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Approach to Asymptomatic HBsAg Positive Child

*Riyaz A

Abstract: Hepatitis B is an important cause of mortality and morbidity, especially in the developing countries. More than 2 billion people have evidence of past or current infection. 90% of neonates and 30% of children exposed to the virus tend to become chronic carriers. In this article, the clinical profile and fate of asymptomatic HBsAg carriers are discussed.

Key words: HBsAg carriers, Genotypes, Cirrhosis, Hepatocellular carcinoma.

Hepatitis B (HB) is one of the world’s leading causes of mortality and morbidity. It is endemic throughout the world, especially in the developing countries. Its prevalence varies from country to country and depends upon a complex mix of behavioural, environmental and host factors. In general, it is lowest in countries or areas with high standards of living. Hepatitis B virus (HBV) is a 42 nm partially double stranded DNA virus belonging to the Hepadnaviridae family and is classified as hepadnavirus type I. It relies on a replicative strategy unique among DNA viruses but typical of retroviruses.

The first epidemic of HB was described in 1883, in people who had received small pox vaccine. In 1942, 28,000 soldiers who were given yellow fever vaccine containing human serum, developed hepatitis. In 1943, Beeson described the first case of post-transfusion hepatitis. Samuel Barb Blumberg from Philadelphia discovered HBsAg in 1965, from the serum of an Australian aborigine. Hence it was initially referred to as the ‘Australia antigen’. This epoch-making discovery, though serendipitous, made it possible to screen blood donors for hepatitis B and also to find out a vaccine against hepatitis B. Blumberg was later awarded the Nobel Prize in medicine for this discovery in 1976. In 1970, Dane described the hepatitis B virus. In 1971, HB core antigen and antibody were identified. In 1983, the structure of hepatitis B virus genome was described. The plasma derived vaccine was available from 1982 and the recombinant DNA vaccine from 1984. More than 130 countries have incorporated HB vaccine in their immunization program now.

HB is highly infectious as the infective dose is extremely minute (0.00001 ml blood), but each ml of infected blood contains 500 μg HBsAg and 10 trillion viral particles. It is a global problem, with 66% of the world population living in areas with high levels of infection. More than 2 billion people have evidence of past or current infection. There are more than 350 million chronic carriers of the virus in the world and over one million deaths per year. 75% of chronic carriers live in Asian countries. India has been placed by WHO under the intermediate zone (2-7%) for HBsAg prevalence along with other South Asian countries, Eastern European countries, the Middle East and some South American countries. There are about 45 million HBsAg carriers in our country, out of which 10 million are positive for HBeAg also. This may actually be an underestimation. More number of
people are likely to be identified due to the increasing awareness of HBsAg and routine HBsAg screening in executive health check up programs, blood donors, people seeking employment abroad and for admission to professional courses.

HB virus has been classified into 8 genotypes(A-H) based on intergroup divergence of 8% or more in the complete nucleotide sequence. The distribution of HBV genotypes may vary with time and population migration. B and C are the predominant genotypes reported from Asia. The genotype B is associated with spontaneous HBeAg seroconversion at a younger age, less active liver disease, and a slower progression to cirrhosis compared to genotype C. Hepatitis flares are rare in these patients; chance of hepatocellular carcinoma (HCC) is also less. The shorter duration of high level HBV replication and less active necro-inflammation may contribute to the better outcome in patients with genotype B.

Genotypes A and D have been described from Western Europe and North America. Genotype D is predominant in the Mediterranean region, the Middle East and Central Asia. Limited data from India suggest that genotypes A and D are most prevalent but their relation to severity of the disease is not clear.

Genotyping of HBV may remain a research tool unless we prove that it can predict the risk of adverse outcomes or can influence decision making in management.

HBV has a remarkable tropism for hepatocytes; replication in the infected hepatocytes produces a large excess of HBsAg, which can be found in the circulation as spherical or tubular forms. HBsAg is the first antigen to appear in the blood about 1 month after infection, and it usually disappears by 6 months. After it disappears, antibody to HBsAg (anti-HBs) which is protective, appears in the serum and persists indefinitely thereafter. HBeAg is the second antigen to appear and it disappears earlier than HBsAg by 3 months. Its persistence beyond the first 3 months of acute infection may be predictive of the development of chronic infection. The presence of HBeAg in chronic HB is associated with ongoing viral replication, infectivity and inflammatory liver injury.

The manifestations of hepatitis B infection can be quite varied. In inapparent hepatitis the patient is asymptomatic, while in anicteric hepatitis the patient has all the features of hepatitis, except jaundice. Chronic hepatitis can produce a range of sequelae, varying from very little liver damage to cirrhosis with all its complications. HCC is a risk of long-standing chronic hepatitis B infection.

Chronic hepatitis is more common when infection is acquired in the perinatal period and is therefore more frequent in areas of the world where the disease is highly prevalent and feto-maternal spread is common.

The frequency of HB infection in sporadic acute hepatitis as shown in the various studies is more or less uniform over the last 10 years. Panda, et al in a multicentre study of children between 1-15 years showed that the frequency of infection increased with age from 11.5% in children less than 5 years to 57.5% in more than 10 years. Thapa, et al have also documented an increasing incidence of HB infection with age. In Thyagarajan’s study, the HBsAg positivity in children below 15 years ranged from 1.3 - 12.7%, while in adults it was 3.3-8.6%. A multicentre study by Tandon, et al reported a positivity rate of 2.5% in children below 1 year, 2.3% between 1-3 years and 1.6% between 4-5 years. The risk of acquiring infection for a neonate can be as high as 90%, if the mother is also HBeAg
positive. However, the risk is only 10-15% if the mother is HBeAg negative and anti-HBe positive.

Asymptomatic HBsAg carriers were previously labelled as hepatitis B carriers and used to be clubbed with patients with active liver disease, who had either chronic hepatitis or active cirrhosis. It is now known that the natural history of this group of patients is different.

**Natural history of HBV infection in children**

The immune system of the host, HBV genotype, age of the patient and route of acquisition of the virus are important factors that determine the natural history of HBV infection. Almost 90% of neonates exposed to the virus become chronic carriers. However, only 10% of adults and 30% children become carriers. As in adults, in children also the outcome of chronic HBV infection depends on the severity of the liver disease at the time HBV replication is arrested.

HBV infection is basically a dynamic process with replicative and nonreplicative phases based on virus-host interactions. The first phase is the immunotolerant phase seen usually with perinatal infection. Here, the patient is asymptomatic, ALT levels are normal or mildly elevated and histological activity is minimal. These suggest that the immune response against the virus is very weak. This phase is characterized by high levels of serum HBV DNA. Both HBsAg and HBeAg are positive.

After a variable duration, the patient enters the second immunoactive phase when the tolerogenic effect is lost due to unknown reasons. Here, the HBV DNA levels are low, ALT levels high and histological activity is increased. These imply immune-mediated lysis of infected hepatocytes. This phase has a variable duration lasting from months to years.

The third non-replication phase occurs after HBeAg disappears, anti-HBe becomes positive and there is a marked reduction of serum HBV DNA. The characteristic features of this phase are normal levels of ALT and resolution of hepatic necroinflammation. This phase is called inactive carrier state. Inactive HBsAg carriers form the largest group of chronic HBV infected patients.

This phase may last for a lifetime. During this stage, HBV DNA is low but may still be detectable by sensitive methods like PC31 in serum and more often in the liver. If the patient becomes immunosuppressed following cancer chemotherapy or prolonged steroid therapy, there may be reactivation of HBV and reappearance of HBeAg and high levels of HBV DNA.

Inactive HBsAg carrier state is diagnosed by the demonstration of HBsAg for more than 6 months and absence of signs and symptoms of liver disease. The other features are absence of HBeAg, presence of anti-HBe and undetectable or low levels of HBV DNA with PCR-based assays (HBV DNA < 10,000 copies/ml). ALT levels are repeatedly normal and liver biopsy shows minimal or no necroinflammation, slight fibrosis or even normal histology. Inactive cirrhosis may be present in patients who had active liver disease during the replicative phase of infection.

Two studies from India have described the profile of patients with asymptomatic chronic HBV infection. In the first study, out of the 157 incidentally detected asymptomatic HBsAg carriers, only 45% were HBeAg positive. In 71% patients with raised transaminases, the histological activity index was > 3, as compared to only 36% of patients with normal transaminases. Inactive carriers who were HBeAg positive and who had normal transaminases were more likely to have a
Fig. 1. Natural history of hepatitis B infection
significant histological lesion than those who were anti-HBe positive.\textsuperscript{8}

In another study from Mumbai, out of 58 asymptomatic HBsAg carriers, 48 (83\%) were HBeAg negative and transaminases were normal in 44. Of the 10 patients who were HBeAg positive, transaminases were high in 5. The liver histology was normal in those with normal transaminases. On a follow up of 12 months, all patients with normal transaminases continued to have normal liver function tests.\textsuperscript{9}

In a long term follow up study of HBsAg carriers with normal transaminases in Canada, it was found that only 2\% had advanced liver disease in the form of cirrhosis or chronic hepatitis. The commonest finding in patients with normal histology is the presence of ground glass hepatocytes with minimal portal tract inflammation. These patients have an excellent prognosis and a very low risk of development of cirrhosis and HCC.\textsuperscript{10}

Thus, there are three categories of inactive HBsAg carriers:

(i) HBeAg positive and anti-HBe negative
(ii) HBeAg negative and anti-HBe, positive and
(iii) both HBeAg and anti-HBe negative. Majority of Indian patients belong to the second group.

The prognosis of the inactive HBsAg carrier state is usually good. Long term follow up of these patients up to 18 years has shown that the vast majority of them have sustained biochemical remission. They are at a very low risk of developing cirrhosis or HCC. However, rarely, even non cirrhotic patients may develop HCC during the inactive HBsAg carrier state.

