Ototoxicity occurs when serum levels of vancomycin are excessively high but rarely occurs when peak serum levels are 40 to 50 µg/mL or less. Deafness may be proceeded by tinnitus and high-tone hearing loss. Nephrotoxicity is similarly rare when vancomycin is used alone and at conventional dosages (eg, 1 g every 12 hours). It is more likely to occur in patients with high troughs (average >15 mg/L) and those receiving concomitant furosemide in the intensive care unit.

Teicoplanin has a more favourable safety profile and this could affect choice between
it and vancomycin.\textsuperscript{49,50} Nephrotoxicity is significantly less likely to occur during treatment with teicoplanin than vancomycin when an aminoglycoside is being given concurrently. “Red man” syndrome is extremely uncommon with teicoplanin. Rash and fever can be dose-related phenomena but patients reacting to one glycopeptide may not react to both. Although thrombocytopenia is more frequent with teicoplanin, it is reversible and seldom seen at standard doses.

**Newer glycopeptides**

Dalbavancin, oritavancin and telavancin are semisynthetic lipoglycopeptides that demonstrate promise for the treatment of patients with infections caused by multi-drug-resistant Gram-positive pathogens.\textsuperscript{51} All three lipoglycopeptides contain lipophilic side chains, which prolong their half-life, help to anchor the agents to the cell membrane and increase their activity against Gram-positive cocci. In addition to inhibiting cell wall synthesis, telavancin and oritavancin are also able to disrupt bacterial membrane integrity and increase membrane permeability; oritavancin also inhibits RNA synthesis. Enterococci exhibiting the VanA phenotype (resistance to both vancomycin and teicoplanin) are resistant to both dalbavancin and telavancin, while oritavancin retains activity. Dalbavancin, oritavancin and telavancin exhibit activity against VanB vancomycin-resistant enterococci. Both dalbavancin and telavancin are active against VISA, but display poor activity versus VRSA. Oritavancin is active against both VISA and VRSA. The long half-life of these newer molecules allows once-weekly dosing for dalbavancin, one dose per treatment course for oritavancin and once-daily dosing for telavancin. Clinical trials involving patients with complicated skin and skin structure infections (cSSSIs) have demonstrated that all three agents are as efficacious as comparators.\textsuperscript{51,52}

**Points to Remember**

- **Glycopeptide antibiotics must be reserved for the treatment of MRSA, coagulase negative staphylococci, enterococci and clostridia.**
- **It may be used for prophylaxis against endocarditis**
- **Oral vancomycin is the second line agent for treating pseudomembranous colitis**
- **Emergence of VRSA and VISA needs monitoring in India**
- **Vancomycin should be given slow IV twice daily; Teicoplanin could be given as IM/IV in a once-daily schedule**
- **Teicoplanin is as effective ac vancomycin and has a better safety profile**

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(XXXI Annual National Convention of National Neonatology Forum)

**Date:** 15th - 18th December, 2011  **Venue:** Chennai Trade Center, Chennai

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NEONATAL VESICULO PUSTULOSIS
- AN APPROACH

* Anandan V

Abstract: Vesiculo pustular lesions are common in new borns; various etiologies, namely infectious and non-infectious which may be benign or serious and can be associated with systemic features. Clinical features are subtle. Correct diagnosis and management are essential.

Keywords: Papules, Vesicles, Pustules, Erosions, Ulcers.

Eventhough vesicopustules are commonly seen in newborns, it is one of the much debated subject as far as the approach is concerned. This article will mainly discuss the causes, diagnosis and appropriate management, since some of the conditions if missed might endanger life of the newborn. The exact epidemiological and statistical data regarding these problems are not accurately available.

Classification

A methodical and simple approach for better understanding and proper management is given in Table 1.

Eventhough the classification is broad, the discussion will be narrowed to a fine beam which will highlight the essential clinical features, necessary investigations and the best treatment available as on date.

Non–infectious conditions

1. Erythema neonatorum

Benign, self limiting, common in full terms described in at least 30% of the full term newborns. Usually occurring on the 2nd day of life and may resolve by the 2nd week. Predeliction towards face, trunk, proximal arms and buttocks, usually sparing palms and soles. The diagnostic confirmation will be the Wright stain which reveals large number of eosinophils. Masterly inactivity is only required as far as treatment is concerned.