Approximately 20-30\% of inactive HBsAg carriers may undergo spontaneous reactivation of hepatitis B during follow up. Multiple episodes of reactivation or sustained reactivation can cause progressive hepatic damage and even hepatic decompensation and may sometimes mimic acute viral hepatitis. Acute flares of hepatitis should be differentiated from super infection with other hepatotropic viruses. Almost 20-30\% of these acute exacerbations may be caused by super infection with HAV, HEV or HCV, which may increase the risk of fulminant hepatic failure.\textsuperscript{11} Treatment with hepatotoxic drugs (antiTB drugs, NSAIDs, antiepileptics) may also cause acute flare ups.

Some carriers eventually become HBsAg negative and develop anti-HBs. The incidence of delayed HBsAg clearance has been estimated to be 1-2\% per year in the West where HBV infection is usually acquired in adulthood. However, if the infection is acquired perinatally or in early childhood as in developing countries, the clearance is only 0.05-0.8\% per year. HBsAg clearance is more in women than men, and in older than in younger carriers. Prognosis is improved by the loss of HBsAg as liver disease is usually inactive and nonprogressive. However, HBsAg clearance does not completely prevent decompensation or HCC in patients who have already developed cirrhosis.

Recommendations for management of an inactive HBsAg carrier\textsuperscript{12,13}

1. Patients and their parents should be reassured that treatment is usually not required.

2. Family members should be screened for HBsAg and anti-HBs, if negative they should be vaccinated and the success of vaccination should be tested by anti-HBs assay.

3. The possibilities of reactivation and super infection with other viruses should be discussed with patients and their parents. They should be advised to come for follow up if there is jaundice, malaise or increased fatigue.
4. All these children should be given the full course of Hepatitis A vaccination.

5. All hepatotoxic drugs should be avoided as far as possible.

6. Adolescents should avoid alcohol consumption

7. They should be regularly followed up at every 6-12 months intervals with transaminase levels, as fluctuations in ALT and HBV DNA levels are common during the course of chronic HBV infection.

8. Adolescents should not be allowed to donate blood, organ or semen.

9. Close monitoring is required and prophylactic lamivudine therapy should be given if undergoing chemotherapy or receiving immunosuppressive medications.

10. HBsAg should be checked every year to see if the patient has cleared the antigen.

11. HBeAg testing: if a person remains HBsAg positive, HBeAg should be checked every year. This latter test will demonstrate in most cases if the virus is actively replicating. A person who is HBeAg positive or has an ALT more than 200 should be evaluated for the need for liver biopsy and anti-viral treatment.

12. Yearly physical and laboratory evaluation to ensure that the patient is healthy without overt evidence of severe liver disease. This should include evaluation of routine liver biochemistry (ALT, alkaline phosphatase) and liver function (bilirubin, albumin, prothrombin time) tests.

13. Hepatitis B education. Each hepatitis B carrier should receive hepatitis B education, as should his/her household members.

Points to Remember

• In developing countries, HB is acquired mainly by perinatal transmission. This is responsible for the vast majority of chronic HBV infection and its complications like cirrhosis and HCC.

• A significant reduction in chronic HB infection and its complications can be achieved by preventing perinatal HB infection.

• The long term prognosis of inactive HBsAg carriers who are HBeAg negative and anti-HBe positive is good.

• Universal immunization is recommended as the best solution to decrease the prevalence of the disease.

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**CLIPPINGS**

**Different methods of manipulation for reducing pulled elbow in young children**

Pulled elbow is a dislocation of the elbow joint in a young child which is usually caused by an adult or taller person, suddenly pulling or tugging on the child’s arm when it is straight; or when a child pulls away from an adult impulsively. The child immediately complains of pain and cannot use their arm.

Treatment usually consists of manipulating the arm to get the bones of the elbow back into their correct position. It is usually treated by manual intervention. In the typical manoeuvre, called supination, the forearm is twisted or rotated outwards (palm of child’s hand faces upwards), sometimes followed by bending of the elbow. While this has become standard practice, it is not always successful. Other methods, particularly the use of pronation, where the forearm is twisted or rotated inwards (palm of child’s hand faces downwards), have also been used. These methods are generally safe, although bruising can occur and they can be painful.

Evidence from three small, low quality trials involving a total of 313 participants indicates that the pronation method (with the hand downward) is more successful in repositioning and less painful for children with a pulled elbow.


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CURRENT STATUS OF PROBIOTICS IN CLINICAL PRACTICE

*Arun Shah

Abstract: There has been renewed interest in clinical application of probiotics in recent past. Large number of randomized trials have shown probiotics with specific strains are useful in viral diarrhea and prevention of antibiotic associated diarrhea. The use of probiotics in clinical conditions other than diarrhea is also very promising. However more studies are warranted to evaluate their efficacy before mass application.

Key words: Probiotics, Biotherapeutic agents, Infective diarrhea, Antibiotic associated diarrhea.

Probiotics are live microbes beneficial to human health and nutrition. WHO definition of probiotics as living organisms when administered in adequate amounts conferring health benefits to host is the most accepted definition. They are supplement to maintain the normal microflora of the gut. The word probiotic is derived from a Greek word meaning “for life”

Different types of probiotics

Bacterial probiotics

- Lactobacilli - Lactobacillus rhamnosus, L.casei, L.acidophilus, L.bulgaricus, L.sporogenes, Bacillus clausi, L.planotorum.
- Bifidobacteria - bifidum, longum, infantis, lactis etc.
- Streptococcus thermophilus
- Yeast - Saccharomyces boulardii (Non Human)

Mechanism of action

They work by multiple mechanisms by antagonizing pathogens, by production of antibacterial substances such as bacteriocin, by competitive inhibition for space and nutrients, by lowering gut pH, by production of lactic acid, acetic acid and butyric acid making gut environment unfavorable for growth of pathogens, by tropic effect on intestinal mucosa, by immuno modulation and immuno stimulation (specific and non specific), by enzyme induction increasing brush border enzyme activity especially disaccharidases, by cementing junction between enterocytes and by maintaining balance between pro-inflammatory and anti inflammatory cytokines.

It should be noted that all probiotics are not the same. Each probiotic has a specific biotherapeutic activity and differs in its characteristics, also there is a strain specificity.

Clinical indications

1. Probiotics and infectious diarrhea

Gut flora is disturbed during diarrhea. Meta-analysis of 23 double blind randomised placebo controlled trials comparing a specific probiotic agent with placebo in patients with acute diarrhea presumed to be caused by an
infectious agent shows reduced risk of diarrhea at 3 days (RR: 0.77; 95% CI: 0.55-0.77) and reduced mean duration of diarrhea by 30.48 hours. Another meta-analysis of 9 RCTs suggests that probiotic treatment of children with infectious diarrhea, mainly Lactobacillus rhamnosus GG and Saccharomyces boulardi induces reduction of diarrhea duration of 0.7 days (95% CI: 0.3-1.2 days) and reduction of diarrhea frequency of 1.6 stools on day 2 of treatment. Thus probiotics appear to be useful adjunct to ORS and zinc in treating acute infectious diarrhea in children.2-4

2. Probiotics and antibiotic associated diarrhea (AAD)

Gut flora is disturbed during and after treatment with antibiotic. Meta-analysis of 9 RCT suggests that probiotics mainly Saccharomyces boulardi, Lactobacillus rhamosus GG and lactobacillus mixtures can be used to prevent antibiotic associated diarrhea. Pooled data from all 9 trials was in favor of active treatment over placebo in the prevention of AAD. However further data are needed. The evidence for beneficial effects is still not definitive.5

Newer indications

Necrotising enterocolitis: Clinical trials have shown that probiotic supplementation reduces the risk of necrotizing enterocolitis in preterm neonates of less than 33 weeks gestation. A systematic review of randomized controlled trials also indicated a reduced risk of death in probiotic treated groups. In summary, there is strong support for the use of certain probiotic strains in preterm infants.6

Inflammatory bowel disease

Pouchitis: There is good evidence for the usefulness of probiotics for the prevention of the initial attack of pouchitis, and in the prevention of further relapse of pouchitis after the induction of remission with antibiotics. Probiotics can be recommended to patients with pouchitis of mild activity or as maintenance therapy for those in remission.7

Ulcerative colitis: The probiotic E.coli Nissle strain may be equivalent to mesalazine in maintaining remission of ulcerative colitis. There are inadequate studies to be certain that other probiotic preparations are effective in ulcerative colitis.8,9

Crohn’s disease: Studies of probiotics in Crohn’s disease have been disappointing, and a recent Cochrane systematic review concluded that there is no evidence to suggest that probiotics are beneficial for maintenance of remission in Crohn’s disease.10

Irritable bowel syndrome

Several studies have demonstrated significant therapeutic gains with probiotics in comparison with placebo. A reduction in abdominal bloating and flatulence as a result of probiotic treatments is a consistent finding in published studies; some strains may ameliorate pain and provide global relief (B. infantis 35624) in addition. Lactobacillus reuteri may improve colicky symptoms within one week of treatment, as shown in a recent trial with 90 breastfed babies with infantile colic. In summary, there is literature evidence suggesting that certain probiotics may improve the principal symptoms in persons with IBS.11

Allergy

The strongest evidence is for the prevention of atopic dermatitis when certain probiotics are administered to pregnant mothers and new borns up to 6 months of age. However, a recent clinical trial did not confirm these results. With regard to the treatment of allergic disease, a few well-
designed studies have provided evidence that specific probiotic strains can be effective in the treatment of a subset of patients with atopic eczema. Little is known about the efficacy of probiotics in preventing food allergy.\footnote{12}

**Lactose intolerance**

Streptococcus thermophilus and Lactobacillus delbrueckii subsp. bulgaricus improve lactose digestion and reduce symptoms related to lactose intolerance. This was confirmed in a number of controlled studies with individuals consuming yogurt with live cultures.\footnote{13}

**H. pylori infection**

Several lactobacilli and bifidobacterial strains, as well as Bacillus clausii, appear to reduce the side effects of antibiotic therapies and improve patient compliance. Several strains were effective in decreasing side effects, but did not have effects on the eradication rate. A recent meta-analysis of 14 randomized trials suggests that supplementation of anti-H. pylori antibiotic regimens with certain probiotics may also be effective in increasing eradication rates and may be considered helpful for patients with eradication failure. There is currently insufficient evidence to support the concept that a probiotic alone, without concomitant antibiotic therapy, would be effective. In summary, there is literature suggesting that certain probiotics may be helpful as adjuvant therapy with antibiotics in the eradication of H. pylori infection.\footnote{14}

**Hepatic encephalopathy**

Probiotics such as lactulose are commonly used for the prevention and treatment of this complication of cirrhosis. Minimal hepatic encephalopathy was reversed in 50\% of patients treated with a symbiotic preparations (four probiotic strains and four fermentable fibres, including insulin and resistant starch) for 30 days.\footnote{15}

**Prevention of colo-rectal cancer**

Probiotics possibly result in significant alteration in composition of the colonic bacterial ecosystem. They have shown inhibitory effect on development of aberrant crypts (precancerous lesions) and tumors in animal models. Other possible mechanism include alteration in metabolic activities of intestinal microflora, the binding and degrading of potential carcinogens, qualitative and quantitative alteration in intestinal microflora incriminated in producing carcinogens and enhancement of host immune response. Future research should focus to identify the specific strain responsible for anti tumour effect. There is a lot of evidence from studies on cell culture in vitro and animals that probiotics and synbiotics can exert anticancer effects. Until date little work has been conducted in humans. However extensive data showing anticancer activities from experiments in animals and isolated cell may be applicable to humans and thus more studies on human volunteers are warranted.\footnote{16}

**Safety profile of probiotics**

By and large probiotics are very safe. Occasionally constipation, increased thirst and flatulence are reported.

Bacteremia and endocarditis are reported in few cases who were immunosuppressed.

Fungemia has been reported with Saccharomyces especially in patients on CVP line.\footnote{17,18}

**Future of probiotics**

BMJ in 1991 in its editorial says “bacterial interference is an increasingly attractive approach to prevention and therapy.” In 1994 WHO deemed probiotics to be the next most important immune defense barrier when commonly prescribed antibiotics shall be rendered useless by antibiotic resistance and recommends
microbial interference therapy. With increasing understanding that the beneficial microbes i.e. probiotics are required for health they may become an important therapeutic tool for health care providers in near future.

There has been progressive increase in immune mediated and gut related health problem such as allergies, auto immune and inflammatory disease due to modern life style. Probiotics help to stabilize the immunological barrier by restoring the intestinal mucosal permeability by down-regulating proinflammatory cytokines.

**Conclusion**

There is sufficient grade “A” evidence for probiotics such as Lactobacillus rhamnosus GG and Saccharomyces boulardii in treatment of viral diarrhea and in prevention of antibiotic associated diarrhea in children. However more controlled studies are required in developing countries before its routine recommendation in diarrhea and AAD.

Various trials have shown clearly that efficacy is strain specific. Unfortunately bacterial probiotics available in Indian market does not mention about strain specificity.

Large number of clinical trials have shown promising results in inflammatory bowel disease, irritable bowel syndrome,lactose intolerance, prevention of colorectal cancer, necrotising enterocolitis, H. pylori infection and atopic diseases etc. However further well designed large randomized clinical trials are needed to define role of probiotics as therapeutic agents in clinical applications other than viral diarrhea and AAD. Dosage and duration of probiotics with specific strain needs further evaluation in different clinical conditions.

**Points to Remember**

- **Probiotics with specific strains have sufficient evidence in treatment of viral diarrhea and in prevention of antibiotic associated diarrhea.**
- **Bacterial probiotics available in Indian market do not mention about strain specificity, and hence their efficacy is doubtful.**
- **Randomized trials for use of probiotics in clinical conditions other than diarrhea is very promising.**

**References**


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**BASIC PEDIATRIC INTENSIVE CARE COURSE**

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OFFICE PRACTICE

MANAGEMENT OF COUGH

* Subramanyam L
* Balachandran A

Abstract: Cough is a very common presentation in pediatric office practice. It is a protective reflex elicited by our body in response to an underlying cause. Systematic clinical assessment is mandatory for proper management. It is advisable not to use irrational combination of pharmacological agents.

Keywords: Cough, Asthma, GERD, Mucolytics, Cough suppressant, Bronchodilators

Cough is a frequent presenting symptom to general practitioners and is one of the most common problems for which child is referred to pediatricians and respiratory physicians. Cough in children causes significant anxiety to parents. It is an important symptom that spans a spectrum of diseases from benign to serious conditions. Cough is an important protective reflex that allows clearance of secretions and particulates from the airways, so as to keep the airway clean and healthy.

Cough occurs through the stimulation of a complex reflex arc except in psychogenic cause. This is initiated by the irritation of cough receptors that exist not only in the epithelium of the upper and lower respiratory tracts, but also in the pericardium, esophagus, diaphragm, stomach and external ear. The term upper airway cough syndrome (UACS) be used in preference to postnasal drip syndrome (PNDS), because whether the mechanism causing cough is postnasal drip, direct irritation or inflammation of the cough receptors in the upper airway is unclear in cough that is associated with upper airway conditions.

In children, the common causes of chronic or persistent cough include post viral cough, asthma, upper airway cough syndrome, gastro-esophageal reflux and foreign body. The causes of cough are listed in Table 1.

Approach to child with cough

The initial evaluation of a child with persistent cough should include a careful history and physical examination. The history should focus on the following key elements: age, nature of the cough, timing and associated symptoms.

Age: Onset of symptoms in early infancy and recurrent cough since birth suggests congenital abnormality. Cough in a young infant, particularly under 6 months of age, is unusual and should be evaluated regardless of duration. While most of these infants will have an upper respiratory viral-induced cough and require no further work-up, a small number will have more serious problems such as cystic fibrosis (CF) and gastroesophageal reflux with aspiration. In sudden onset of cough with respiratory distress or acute life threatening event (ALTE) aspiration secondary to inhalation or ingestion has to be ruled out (Table 2).

Nature of the cough: Chronic dry paroxysmal cough triggered by exercise, cold air, sleep or allergens is often seen in patients with asthma and typically worsens during sleep. In contrast,
a chronic productive or “wet” cough suggests a suppurative process and may require further investigation to exclude bronchiectasis, cystic fibrosis or immune deficiency. Staccato cough in infants can be the result of infection with Chlamydia trachomatis (Table 3).

Timing and triggers: Cough due to postnasal drip is typically worse at night, while cough due to bronchiectasis is worse and most productive early in the day. Cough in the first hour after eating, or which is worse while supine may suggest gastroesophageal reflux. Psychogenic

**Table 1. Causes of cough**

<table>
<thead>
<tr>
<th>Common causes</th>
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<tbody>
<tr>
<td>Viral respiratory tract infections</td>
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<tr>
<td>Asthma</td>
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<td>Environmental pollution</td>
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<table>
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<tr>
<th>Less common causes</th>
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<tbody>
<tr>
<td>Infection: Chlamydia, pertussis, tuberculosis</td>
</tr>
<tr>
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<tr>
<td>Aspiration (Foreign body)</td>
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<tr>
<td>Gastro esophageal reflux disease (GERD)</td>
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<td>Habit or psychogenic cough</td>
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<tr>
<th>Rare causes</th>
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<tr>
<td>Congenital abnormalities: Cricopharyngeal incoordination, tracheo-esophageal fistula, bronchogenic cyst, tracheobronchomegaly, vascular ring, cardiac disease</td>
</tr>
<tr>
<td>Abnormal mechanical clearance: Immotile cilia syndrome including Kartagener’s syndrome and cystic fibrosis (CF)</td>
</tr>
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<td>Immune deficiency states: Congenital (hypogammaglobulinemia) and acquired (HIV)</td>
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<tr>
<td>Interstitial lung disease: Collagen vascular disease, infiltrative diseases, cytotoxic drugs and radiation.</td>
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<tr>
<td>Miscellaneous: Pulmonary hypertension, ACE-inhibitors, Allergic bronchopulmonary aspergillosis (ABPA), hemosiderosis and bronchopulmonary dysplasia (BPD)</td>
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<th>Table 2. Age and onset of cough</th>
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<td>Infancy</td>
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<td>Early childhood</td>
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<td>Older children</td>
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<tr>
<td><strong>Acute</strong></td>
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<tr>
<td>Viral infection</td>
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<td>Foreign body</td>
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<tr>
<td>Asthma</td>
</tr>
<tr>
<td><strong>Recurrent</strong></td>
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<tr>
<td>GERD</td>
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<tr>
<td>Asthma</td>
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<tr>
<td>Rhinosinusitis Psychogenic</td>
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<tr>
<td><strong>Persistent</strong></td>
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<td>Congenital anomalies</td>
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<tr>
<td>Retained FB</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>ILD Bronchiectasis (CF/Immuno deficiency)</td>
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cough is typically worst and most disruptive during the day and disappears at night (Table 4).

**Associated symptoms**: Family history of atopy suggests a diagnosis of either allergic rhinitis or asthma in the child with chronic cough. Response to prior therapy may yield some diagnostic clues regarding the cause of chronic cough. The less common disorders like, recurrent aspiration, immunodeficiency, chronic viral infection, bronchiectasis (cystic fibrosis, ciliary dysfunction), cavitary lung disease (tuberculosis or bacterial abscesses), congestive heart failure, hemosiderosis, neoplasm, vascular lesions and endobronchial lesions must be excluded if the cough is unusually severe and frequent or when there is evidence of failure to thrive, growth retardation, purulent sputum, exertional dyspnea, clubbing, hypoxemia, chest pain or hemoptysis. History of progressive dyspnea, tachypnea, exercise intolerance and failure to thrive may suggest interstitial lung disease (Table 5).
Evaluation

In evaluation of cough, it is most important to differentiate presence or absence of infection. Acute infection is mostly associated with acute onset of fever. Chronic respiratory infection may often be present without fever. It may favor infection when accompanied by purulent nasal, ear or bronchial discharge. In infection, it is necessary to assess the probable etiology (bacterial or viral). Presence of high fever with toxicity and purulent discharge (upper or lower respiratory) usually favors bacterial infection. Fever without toxicity and illness affecting both upper and lower respiratory tract, without localization are more suggestive of viral etiology.