2. Miliaria

Miliaria is due to obstruction of the eccrine duct, which occurs in atleast 15% of neonates, more commonly in warm climates, in nurseries without airconditioning and in febrile infants. Miliaria crystallina is the most common type encountered which usually manifests as asymptomatic, 1-2 mm clear non-inflammatory vesicles without surrounding inflammatory halo in the first week of life, pre dominantly over the forehead, upper trunk and intertriginous areas. All stains will be negative but occasionally neutrophils can be visualized. Cool baths and proper ventilation is all that is required.

3. Transient neonatal pustular melanosis

The incidence is rated at 0.2 – 4% for all term newborns and is observed commonly in black infants. They clinically present as
# Table 1. Conditions presenting with vesicopustules

<table>
<thead>
<tr>
<th>Non infectious</th>
<th>Infectious</th>
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<tbody>
<tr>
<td><strong>Benign</strong></td>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td>Erythema toxicum</td>
<td>Neonatal candidiasis</td>
</tr>
<tr>
<td>Miliaria</td>
<td>Impetigo neonatorum</td>
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<tr>
<td>Transient neonatal pustulosis</td>
<td>Scabies</td>
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<tr>
<td>Eosinophilic pustular folliculitis</td>
<td></td>
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<tr>
<td>Acropustulosis of infancy</td>
<td></td>
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<tr>
<td><strong>Serious</strong></td>
<td><strong>Serious</strong></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Bacterial: Staph, Strepto, Klebseilla, E.coli, Chlamidia, Listeria, Pseudomonas</td>
</tr>
<tr>
<td>Herpes gestationis</td>
<td>Viral – Cytomegalic, Herpes, Varicella</td>
</tr>
<tr>
<td>Incontinentia pigmenta</td>
<td>Spirochaetes- Syphilis</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>Fungal – Congenital candida</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
<td></td>
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<tr>
<td>Epidermolysis bullosa</td>
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<tr>
<td>Epidermolytic hyperkeratosis</td>
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Vesicopustules at birth, without surrounding halo rupturing to produce a crust with collarette of scales, healing with post-inflammatory hyperpigmentation. Wright’s stain reveals neutrophils and no intervention is required.

## 4. Eosinophilic pustular folliculitis

This is an uncommon condition described in 1984 presenting as 1-3 mm sized yellowish crops of pustules predominantly over the face, scalp, trunk and extremities. The course may be waxing and waning, lasting to weeks, with occasional relapses. The child may be irritable due to intense pruritis. Wright’s stain reveals both eosinophils and neutrophils. Low potent topical steroids with antibiotics and antihistaminics are recommended therapeutic modalities. The systemic drugs which have been tried include dapsone, cimetidine and prednisolone.

## 5. Acropustulosis of infancy

It is chronic, recurrent, benign, pruritic vesicles and pustules occurring in the hands and feet, presenting at birth and may persist through out infancy. Commonly seen in males and in blacks. The mucosa is spared. The child will be irritable with disturbed sleep and refusal of feeds. Pustules might reveal neutrophils and eosinophils with peripheral eosinophilia. Topical corticosteroids, oral antihistamines and oral dapsone result in speedy recovery.

## 6. Incontinentia pigmenti

This is a rare X-linked dominant genodermatosis, usually lethal in males, presenting as firm, yellowish vesicles in linear streaks following “Lines of Blaschko”. The lesions are seen commonly over the limbs and maybe
associated with seizures in the neonatal period. Skin biopsy is a must to identify the disease.

7. Herpes gestations

This is an acquired autoimmune disorder with an estimated incidence of 1 in 10,000 pregnancies and only 2-11% will develop cutaneous manifestations. Transplacental passage of maternal immunoglobulin against the maternal basement membrane zone is responsible for the disease in the neonates. The clinical presentation may vary from papules, vesicles, pustules or even bullae in a herpetiform pattern presenting at birth and may resolve by one month of age. Wright’s stain predominantly shows eosinophils and a biopsy is a must to support the diagnosis. Therapy is symptomatic which includes wet compresses, topical antibiotics and prevention of secondary infection.