Recurrent non-progressive cough usually results from viral infection, GERD or asthma, while recurrent progressive cough is due to more serious conditions like immune-deficiency, cystic fibrosis or immotile cilia syndrome. Persistent infectious cough is caused by tuberculosis, pertussis or sinusitis, while persistent non-infectious cough results from rare diseases e.g. hemosiderosis, idiopathic pulmonary fibrosis, alveolar proteinosis and alphal-antitrypsin deficiency. Most often non-infective cough (asthma, GERD) are misdiagnosed as chronic infections and are treated with antibiotics. In isolated cough with no evidence of chronic disease on detailed history, physical examination, radiography and pulmonary function testing, consider conditions like cough-variant asthma, prolonged post-viral cough, increased cough receptor sensitivity and functional disorders like habit cough.

Management

The treatment of cough depends on whether the cough is productive or non-productive. Non-productive cough is considered serving no useful purpose for the patient. The commonest cause of this is common cold and supportive therapy alone is recommended. In Latin “tussis” means cough. The various cough remedies that are used for cough control like antihistamines, decongestants, antitussives, bronchodilators, mucolytics and expectorants, singly or in combinations, not only lack proven efficacy but also have the potential for enhanced toxicity in children and hence not generally recommended.

The central cough suppressants are drugs that reduce sensitivity of cough centre, e.g. opioids (Noscapine, dextromethorphan, codeine, pholcodine, methadone and diamorphine) antihistaminics (diphenhydramine, chlorcyclizine) and benzonatate (local and central effect). They are effective in symptomatic management of irritant, non productive cough, but are associated with side effects and the potential for abuse. Pharyngeal demulcents i.e. drugs that reduce receptor activation, e.g. lozenges, cough drops and linctus, act by increasing salivation which exerts protective effect.

In productive cough (characterized by the presence of sputum) cough suppressants are inappropriate, but expectorants have been used on the grounds that increasing the volume of secretions in the respiratory tract facilitates removal by ciliary action and coughing. However, clinical evidence of efficacy is lacking and many consider expectorants to be of no value other than a placebo. Commonly used expectorants include guaifenesin, ammonium salts, ipecacuanha, sodium citrate and iodides.

Mucolytics are thought to alter sputum viscosity, alleviate symptoms and improve lung functions in patients with thick, viscous sputum eg. bronchiectasis or cystic fibrosis. Commonly used mucolytics are bromhexine, ambroxol, acetylcysteine, carbocysteine, but these have not demonstrated consistent improvement in lung function.
Bronchodilators such as salbutamol (ß2 agonist) or ipratropium (anti-muscarinic) alleviate cough associated with bronchospasm. However, they are not of much benefit in other forms of cough and hence are not recommended for use in any patient with cough.

Pharmacologic treatment of cough is either protussive or antitussive. Protussive (to make cough more effective) therapy is indicated when cough performs a useful function and needs to be encouraged (eg, in bronchiectasis, CF). Antitussive, (cough suppressants to prevent, control, or eliminate cough) therapy is indicated when cough serves no useful function such as clearing the airways. Very often antitussive therapy is indicated for post nasal drip, allergic dry cough, whooping cough, habit cough and disturbing cough (which affects the feed and sleep of the child).

Cough suppressants have a specific role in cough management. When the cough is too distressing for the patient (disturbing his sleep and feed), it would be ideal to prescribe cough suppressants. Several agents are used as cough suppressants. Most common among these are codeine, pholcodine and dextromethorphan. While the efficacy of codeine has never been questioned, it is not a preferred choice in pediatric practice due to the problems of constipation, excessive drowsiness and the addictive potential. In this context pholcodine or dextromethorphan are safe agents, with no side effects.

Cough and cold preparations containing various combinations of cough suppressants, expectorants, sympathomimetics, antihistamines, or analgesics are available. These combinations are not scientifically approved and have little evidence to support their efficacy. With many combinations, dose of each individual drug may be inadequate or inappropriate and a large number of ingredients may expose the patient to unnecessary adverse effects.

In children with bronchiectasis, chest physiotherapy is recommended as an effective technique to increase mucus clearance. In patients with neuromuscular disease with impaired cough, mechanical cough assist devices are recommended to prevent respiratory complications as nonpharmacologic airway clearance therapy.

The usual treatment of cough is to address the underlying disorder. Empiric therapy for asthma, allergic rhinosinusitis or gastroesophageal reflux can be considered if suggestive findings exist. The management of nonspecific chronic cough is largely reassurance and periodic reevaluation for the identification of signs and symptoms, which would suggest underlying chronic disease.

Points to Remember

- **Chronic cough requires systematic evaluation** along with a chest radiograph and other investigations for specific diagnosis, except when asthma is the etiologic factor.
- **In non specific cough, a course of bronchodilator can be tried. If the cough does not resolve within the expected response time, the medication should be withdrawn and other diagnosis to be considered.**
- **Cough is a protective reflex –do not suppress, unless it interferes with feeding/sleeping.**
- **In a disturbing cough which affects sleep and feed, the cough medications can be used preferably on an SOS basis.**
- **Use single active ingredient only if indicated.**
- **Avoid irrational combination of pharmacological agents like suppressants and expectorants.**
• **Steam inhalation may be beneficial as home remedy.**

• **Prevention is better than cure - protecting the child from pollutants and allergens is the first best option.**

**Bibliography**


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**NEWS AND NOTES**

**NEOCON 2010**

**Organized by Kanpur NNF branch**

**6th & 7th February 2010, Venue: GSVM Medical College**

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Mobile: 919839086558, 91512 3216539, 919415042673.  
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**CLIPPINGS**

**Rapid viral diagnosis for acute febrile respiratory illness in children in the Emergency Department**

Children admitted to Emergency Departments (ED) with fever and respiratory symptoms represent a major burden to the health care system, as well as significant anxiety and expense to parents and caregivers. Physicians often order diagnostic tests and may prescribe antibiotics when they are unsure of the cause of the illness and are concerned about the possibility of serious bacterial infection. However, in most cases, fever and respiratory symptoms are caused by viruses. In addition, in children in whom a virus is found to be the cause of their illness, the risk of serious bacterial infection is very low. This review was conducted to assess whether a rapid viral test done in the ED changes what physicians do when treating these children. We found that in previously healthy children coming to the ED with fever and respiratory symptoms, a rapid viral test reduces the use of chest X-rays and that there is a trend toward less antibiotic usage, and blood and urine investigations. The true impact of this intervention on the latter three outcomes requires trials with larger enrollment numbers.


This version first published online: October 07, 2009
GROWING PAINS IN CHILDREN

*Mathur Sailesh Kumar
**Mathur N C

Abstract: A common presenting complaint of children visiting pediatricians in out-patient department is pain in the lower extremities. The common cause of childhood musculoskeletal pain is termed “growing pains” (GP). The pain usually appears late in the day or is nocturnal, often awakening the child. The duration ranges from minutes to hours. GP is not associated with serious organic disease and usually resolves by late childhood. The diagnosis is always by clinical examination and no laboratory investigation or imaging is required. Conservative management should be employed to ease the child’s discomfort along with other supportive measures.

Key Words: Growing pains, Nocturnal, Etiology, Management

It is a type of a non-inflammatory pain syndrome. These pains are much more common than all other inflammatory rheumatic diseases.

The prevalence of GP ranges from 3–37% of children. It is slightly more common in girls than boys. GP affects children between the ages of 3 and 12 years. There are two peaks - early childhood i.e 3 to 5 years and later from 8 to 12 years. They normally never occur beyond the teen years. The typical case of growing pains occurs in a healthy, clinically normal, young child, in the middle of the night, causing intense pain for 10 to 15 minutes in both legs. It is usually nonarticular, in 2/3rd of children is located in the shins, calves, thighs or popliteal fossa and is almost always bilateral. The pain usually appears late in the day or is nocturnal, often waking up the child. The duration ranges from minutes to hours. The intensity can be mild or very severe. By morning the child is almost always pain free.

It is rarely accompanied by headache or abdominal pain.

There are no objective signs of inflammation on physical examination. GP is episodic, with pain-free intervals from days to months. In severe cases the pain can occur daily. Often parents can predict when the child will have pain on days of increased activity or when the child is more moody. GP is not associated with serious organic disease and usually resolves by late childhood. However, frequent episodes may have a major impact on the child and his family’s daily routine, including absences from school and work, daytime fatigue, reduced physical activity and frequent or chronic use of pain relief medications.
Etiology

No clear mechanism has yet been identified which explains these pains, but there is an increasing body of evidence indicating that several factors, individually or in combination, might be responsible for this phenomenon. Few studies have been done to elucidate the etiology and pathogenesis of this common syndrome. Hashkes P, et al assessed the pain threshold by dolorimeter in 44 children with GP and found that children with GP have a decreased pain threshold compared to age and gender matched controls. Friedland O, et al found that the bone strength density of children with GP was significantly less for population norms of healthy children, especially in the painful tibia region. Mechanical factors, such as joint hypermobility and flat feet might be responsible for this phenomenon. Evans et al investigated and compared findings of foot posture and functional health between groups of children aged 4-6 years with and without GP but did not find a meaningful relationship between foot posture or functional health measures and GP. Mechanical factors, such as joint hypermobility and flat feet might be responsible for this phenomenon but not proven. Emotional factors involving the patient’s family and other social stressors have also been investigated without conclusive results.

The sudden onset and severity of GP as well as the transience of the attacks support a hypothesis that GP has a vascular perfusion component, similar to migraine. Furthermore a higher prevalence of GP was found among children with migraine headaches. Hashkes PJ, et al using perfusion changes study did not find differences between children with GP and controls.

There is no evidence, that GP is actually associated with rapid growth as originally thought. The peak age of GP (about 6 years) is usually not part of the child’s rapid growing phase. Many clinicians have an impression that many children with GP are hypermobile but have not been studied due to lack of criteria for hypermobility. Thus GP may represent a local lower extremity overuse syndrome with bone fatigue in children with low pain thresholds. These children may experience more pain after physical activity.

Differential diagnosis

Rarely, GP may be a manifestation of an organic disease like metabolic muscle disease (when occurring after exercise) or restless leg syndrome, especially in families with a history of this syndrome.

Investigations and diagnosis

Correct diagnosis of growing pains requires a thorough history and physical examination. The diagnosis can be safely established without unnecessary laboratory investigations or imaging. However, if the symptoms are atypical, such as unilateral pain, morning stiffness, joint swelling and systemic symptoms (e.g. fever, weight loss and malaise) the diagnosis of GP should not be assumed without evaluating other causes. One important method of diagnosis is to ascertain how the child responds to touch. In a serious disease – children don’t like to be handled because movements increase pain, whereas, child with GP feels better when massaged and cuddled.

Management

Once the diagnosis has been established, conservative management should be employed to ease the child’s discomfort using massage and other supportive measures like rub, stretch the child’s leg, use heating pad, etc. This may continue until the syndrome self-resolves with time. An important intervention is to explain the natural benign course of the GP, thus decreasing
anxiety and fear. Despite the benign prognosis, GP may have an impact on the child and family, especially among children with frequent nocturnal attacks. Sometimes, children need symptomatic pain medications. Rarely do they need long term use medications, especially acetaminophen and non-steroidal anti-inflammatory drugs (NSAID).

Points to Remember

• *Growing pains is very common and easy to diagnose once the typical clinical characteristics are presented.*

• *The diagnosis of growing pains is made clinically utilizing both inclusion and exclusion criteria.*

• *Once the diagnosis has been established, conservative management should be employed until the syndrome self-resolves with time, usually by adolescence.*

References


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**NEWS AND NOTES**

**PALS INSTRUCTOR COURSE** 5th February 2010

**PALS PROVIDER COURSE** – 6th & 7th February 2010

Venue: Kanchi Kamakoti CHILDs Trust Hospital, Chennai - 600 034.

**Contact**

**Dr. Janani Sankar**

National Convenor – PALS

Mobile: 9841078101, E-mail: jananis_2000@yahoo.com
OFFICE PRACTICE

DIARRHEA IN CHILDREN - AN OVER VIEW

*Indra Shekhar Rao M

Abstract: Diarrhea continues to be one of the major causes of mortality and morbidity among under fives of developing world. An over view of classification, etiology, pathophysiology, investigations, principles of management including IMNCI approach and prevention of diarrhea are covered in this review.

Keywords: Diarrhea, Etiology, Pathophysiology, Management, Prevention.

Worldwide, especially in the developing countries, diarrhea still constitutes one of the major causes of infant mortality and morbidity. 73% of the 10.6 million annual deaths in children younger than 5 years are primarily due to pneumonia (19%), diarrhea (18%), malaria (8%), neonatal pneumonia or sepsis (10%), preterm delivery (10%) and asphyxia at birth (8%). Of the 6.6 million deaths among children aged 28 days to five years, deaths from diarrhea are estimated to be 1.87 million (26%), approximately 19% of total child deaths. 1 million (61%) of these deaths also have an added problem that is under nutrition. Millions more survive only to face diminished survival, unable to develop to their full potential. An average Indian child less than 5 years of age can have 2-3 episodes of diarrhea per year. In urban slums, a child can have 6-8 such episodes per year. About 2 million episodes of diarrhea occur each year in India. The mortality due to diarrhea is still high though it has decreased after the introduction of ORS. One out of every five children who die of diarrhea worldwide is an Indian.

Diarrhea is characterized by abnormal fluidity and frequency of fecal evacuations, generally the result of increased motility in the colon. Diarrhea is the passage of watery stools, usually at least three times in a 24 hour period. However, it is the consistency of the stools rather than the number that is most important. Frequent passing of formed stools is not diarrhea. Babies fed only breast milk often pass loose, “pasty” stools which is not diarrhea. Mothers usually know when their children have diarrhea and may provide useful terminologies in local languages.

Based on the duration and etiology, diarrhea is classified into 3 types. They are: a) Acute diarrhea, b) Dysentery and c) Persistent diarrhea.

Acute watery diarrhea

It refers to diarrhea that begins acutely, lasts less than 14 days (most episodes last less than seven days) and involves the passage of frequent loose or watery stools without visible blood. Vomiting may occur and fever may be present. Acute watery diarrhea causes dehydration; when food intake is reduced, it also contributes to under nutrition. When death occurs, it is usually by acute dehydration.
**Etiology:** Acute watery diarrhea can result due to various etiological factors of which the most important is infection followed by diet, use of antibiotics and surgical procedures. Most prominent microbes causing diarrhea due to infections include:

a) Viruses - Rota, Adeno, Calci, Norwalk, HIV
b) Bacteria - Vibrio cholera, E.coli, Salmonella, Shigella, Staphylococci, Aeromonas hydrophila, Plesiomonas shigelloides.
c) Protozoa – Giardia, Cryptosporidia and E.histolytica
d) Fungal – Candida
e) Systemic infections – LRTI, UTI,AOM

Other causes of watery diarrhea are due to
i) Antibiotic usage
ii) Diet – food intolerance, food allergy and food poisoning
iii) Surgical procedures – Appendicitis, intussusception, short bowel syndrome.
iv) Miscellaneous – Encopresis.

**Dysentery**

It refers to diarrhea with visible blood in the feces. Important effects of dysentery include anorexia, rapid weight loss, and damage to the intestinal mucosa by the invasive bacteria. A number of other complications may also occur. The most important cause of acute dysentery is Shigella; other causes are Campylobacter jejuni and, infrequently, entero invasive E coli or Salmonella.

Entamoeba histolytica can cause serious dysentery in young adults but is rarely a cause of dysentery in young children.

**Etiology of dysentery:** Etiology of dysentery can be classified into two types based on the cause,

a) Infective causes
   - Shigella- S.dysenteriae,
   - Escherichia coli – Enterohaemorrhagic (EHEC), Enteroinvasive (EIEC),
   - Campylobacter jejuni,
   - Salmonella,
   - Yersinia enterocolitica,
   - Entamoeba histolytica, Clostridium difficile

b) Non-infective causes
   - Pseudomembranous colitis,
   - Inflammatory bowel disease,
   - Radiation-induced colitis,
   - Segmental enteritis.

**Virus**

Rotavirus is the most important etiological agent of acute watery diarrhea in nearly 22-25% of infants. The virus selectively infects and destroys the tip of villi of small intestine leading to disturbance of intestinal absorption as a result of which infant presents with acute watery diarrhea. There is also secondary lactose intolerance due to loss of disaccharidases present in the mature villi tip cells.

**Bacteria**

a) **Vibrio cholera:** V.cholera secretes enterotoxins, which stimulate an enzyme called adenylate cyclase. The activated/stimulated adenylate cyclase increases the concentration of cyclic AMP, resulting in the hypersecretion of water/electrolytes (sodium ion, chloride ion) resulting in the clinical manifestations of diarrhea.
b) Escherichia coli: Various strains of E.coli cause acute watery diarrhea. Among all strains, the two most important/prominent strains are entero toxigenic E.coli(ETEC), entero hemorrhagic E.coli(EHEC). ETEC produces enterotoxins in a similar fashion to that of V.cholera and cause diarrhea. EHEC on the other hand interferes with the intestinal mucosal integrity through phosphorylation of the myosin component of the cells of intestine leading to opening of the junction and decrease in pathogenic bacterial translocation leading to intestinal cell damage and exhibiting clinical manifestation of acute watery diarrhea often with inflammation and blood in the stools.

c) Salmonella typhi: Among the various serotypes of S.typhi, the most common strains that cause diarrhea are S.typhimurium, S.enteritidis, S.heidelberg and S.newport. These pathogenic bacteria strongly adhere to the mannose rich cell membrane via lecithin receptors and produce enterotoxins/prostaglandins, leading to the increase in levels of cAMP causing a net efflux of water and electrolytes into the intestinal lumen.

d) Shigella: Is the main causative pathogen for dysentery. It often causes acute watery diarrhea without progressing to bloody stools. Among various serotypes of Shigella the two most prominent serotypes that cause dysentery/AWD are S.sonnei, S.flexneri, S.dysenteriae and S.boydii. Similar to other pathogenic bacteria, Shigella secretes enterotoxins thus leading to diarrhea. S.flexneri, secretes a unique enterotoxin called Shigella enterotoxin1 leading to diarrhea in infants and children.

Protozoa

Protozoa attach themselves to the brush border of the intestinal epithelial cells of the duodenum and proximal jejunum. These pathogenic protozoans destroy the villi resulting in malabsorption of disaccharides/fats leading to diarrhea. The common examples are Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica etc.

Non-infective diarrhea: Apart from infections, intolerance to various food components like lactose, gluten, cow milk proteins, can also cause acute diarrhea progressing to either chronic diarrhea or persistent diarrhea.

Persistent diarrhea: It refers to diarrhea that begins acutely but is of unusually long duration (at least 14 days). The episode may begin either as watery diarrhea or as dysentery. Marked weight loss is frequent. Diarrheal stool volume may also be great, with a risk of dehydration. There is no single microbial cause for persistent diarrhea; enteroadherent E. coli and cryptosporidia may play a greater role than other agents. Persistent diarrhea should not be confused with chronic diarrhea, which refers to recurrent or long-lasting diarrhea due to non-infectious causes, such as sensitivity to gluten or inherited metabolic disorders.

Pathophysiology of watery diarrhea: dehydration and rehydration

Watery diarrhea results from disordered water and electrolyte transport in the small intestine. Intestinal transport mechanisms are also the basis for the management of diarrhea, through oral fluid therapy and feeding. It is therefore important to understand some of the normal mechanisms of intestinal transport and how they are altered during diarrhea.

Normal intestinal fluid balance

Normally, absorption and secretion of water and electrolytes occur throughout the intestine. For example, a healthy adult takes in less than two litres of fluid each day. Saliva and secretions from the stomach, pancreas, and liver add about seven litres, making a total of about nine litres
that enter the small intestine every day. Water and electrolytes are simultaneously absorbed by the villi and secreted by the crypts of the bowel epithelium. This causes a two-directional flow of water and electrolytes between the intestinal lumen and the blood. Since fluid absorption normally is greater than fluid secretion, the net result is fluid absorption.