8. Bullous dermatosis

Autoimmune bullous dermatitis like pemphigus vulgaris and mecononobullous disorders like epidermolysis bullosa presents with bullae with or without mucus membrane involvement and with varying degrees of nail involvement. Skin biopsy is a must to confirm the diagnosis and the condition may necessitate the usage of systemic steroids, antibiotic and saline wet compresses to bring it under control. Remissions and relapses are encountered.

Infectious conditions

1. Neonatal scabies

Scabies is caused by Sarcoptes scabiei and is rare in neonatal period and has been reported as early as 9 days clinically presenting itself as pruritic papules, vesicles, pustules and nodules any where in the body including palms and soles. Burrows are pathognomonic of scabies. Skin scraping and demonstration of mite and its products confirms the diagnosis.

2.5% topical sulphur precipitate is preferred in a neonate or LBW babies and 5% permethrin in infants.

2. Impetigo neonatorum

Bullous Impetigo neonatorum is the commonest infection seen in NICU especially in a premature baby presenting commonly in the 2nd week of life in the neck creases, periumbilical areas and perineum. Since the disease extension is very fast early aggressive treatment with systemic drugs is imperative.

3. Congenital and neonatal candidiasis

Candida is the most common fungal pathogen in a neonate acquired either vertically or horizontally. Congenital candidasis presents itself on the very first day of life as diffuse erythematous macules, papules, vesicles and pustules on an erythematous base occurring anywhere in the body sparing oral cavity and diaper area. It presents as desquamating dermatitis with ecchymosis and necrosis in VLBW. Swab cultures confirm the diagnosis and responds well to topical anti fungals or oral fluconozole.

Candida infection in an otherwise sterile body fluids (eg. blood) is termed as systemic candidiasis which has an incidence of 2-4% in VLBW infants clinically presenting similar to congenital candidiasis but this also involves diaper area and has systemic symptoms like apnea, bradycardia, hypotension, abdominal distention, hyperglycemia and leukemoid reactions.

Simple investigations like skin scraping for KOH mount will demonstrate pseudohyphae and spores. Nystatin solution (100000 units/ml) topically over the oral mucosa 4 times /day for one week cures oral thrush. In most severe and serious cases systemic amphotericin-B in the dose of 0.5mg/kg/day for 14-21 days is most promising.
4. Congenital toxoplasmosis

Cutaneous manifestations of congenital toxoplasmosis is rare but 14-25% symptomatic infants presents with maculopapular punctate eruptions, petechiae, ecchymosis, blue berry muffin lesions and calcinosis cutis anywhere in the skin sparing the mucosa and heal with desquamation. Classical systemic associations are chorioretinitis, hydrocephalus, seizures, microcephaly and intra cranial calcification. The diagnosis is by parasite isolation, antigen detection and PCR.

The best treatment will be pyrimethamine (1mg/kg/day), sulphadiazine (100mg/kg/day) and folic acid (2mg/kg/day) for 3 weeks followed by spiramycin (50-100mg/kg/day) for 4-5 weeks.

5. Rubella

20-50% of the babies having neonatal rubella do have cutaneous manifestations and the most common presentation would be blue berry muffin spots, sometimes hemorrhagic changes due to thrombocytopenia may give these lesions a cranberry muffin appearance. These lesions might present at birth or little later and can present up to 8 weeks. The other associations that are reported are recurrent urticaria, cutis marmorata, seborrhoea, hyperpigmentation and necrosis of the inner enamel epithelium of the teeth. Viral cultures, antigen identification and increase in IgM antibodies >20mg/dL will help to make a confident diagnosis. Supportive management is all that is required.

6. Cytomegalo virus disease

5-10% of the affected neonates have cutaneous manifestations. Of that, the commonest presentation would be petechiae and blue berry muffin spots appearing on the 2nd day of life. PCR for CMV-DNA is highly sensitive test for the evaluation of newborns. Ganciclovir, a nucleoside analog has been tried to suppress the CMV disease.

7. Neonatal herpes simplex

The incidence is rated at 1-2.5/5000 live births and 4.5% of the affected neonates manifest with skin lesions like vesicles, bullae, erosions, absence of skin over scalp and scars over the face, trunk and extremities oral ulcerations are also reported in 1/3rd of the cases. Tzanck smear is a rapid test for early diagnosis, but viral culture is the gold standard test. Treatment of choice would be IV Aciclovir (15mg/kg/day/in 3 div.doses/7-10 days).