Usually, more than 90% of the fluid entering the small intestine is absorbed, so that about one litre reaches the large intestine. There, further absorption occurs, only 100 to 200 milliliters of water being excreted each day in formed stools. Any change in the two-directional flow of water and electrolytes in the small intestine (i.e., increased secretion, decreased absorption, or both) results in either reduced net absorption or increased net secretion and causes an increased volume of fluid to enter the large intestine. When this exceeds its limited absorptive capacity, diarrhea occurs.

**Intestinal absorption of water and electrolytes**

Absorption of water from the small intestine is caused by osmotic gradients that are created when solutes (particularly sodium) are actively absorbed from the bowel lumen by the villous epithelial cells. There are several mechanisms whereby sodium is absorbed in the small intestine. To enter the epithelial cells, sodium is linked to the absorption of chloride, or absorbed directly as sodium ion, or exchanged for hydrogen ion, or linked to the absorption of organic materials such as glucose or certain amino acids. The addition of glucose to an electrolyte solution can increase sodium absorption in the intestine as much as threefold.

After being absorbed, sodium is transported out of the epithelial cells by an ion pump referred to as Na+ K+ ATPase. This transfers sodium into the extracellular fluid (ECF), which elevates its osmolality and causes water and other electrolytes to flow passively from the bowel lumen through intercellular channels and into the ECF. This process maintains an osmotic balance between fluid in the bowel and ECF in the intestinal tissue.

**Intestinal secretion of water and electrolytes**

Secretion of water and electrolytes normally occurs in the crypts of the small bowel epithelium where NaCl is transported from ECF into the epithelial cell across its basolateral membrane. The sodium is then pumped back into the ECF by Na+ K+ ATPase. At the same time, secretory stimuli increase the ability of chloride to pass through the luminal membrane of the crypt cells, allowing that ion to enter the bowel lumen. This movement of chloride ion creates an osmotic gradient that causes water and other electrolytes to flow passively from the ECF into the bowel lumen through the intercellular channels.

Based on the pathophysiology diarrhea is divided into 4 types. They are: Osmotic diarrhea, Secretory diarrhea, Inflammatory/Exudative diarrhea, Motility diarrhea.

**Osmotic diarrhea:** Osmotic diarrhea results when unabsorbed or poorly absorbed osmotically active solutes (eg- Lactose) creates an osmotic load and inhibits water absorption, leading to a net secretion of water and consequently osmotic diarrhea. The diarrhea usually stops when feeding is discontinued. It is characterized by a sizable osmotic gap usually greater than 50.

The lower electrolyte concentration in osmotic diarrhea suggests that some other osmotic substance is contributing to the isotonic load in the fluid expelled from the colon.

**Secretory diarrhea:** Secretory diarrhea is caused by abnormal ion transport in the intestinal epithelial cells. A net secretory state develops in the GIT as a result of reduced absorption or increased secretion of ions and water.
It can be due to (a) abnormal mediators- Bacterial endotoxin, (b) diffuse mucosal disease, (c) internal resection and (d) congenital defect of ion transport.

**Inflammatory diarrhea:** Inflammation due to Shigella, EHEC produces ulceration in the small intestine and colon which can cause diarrhea. This results in the passage of pus, mucus, serum and blood in addition to water and electrolytes.

**Motility diarrhea:** Increased motility can cause diarrhea by reducing the contact time of chime with the intestinal epithelium. The reduced motility can also cause diarrhea by allowing small bowel bacterial overgrowth, bile acid deconjugation and malabsorption. Motility disorders affecting the rectum and reflexes involved in defecation may cause an increase in stool fluidity and frequency without increase in weight.

**Investigations**

1. Stool
   - Macroscopic examination
     a. colour, consistency, mucus, odour
     b. pH, reducing substances
   - Microscopic examination
     a. Leucocytes
     b. Ova, cyst, trophozoites
     c. Hanging drop for V. cholera
   - Culture and sensitivity for shigella and salmonella.

2. Blood tests
   - CBC (for band forms for suspected systemic infection)
   - Serum electrolytes
   - BUN and Creatinine
   - Culture and senstivity

3. Urine routine, Urine culture

Clinical assessment of diarrhea according to IMNCI Guidelines is shown in Figs.1 and 2.

**Principles of management**

The main objectives in the management of acute diarrhea are: 1. Prevention of dehydration and providing nutritional support. 2. Treatment of dehydration if present. 3. Specific antimicrobial therapy if required.

Two recent advances in managing diarrheal disease can drastically reduce the number of child deaths:

1. **Newly formulated oral rehydration salts (ORS) solution**, containing lower concentrations of glucose and salts, to prevent dehydration and the need for intravenous therapy. The new formula for ORS has been scientifically proven to be more efficacious than the older one, and is now the formula recommended by WHO and UNICEF (Table 1).

**Table 1. WHO/UNICEF recommended oral rehydration salts solution for the treatment of all causes of diarrhea in all age groups.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>OLD –ORS mmol/L</th>
<th>New ORS mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>Potassium</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Chloride</td>
<td>80</td>
<td>65</td>
</tr>
<tr>
<td>Citrate</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Glucose</td>
<td>111</td>
<td>75</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>311</td>
<td>245 mosmol/L</td>
</tr>
</tbody>
</table>

Recommended in 1976 Recommended in July, 2001
Fig. 1. Clinical approach to an infant (0-2 months) with diarrhea (Source: IMNCI WHO)
Fig. 2. Clinical approach to child (2months-5years) with diarrhea (Source: IMNCI)
2. Drug therapy in acute diarrhea

a. Antimicrobial therapy for bacterial enteropathogens

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antimicrobial agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aeromonas</td>
<td>TMP/SMZ</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Erythromycin or Azithromycin</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Metronidazole or Vancomycin</td>
</tr>
<tr>
<td>E.coli</td>
<td>TMP/SMZ</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Cefotaxime or Ceftriaxone or Ampicillin or TMP/SMZ</td>
</tr>
<tr>
<td>Shigella</td>
<td>Ampicillin or Ciprofloxacin or Ofloxacin or Ceftriaxone</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Doxycycline or Tetracycline</td>
</tr>
</tbody>
</table>

b. Zinc supplementation

Zinc is an important micronutrient for a child’s overall health and development. Zinc is lost in greater quantities during diarrhea. It has been shown that zinc supplements given during an episode of diarrhea reduce the duration and severity of the episode, and lower the incidence of diarrhea in the following 2–3 months. For these reasons, all patients with diarrhea should be given zinc supplements as soon as possible after the diarrhea has started. Replacing the lost zinc is important to help the child recover and to keep the child healthy in the coming months. Zinc supplementation is a new addition to the diarrhea treatment strategy and one that promises to greatly improve diarrhea management. Zinc supplementation is now being recommended by WHO, UNICEF, and countries around the world for the treatment of all diarrhea episodes among children in a dose of 20mg per day or 10 mg per day for infants under 6 months for 10 to 14 days.

c. L-glutamine

L-glutamine is a major fuel for the enterocytes, signals proliferation in intestinal and epithelial cell lines and helps in cellular integration and repair of intestinal cells.

d. Probiotic

Probiotics favourably alter the intestinal microflora balance, inhibit the growth of harmful bacteria, promote good digestion, boost immune function, and increase resistance to infection. People with flourishing intestinal colonies of beneficial bacteria are better equipped to fight the growth of disease-causing bacteria. Diarrhea flushes intestinal microorganisms out of the gastrointestinal tract, leaving the body vulnerable to opportunistic infections. Replenishing the beneficial bacteria with probiotic supplements can help prevent new infections. The role of probiotics in treating sporadic infectious diarrhea in children do show clear evidence of efficacy, with the 2 most effective strains being Lactobacillus GG and S boulardii. Recent studies have shown that the effect is not only strain dependent, but also dose dependent, with doses of at least 10 billion/day being necessary.

e. Racecadotril

Racecadotril is an enkephalinase inhibitor that reduces intestinal hypersecretion by inhibiting this intestinal enzyme. It prevents the inactivation of endogenous enkephalins and prolongs their physiological actions. Through enkephalins it acts on cAMP and reduces the secretions of water and electrolytes without any effect on intestinal motility. This specific action is seen only when hypersecretion is present. It is shown to reduce the stool output by 46%. Also it does not produce toxic megacolon or bacterial overgrowth.

Dietary management of diarrhea

Since children with diarrhea may develop protein energy malnutrition the diet should be
easily digestable and nutrionally balanced. This helps the gut to promote absorption of sodium and water and hastens the recovery.

1. Continue normal feeding during acute diarrhea, since feeding is physiological

2. Continue to breast feed uninterrupted during diarrhea.

3. Give optimum energy dense food with less bulk by enriching with oil or sugars

4. Avoid food with high fibre contents.

5. Routine lactose free feeding is not required during acute diarrhea.

Prevention of diarrhea

Prevention of diarrhea and its nutritional consequences should receive major emphasis in health education. Promotion of breast feeding for its protection against diarrhea should be emphasised. Mothers should be properly guided to prepare supplementary home made food avoiding contamination, to use safe water and to thoroughly wash vegetables, cooking utensils and their hands while preparing the food. All these hygienic food measures should be sustained during all times.

Points to Remember

- Diarrhea remains one of the major causes of morbidity and mortality among under fives
- Diarrhea can be acute or persistent and some times may present as dysentery
- Rotavirus is the most important cause of acute watery diarrhea in infants
- Prevention of dehydration, treatment of dehydration if present with nutritional support are the mainstay in management. Antibiotics are indicated in dysentery cholera and when there is evidence of other significant infections.
- Role of ORS and Zinc supplementation are vital
- Role of promotion of breastfeeding and proper hygiene in prevention of diarrhea and under nutrition should receive major emphasis in health education.

Bibliography

IMPORTANCE OF CASE RECORD MAINTENANCE

*Satish Kamtaprasad Tiwari

Abstract: A proper record or document is the most important evidence in cases of deficiency in service or medical negligence. But there is lot of carelessness on part of medical practitioners while maintaining the records. This may result in problems in the era of legal activism. The records include history, examination, investigations, treatment including various charts, complications and referrals, etc. It is rightly said that case paper speaks for them. Just as advances in medicine are progressing in leaps and bounds, the need for good hospital records is also ever increasing.

Keywords: Documentation, Record maintenance, Medical negligence.

The age old doctor-patient relationship is no exception to the negative changes in the society. Since the patient is paying money and going for “doctor shopping” his expectations are soaring and the end result is naturally frustration if something unexpected happens. The enactment of Consumer Protection Act in 1986 and its subsequent application to medical practitioners has added fuel to the fire. Documentation of records including history, examination, investigations, referrals, etc should be properly maintained. A properly maintained document may result in favorable outcome in the hours of crisis.¹

Definition

Document means any matter expressed or described upon any substance by means of letters, figures or marks or by more than one of those means, intended to be used, or which may be used, for the purpose of recording that matter.² The documents can be handwritten, printed, recorded, computerized or even photographed. They become the part of documentary evidence in the court of law. The Section 159, of Evidence Act prescribes it for ‘Refreshing the memory’.

The computerized records are now-a-days becoming very popular. There is not only need for ideal software but also for increased awareness and training of the health personnel. The Medical Council of India has made it mandatory to have a medical records department in each and every medical college and hospital.

The contents

The contents of hospital records will vary depending on multiple factors. The records must be clean, chronological, comprehensive, complete, correct and without manipulations. In, Dr. Sri Mohan v. Sukhpalsingh I (2008) CPJ 458 (NC); the doctor adopted for traction as surgery was refused by the complainant. But it was found that the document showing “advised surgery but refused” is not genuine. This was considered as clever and unbecoming effort on part of petitioner to conceal the fact of one leg getting shortened. This manipulation was declared as professional failure and violation of professional ethics by the National Commission.

¹ Professor of Pediatrics, M G Institute of Medical Sciences, Sewagram
A proper record must be maintained including history, examination and investigation reports. The treatment adopted, consent for various procedures and referrals if advised should also be recorded. The refusal on part of patient or relative must also be recorded in writing preferably in presence of neutral witnesses.

While recording history it is important to note down any previous drug sensitivity. In, B Kaur v. C Malhotra I (2008) CPJ 265; pre-operative sensitivity test didn’t show any reaction. But patient succumbed on table due to cardiac arrest. The allegation of drug reaction was also negated in postmortem report and hence negligence was not held.

The “negative history” is equally important in finalizing the clinical diagnosis. It is important to rule out many other differential diagnosis or associated diseases to prevent subsequent outcome in any patient. For any reason, if the patient is examined in hurry ask him to come on next day. If the diagnosis is not confirmed record other possibilities.

Sometimes it may not be possible to arrive at a proper clinical diagnosis. In such cases relevant investigations must be advised and recorded on the case sheets. Failure to do the suggested investigation amounts to “contributory negligence” on part of patient or relatives. In a case, Sudhakar Gupta v. Anugraha Nursing Home I (2008) CPJ 57 (NC); patient was suffering from leukemia but received treatment for typhoid. Bone marrow aspiration was advised by the doctor but complainant himself refused repeatedly. It was held that complainant himself was negligent. If patient is not willing for any procedure or investigations, the dissent shall also be documented.

After investigations and diagnosis a proper, adequate and prescribed treatment shall be provided. Failure to provide proper and adequate treatment may amount to deficiency in service. This was held in, Dean, Tirunelveli Medical College v. U Subramaniyan I (2008) CPJ 188; the State Commission held that the non-providing of Inter Costal Drainage may not be the cause of death but the fact remains that the treatment prescribed was not provided and this amounts to deficiency in service. The courts may infer otherwise even if you have vigorously treated but not documented properly. A patient was started anti-tubercular drugs without conducting mandatory tests for tuberculosis. Condition of patient deteriorated, no instructions were given regarding side effects of the drugs. The patient ultimately died due to drug induced hepatitis. In this case, Shyamsunder v. Pandharinath I (2008) CPJ 53; principle of res ipsa loquitur was applied and negligence was held. It means that “the things speak for themselves”. In such cases the deficiency or negligence is so obvious that usually there is no need for any proof or expert opinion. Some examples of res ipsa loquitur are; i) Performing any procedure or surgery on wrong patient, ii) Operating on wrong side, iii) Leaving or forgetting swabs, sponges or instruments at operation site, iv) Transfusing wrong blood etc.

In a recent judgment of National Commission (Administrator, Pukhraj General Hospital v. Master M Rajput I (2009) CPJ 114 NC), it was observed that no record of nurse’s chart was produced. According to the commission, this was germane of the issue at hand. In this case the child had developed gangrene after administration of injection. The observation of State commission was that, the case papers were filed after about five years. Suffice it to say that this it-self speaks volumes about the conduct of the appellant.

Sometimes the disease process may be progressive resulting in deterioration of the patient though he is admitted in hospital and is receiving proper treatment. Such cases may
require further investigations, sophisticated equipments and further expertise. These facilities if not available then the patient shall be referred to a higher center. Unnecessary detention of patient may also amount to deficiency in service. Almost all courts agree that, the standard to be applied for judging would be that of an ordinary competent person exercising ordinary skill in that profession. This has to be judged in the light of knowledge available at the time (of the incident), and not at the date of trial. The law does not require professional man that he be a paragon combining the qualities of polymath and prophet. This was held by Supreme Court in Dr. Jacob Mathews v. State of Punjab III (2005) CPJ SC 9. Hence a medical practitioner should neither exceed his/her level of competence nor care beyond one’s qualification, skill and experience. In case of deviation from standard practice, the reasons should be mentioned.

In addition to all these, one should maintain temperature chart, diet chart, intake / output chart, weight / anthropometry records, etc. In cases of death, if the relatives refuse post mortem it should also be recorded. If, there are telephonic consultations with the seniors, that should also be recorded and endorsed subsequently. Most of the times, these instructions are carried out by the nursing staff. If the nurses are qualified and make some mistakes the consultant may not be held liable. But if the nursing, paramedical or junior staff is not qualified as per the requirement then the senior consultant may be held negligent. This concept of vicarious liability was accepted by Supreme Court in M/s Spring Meadows Hospital v. Harjot Ahluwalia (AIR 1998 SC 1801) and many other judgments. If some nursing staff or junior assistant refuses / fails to carry out the instructions the ultimate responsibility is that of the consultant or the hospital. The law will hold them vicariously liable. It is up-to the administration or authorities to take action on erring staff-member subsequently. Such views were expressed by National Commission in S Sharma v. Bombay hospital II (2007) CPJ 9 (NC) and Bombay Hospital v. Sharifabai Ismail I (2008) CPJ 432 (NC).

Consent forms

The consent forms are the most vital documents since they contain lots of information and decisions taken in critical cases or specific situations. According to sec. 90 of Indian Penal Code (IPC), a person who consents can not complain as it is usually given after an act of reasoning and deliberations after balancing the good and evil.

In, Samira Kohli v. Prabha Manchanda I(2008) CPJ 56 (SC) the Supreme Court has held that performance without proper consent is unauthorized invasion and interference with appellant’s body and amounts to torturous act of assault. In this case the Apex court has commented that the consent should be real and valid. The doctor should communicate all inherent and potential hazards of the proposed treatment, the available alternatives, if any, and the likely effect if patient remained untreated. The important components in consent are information, voluntariness and capacity. In, another recent judgment R G Varshney v. Laser Sight India Ltd I (2009) CPJ 23 (NC); the National Commission has observed that the consent was on an ordinary sheet of paper without the name of treating surgeon printed on it and it was signed by the grand-son of the complainant. There was no date on the consent paper. This was considered as deficiency in service and compensation was awarded though there was no negligence or deficiency as far as treatment was concerned.

Who is the custodian?

The hospital or the individual doctor is the legal custodian of the records. The original record
is the property of the hospital. The copy of the record shall be given to the patients or relatives specially when asked for. National Commission in, T Ramarao v. Vijay Hospital I (2008) CPJ 170 (NC) held that non-production of documents will lead to draw adverse inference. The Medical Council of India has also suggested giving the documents within 72 hours.6

The original record shall be handed over only to the police or court usually on demand. The police have the power to seize the documents in some specific situations and the courts can ask to produce the original documents. In such situation a proper acknowledgement should be obtained. Many times the records carry confidential information of the patients and hence should be released after patient’s consent.

Duration

The duration for which particular record should be preserved also varies. It will change according to its nature, contents, severity of illness or complications and associated medico-legal significance (if any). The records shall be maintained for i) Outdoor Patient Records - 3 (three) years, ii) Indoor Patient Records - 5 years, iii) Medico-legal cases - 30 years.

In case of children, till the child becomes competent to take his own decision.

Importance of record maintenance

A properly maintained record or document can be a friend in this era of legal activism. It is the only evidence which will suggest whether the steps taken during the treatment were as per the accepted practice of the medical science. The paper work is as important (if not more) as clinical work. The records can be used for a) Diagnosis, treatment and progress of the illness. b) To anticipate complications and to decide preventive measures. c) For legal and ethical purposes. d) Training and communication between medical or health personnel. e) information on epidemiology, statistics, clinical research and audit, etc.

Court’s views

The observations or views taken by consumer forum or other courts indicate the importance of proper record maintenance.

The National Commission had following observations in, PS Grewal v. CS Chawla I (2007) CPJ 125 (NC); it is high time for doctors to write correct notes in operation record / discharge summary and these documents to be made available to patient as a matter of right. Not maintaining proper written record of the treatment given was considered as deficiency in service and a cost of Rs/- Ten thousand were allotted to the complainant.

The documents or records should be patient friendly and not mechanical. This observation was made by National Commission in HS Sharma v. Apollo Hospital II (2007) CPJ 21 (NC). The commission also held that the discharge summary must have details including pre and post operative treatment chart, details of precaution to be taken, etc.

If we look at the overall scenario, it can be accepted that the medical record keeping is shoddy. Though it is required that the record should be explicit and accessible, the actual situation is quite appalling. We will have to change ourselves by understanding the importance of documentation if we want to reduce litigations in medical practice.

Points to Remember

• Documents can be friend as well as foe of the medical practitioner.