8. Neonatal varicella

The rash of neonatal varicella is usually seen between 9-15 days, vesicles may be discrete or grouped and could be hemorrhagic. Tzanck smear, viral cultures, direct fluorescence antibody test and PCR will be helpful for diagnosis. VZIG 125 units should be given to the neonates born to a mother who has developed varicella from 5days before and 2days after delivery to reduce the incidence of neonatal varicella by 50%. The specific treatment will be IV aciclovir 15-20mg/kg/in 3 div.doses/5 days.

9. Neonatal congenital syphilis

40-50% of the affected will present with muco cutaneous lesions which might be annular, erythematous, maculopapular or papulosquamous seen predominantly over the face posterior trunk, palms, soles and diaper areas in the 1st week of life and may persist for several weeks if untreated. Desquamatic dermatitis has also been reported. Other less common skin lesions are vesicles, pemphigus syphiliticus, pustules, erosions, ulcerations and petechiae. Hemorrhagic vesiculo bullous lesions over palms and soles are considered to diagnostic of
congenital syphilis. Muco cutaneous lesions include snuffles, condylomata, vesicles bullae, erosions, palatal perforation and rhagades which usually occurs between 2-6 weeks of life.

The IgM FTA-ABS test is specific and the treatment of choice is aqueous crystalline penicillin G for 10-14 days.

10. Neonatal HIV

Skin and mucus membrane disease is extremely common in infants with HIV.26 Wide spread protracted seborrheic dermatitis could be the first clue for the diagnosis. Cutaneous diseases of infectious etiology with atypical and prolonged presentations posing difficulties in treatment should arise suspicion of neonatal HIV. PCR is very sensitive. ART could be suggested if the diagnosis is established.

Conclusion

Eventhough vesiculo pustules may look very simple in a newborn it could be due to for a life threatening infection which may prove fatal unless and otherwise properly identified and treated correctly. Hence let us not see things but notice what we see.

Points to Remember

- **Vesiculo bullous lesions can be due to a variety of infectious and non-infectious condition.**

- **Thorough knowledge of the subject will help us to make a confident diagnosis.**

- **Some of the conditions especially of infectious etiology may prove fatal.**

References


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Sri Ramachandra Medical College & Research Institute,
No 1 Ramachandra Nagar, Porur, Chennai 600161
SELLAR TUMORS

* Vijayalakshmi G
** Malathy K
*** Venkatesan E
**** Elavarasu MD

The sella is a depression in the sphenoid bone and contains the pituitary gland. The sphenoid sinus lies below and anterior to the sella turcica. The suprasellar cistern with the optic chiasma form the superior structures. Posteriorly, there is the basilar artery and the brain stem while the cavernous sinus and its contents lie laterally.

The pituitary gland consists of the anterior lobe and the posterior lobe which are anatomically, functionally and radiologically distinguishable.

Embryologically the anterior lobe is formed from an invagination of the oral ectoderm called the Rathke’s pouch. The posterior pituitary is formed from a protrusion of the neural ectoderm from the diencephalon. In between is the vestigial intermediate lobe which is a common site for the Rathke cleft cysts. Histologically the neurohypophysis or the posterior lobe consists of axon bundles and glial tissue. The adenohypophysis or the anterior lobe contains distinct cells which secrete specific hormones. The acidophilic cells secrete growth hormone and prolactin. The basophilic cells secrete TSH, FSH, LH and ACTH. The chromophobes are not secretory and are thought to be degranulated acidophils and basophils.

MR is the imaging of choice for the pituitary gland. Thin sections (2mm or 3mm) targeted to the pituitary fossa in both the sagittal and coronal planes are used for good visualization of the gland. CT does not provide such excellent soft tissue resolution as MR but can be a very useful investigation if MR is not possible and also if it is important to identify the presence of calcification in or around the sella. CT study should also use thin 1mm slice thickness in the axial plane and then reconstruct in the sagittal and coronal planes. The pituitary gland along with the pituitary stalk and cavernous sinuses are all vascular structures which enhance after contrast injection. The optic chiasma and hypothalamus, however, do not show enhancement. A microadenoma may show delayed enhancement. Fig.1 is a CT image of a densely enhancing pituitary mass.

Radiologically (MRI) too, the anterior lobe appears different from the posterior lobe. The signal intensity of the anterior lobe is similar to cerebral white matter while the posterior lobe is hyperintense in T1 images due to the presence of vasopressin and phospholipid. The anterior lobe may be hyperintense in pregnancy and neonates due to hypertrophy and high protein synthesis.
Fig. 1. Enhancing pituitary tumor – CT

Fig. 2. Note the optic chiasma stretched over a pituitary macroadenoma

Fig. 3. Pituitary macroadenoma. Note the constriction. (arrow)

Fig. 4. Craniopharyngioma - CT
Pituitary adenomas are rare sellar tumors. They are slow growing. Unlike adults, non-functioning adenomas are rare in children. Most pituitary tumors present after age twelve and the most frequent type of adenoma is prolactinoma. Prepubertally, the commonest is corticotropinoma. The microadenoma is less than 1 cm. and is a tumor of adulthood. These tumors do not expand the sella and 75% of them are functional. Macroadenomas are greater than 1 cm and may extend above the sella or expand the sella. Later, they can erode the floor of the sella and extend into the sphenoid sinus. The optic chiasma just above the sella is often compressed or stretched (Fig.2) giving rise to visual disturbances. Further superiorly they can protrude into the suprasellar cistern, into the recess of the third ventricle and then into the third ventricle.

Pituitary macroadenomas are isodense or hypodense to brain and enhance variably. Calcification is rare. In MRI, they are hypointense in T1 images and though they enhance, it is to a lesser extent than the surrounding normal gland. In T2 they are hyperintense. Fig.3 is a pituitary macroadenoma in a 22 year old. This is a flair sequence (Fluid attenuation inversion recovery- type of T2 image with fluid suppression) that nulls the appearance of fluid. Both CSF and tumors are hyperintense in T2 images. If fluid intensity is nulled, CSF in the ventricles and cisterns is black while the solid tumor is white and brought out in high contrast. The diaphragma sella is the membranous dura that covers the cup shaped depression of the sella. The pituitary stalk passes through an opening in the diaphragma sella to the hypothalamus. The enlarging pituitary adenoma, being benign in nature, passes through this existing opening. Since it is a soft tumor it undergoes a characteristic constriction (arrow in Fig.3) at this opening giving it a snowman or figure of 8 appearance. This feature helps in distinguishing pituitary adenoma from a meningioma which will not show any constriction. Meningiomas near the sella can also cause constriction of the internal carotid artery while pituitary adenomas with vascular encasement do not constrict the artery. The chiasmatic glioma is isointense or hypointense and is seen separate from the pituitary gland.

The other sellar tumor is craniopharyngioma which arises from squamous cell rests from the Rathke’s pouch. Craniopharyngiomas are ten times more frequent in children, than pituitary adenomas.

Fig.4 is a predominantly cystic sellar mass with multiple, thick, nodular calcifications in the periphery. Calcifications as well as cyst formation are common and important features of craniopharyngioma in contrast to the macroadenoma. They can also have enhancing solid components along with the non-enhancing cystic areas. In MRI, they are hypointense in T1 and hyperintense in T2 but there may be hyperintensities in T1 sequences due to the presence of cholesterol crystals. They tend to invade nearby vascular structures. Although craniopharyngiomas may arise at any time in life, there is a bimodal peak in incidence at 5–14 years of age and again after the age of 50. The histological type varies in both age groups. The adamantinomatous type occurs in children. Although histologically benign, these tumors can be aggressive, sending papillae that invade surrounding bony structures and tissues. This makes total excision difficult and recurrence rate very high. The adult type is the squamous type and they are more solid, do not have calcifications and recurrence is rare.

Other rare sellar lesions are meningiomas, epidermoid and dermoid cysts and aneurysms.
**CASE STUDY**

PANTOTHENATE KINASE ASSOCIATED NEURODEGENERATION

* Usha Rani Singh  
** Ajai Pratap Singh

Abstract: Pantothenate kinase neurodegeneration (PKAN), or neurodegeneration brain with iron accumulation (NBIA) describes a group of progressive extrapyramidal disorders with radiographic evidence of focal iron accumulation in the brain, usually in the basal ganglia. We report a case for its rarity and interesting features.

Key words: Dystonia, Eye of tiger sign.

Hallervorden and Spatz first described the disease in 1922 as a form of familial brain degeneration characterized by iron deposition in the brain. Symptoms include progressive dystonia, dysarthria, ballismus, choreoathetosis, spasticity, dementia and pigmentary retinal degeneration, with corticospinal tract involvement.\textsuperscript{1,2} Until recently the diagnosis depended upon classical clinical features and MRI abnormalities. Zhou, et al linked it to a defect in PANK2 gene on the short arm of chromosome 20 (20p13.2).\textsuperscript{2}

**Case Report**

A 12 years old girl, born of 3\textsuperscript{rd} degree consanguineous marriage, with normal physical and mental development until the age of 10 years, presented with a history of progressive involuntary movements for 2 years. Her 9 years old brother is healthy.

Her illness started with dystonia of left arm, followed by abnormal movements of trunk and limbs. These were intermittent at first, but soon became continuous. For the last one year she is bed ridden. They disappear during sleep and increase in the presence of strangers. There was history of head banging when annoyed.

She looked alert, wasted and was having dysarthria. Cranial nerves were normal. Examination of motor system revealed variable tone and constant dystonic movements involving the trunk and limbs with grossly abnormal posturing (Fig.1). Deep tendon reflexes were brisk and plantar reflexes were extensor bilaterally. It was difficult to examine her as she kept moving constantly. She would flex her neck, spine and knees and would roll over in a slow somersault.

Investigations: Relevant investigations were as follows:

S. ceruloplasmin: 45mg/dL (18-45); serum copper: 129 mg/dL (50-120); Slit lamp examination: K F ring absent; Fundus was normal. Iron studies (serum iron & TIBC) and liver function tests were within normal limits. MRI brain showed bilateral symmetrical altered...
signal intensities in both basal ganglia (which appear hyperintense in T1 weighted images), consistent with metabolic changes (Fig. 2). We could not find any centre in India that offers facilities for prenatal/ genetic diagnosis of this defect.

Our patient did not respond to benzodiazepine, dopaminergic drugs or baclofen, which were all tried for several months. Her parents could not afford botulinum toxin, hence it was not tried.

**Discussion**

PKAN is a rare autosomal recessive disorder. To date only seven cases have been reported from India. Using linkage analysis, Zhou, et al defined an interval on chromosome 21p13 that contains the gene for PANK2.

Major causes of dystonia include perinatal asphyxia, kernicterus, generalized primary dystonia, dopa-responsive dystonia; drugs, Wilson disease, Huntington disease, Leigh Syndrome and Juvenile neuronal ceroid lipofuscinosis. These were excluded by clinical findings and investigations. She had the typical “eye of the tiger” sign on MRI brain. This virtually pathognomonic radiographic abnormality comprises hyperintensities within a hypointense medial globus pallidus on T2-weighted images. Hayflick, et al have shown that all patients with mutations in PANK2 had the specific pattern known as the “eye of the tiger”. No PANK2 mutation-positive patients lacking the eye of the tiger sign have been found. The reciprocal was also found to be true; no evidence of the eye of the tiger pattern was found in any of the mutation negative patient. Gregory, et al reviewed 123 patients from 98 families and found retinopathy in 68%, optic atrophy and acanthocytes in 3% and psychiatric symptoms in 30% of cases. More than 50 different mutations have been identified in patients with NBIA.
PKAN has been divided into the characteristic type (average onset at 3 years), and an atypical form with onset in the second decade (between 10 and 30 years). The latter has slower progression and retinopathy is rare. Patient presents with psychiatric disturbances. Our patient seems to be of the atypical variety, with no retinopathy or dementia, though some violent behavior was noticed by the parents.

Pantothenate kinase is an essential regulatory enzyme in coenzyme A (CoA) biosynthesis from pantothenate (vitamin B₅). CoA plays a central role in intermediary and fatty acid metabolism. In PKAN, a deficiency of PANK2 is thought to result in mitochondrial accumulation of cysteine and cysteine-containing substrates, which may undergo rapid auto-oxidation in the presence of iron, leading to free radical production and lipid peroxidation and resulting in cell death. Whether iron accumulation is the cause or effect is not known.

Treatment is symptomatic. The prognosis is universally poor, with death from medical complications within 10-20 years of onset.

References

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