• Take a valid consent and maintain near perfect records of your patients.
As far as possible avoid using vague, non-specific terminologies, short forms or abbreviations. The documents shall be legibly written and easily retrievable.

The records or documents should be patient friendly and not mechanical.

Do not give unnecessary details and do not volunteer to hand over the records.

References

CLIPPINGS

Antiviral treatment for Bell’s palsy (idiopathic facial paralysis)

Bell’s palsy is a disease of the facial nerve which causes one side of the face to be paralysed. Some studies have suggested that it is caused by infection with the cold sore (herpes simplex) virus. If this is correct, antiviral drugs against herpes simplex would be likely to help recovery. It has also been suggested that corticosteroids may help. The paralysis is usually temporary even when untreated, although without treatment about one person in five is left with permanent facial disfigurement or pain.

This updated review provided high quality evidence that antivirals are no more effective than placebo (dummy) treatment in producing complete recovery. On the other hand moderate quality evidence showed that antivirals were less effective than corticosteroids and that combined antiviral-corticosteroid treatment were more effective than placebo. Taken together, these results suggest that corticosteroids might be effective but this requires confirmation from the Cochrane review of corticosteroids which is being updated. There was no evidence that antivirals produced significantly more or significantly fewer adverse events than dummy treatment.

As this analysis shows that antivirals against the cold sore virus are not significantly effective, other causes for Bell’s palsy than infection by the cold sore virus now need to be considered.


Last assessed as up-to-date: December 09. 2008
PAIN MANAGEMENT IN CHILDREN

*Nitesh Singhal
** Praveen Khilnani

Abstract: Pain is a common occurrence in children often raising the anxiety level in the patient as well as the family members. Pediatricians deal with the issue of pain on a day to day basis both in inpatients and outpatients whether it is induced by the disease or a procedure or minor surgery. In this article various issues regarding the practice of pain assessment and management in pediatric and neonatal age group are presented based on evidence as well as clinical experience. Various commonly available pharmacologic agents and non pharmacologic techniques are discussed.

Keywords: Pain, Management, Children.

Acute pain is one of the most adverse stimuli experienced by children as a result of injury, illness and medical procedures. Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. While children have the physiologic capability to experience pain they may not have the cognitive ability to report the intensity or the location of their pain. Healthcare professionals, however, have a responsibility to recognize the expressions of pain and render appropriate treatment in all children, from infancy through adolescence.

Barriers and misconceptions

The American Academy of Pediatrics (AAP) and American Pain Society (APS) joint policy statement on pediatric pain identifies that there are many barriers to treating pain in children including a) myth that children, especially infants, don’t feel pain the way adults do b) lack of assessment and reassessment for pain c) fears about the side effects of pain medications, including respiratory problems and addiction.

In 1992, Anand demonstrated that even neonates respond to painful stimulus in deleterious ways including increased stress response, complications and mortality. Unrelieved pain in infants and children has detrimental physiological, anatomical and behavioral effects. Pain left untreated can result in periventricular hemorrhage in neonatal and increased chemical and hormone release and breakdown of fat and carbohydrate stores. Studies have shown that following intensely painful procedures, many children report long-term sequelae that resemble post-traumatic stress syndrome.

Physiology of pain

Nociceptive pain

The sensation of nociceptive pain occurs when the nerve endings in the periphery are activated by a noxious stimuli. Nociceptive pain
generally results as a response to direct tissue damage. The initial trauma causes the release of several chemicals including bradykinin, serotonin, substance P, histamine and prostaglandin. These chemicals facilitate the transmission of the pain impulse to the spinal cord from the periphery. Small ‘C’ fibers and large ‘A’ delta fibers pick up the messages at the site of injury and transmit the signals to the dorsal horn of the spinal cord. Neurotransmitters that include glutamate, substance P and adenosine triphosphate allow the pain message to ascend to the brainstem by the spinothalamic tract and enter the higher centers of the brain. The cerebrum and thalamus are known as the control centers that process and register the experience of pain. Once the impulse enters the higher centers of the brain, information about the pain such as location and intensity is processed as well as other factors that include fear of the situation, past and present experiences and the child’s current emotional status. All these factors are considered before a response occurs in an attempt to stop the pain. The brain may respond by blocking further pain impulses from reaching the higher centers or by producing endogenous opioids (i.e., endorphins), which saturate pain receptor sites along the spinal cord and in the brain, providing an analgesic effect.

Neuropathic pain

Neuropathic pain is caused by altered excitability of the peripheral or central nervous system, usually caused by dysfunction or injury. Neuropathic pain is distinguished from nociceptive pain by its persistence over a longer period of time. Neuropathic pain is frequently described as a burning, stabbing, or shooting sensation. A complete neurologic exam is essential to evaluate sensory, motor, cranial nerve, cerebellar, cognitive and emotional function. Sensory evaluation may elicit the presence of hyperalgesia (an increased sensitivity to pain), or allodynia (pain caused by benign stimuli such as touch). These findings are significant symptoms associated with neuropathic pain, especially when no apparent skin pathology is present.

Pediatric pain response

The basic mechanisms of pain perception in infants and children are similar to those of adults. Infants have the neurologic capacity to perceive pain at birth, even premature birth. The peripheral and central nervous structures necessary for nociception are present and functional early in gestation. Newborn infants possess well-developed hypothalamic-pituitary-adrenal axes and can mount fight-or-flight responses with the release of catecholamines and cortisol. Because of neurophysiologic and cognitive immaturity, however, some differences in nociceptive processes exist between infants and adults.

Pain evokes negative physiologic, metabolic and behavioral responses in children, including tachycardia, tachypnea, elevated blood pressure and increased release of catecholamines, glucagon and corticosteroids. The catabolic state induced by acute pain may be more damaging to infants and young children who have higher metabolic rates and less nutritional reserves than adults.

The first experience of pain has a profound effect on subsequent pain perceptions and responses. Memory of pain in infants is evident in their responses to painful vaccinations after having undergone unanesthetized circumcision.

Pediatric pain assessment/tools

Pediatric patients present a challenge to healthcare professionals who must quantify pain intensity in non-verbal infants and children and assist pre-verbal and verbal children in describing
their pain intensity. Accurate pain assessment requires consideration of the child’s developmental level, type of pain experienced, history and context of pain, family influences and interaction with the healthcare team. The QUEST approach to pain assessment is comprehensive and promotes the use of multiple sources to evaluate pain in a child.\(^8\)

**QUEST principles of pain assessment** (Baker and Wong, 1987)

- Question the child
- Use pain rating scales
- Evaluate behavior
- Secure parents involvement
- Take pain into account
- Take action

**Question the child**

Self report is the most critical component of pain assessment. Children should be encouraged to describe their pain since their statements reflect the most reliable indicators of pain. Know what word the child uses for pain (e.g., hurt, “owie” or “boo-boo”). Children have words for pain by about 18 months of age and younger children may prefer to use the word “hurt” instead of “pain”. School age children and adolescents who understand concepts of order and numbering are capable of providing more detailed ratings of intensity and descriptions of the quality and location of pain. In obtaining the patient’s pain history, involve the parents, since they know their child.

**Assessment involves both the clinician and the patient and should describe the pain:**

- Location (does the pain radiate, is there referred pain)
- Intensity/severity
- Aggravating and relieving factors

- Goals for pain control [document the patient’s preferred assessment tool and goals for pain control (scores)]
- Description of the pain (i.e., sharp, pulsing, dull)
- Duration

**Use pain rating scales**

Pain rating scales provide subjective, quantitative measures of pain intensity.\(^8\) A scale should be selected that is suitable to the child’s age, cognitive development and cultural background (Table 1).

**Infants**

Neonatal and infant pain assessment requires a scale that relies on behavioral and physiologic cues.

**Behavioral indicators of pain include** facial expressions, cry, gross motor movements, changes in behavioral states and patterns such as sleep.\(^5\) Pre-term infants’ responses to pain are less robust than full term infants.\(^5\) More subtle cues include less crying, weaker grimace, limp, flaccid, listless posturing.\(^5\)

**Facial expression** has been the most widely studied behavioral pain measurement and should be considered the gold standard of behavioral responses for pain in infants. The facial expressions of infants experiencing acute pain include the following characteristics: eyes forcibly closed, brows lowered and furrowed, nasal roots broadened and bulged, deepened nasolabial furrow, a square mouth and a taut cupped tongue.\(^5\) The evaluation of procedural pain in infants can be performed using the NFCS (Neonatal Facial Coding System) which is a valid and reliable coding system for quantifying facial actions associated with acute pain in infancy.\(^5\) Other behavioral assessment tools include the NIPS (Neonatal Infant Pain Scale). The NIPS
Pain Scales Description Age Range Considerations

<table>
<thead>
<tr>
<th>Pain Scales</th>
<th>Description</th>
<th>Age Range</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIPS Neonatal Infant Pain Scale</td>
<td>Neonatal Infant Pain Scale assesses facial expression, cry, breathing patterns, movement of arms and legs and state of arousal</td>
<td>Preterm and full term neonates</td>
<td>NIPS rely on behavioral indicators. Quick and easy to use, however less specific due to the use of only behavioral indices and fewer gradations per category</td>
</tr>
<tr>
<td>(FLACC) Faces, Legs, Activity, Cry, Consolability</td>
<td>Faces, Legs, Activity, Cry, Consolability incorporates categories of pain behaviors</td>
<td>&gt;2 months</td>
<td>Simple framework for quantifying pain behaviors in children who may not be able to verbalize the presence or severity of pain</td>
</tr>
<tr>
<td>Faces Pain Scale (Wong and Baker 1988)</td>
<td>Scale consists of 6 cartoon faces ranging from a very happy smiling face depicting no pain to a tearful sad face depicting worst hurt.</td>
<td>3-8 years old</td>
<td>Children may use scale to reflect mood vs. pain; may be inaccurate for chronic pain</td>
</tr>
<tr>
<td>Numerical Rating Scale</td>
<td>Children rate their current pain using numbers with 0 representing the least amount of pain.</td>
<td>5-13 years old</td>
<td>Requires child’s ability to count and have some concept of numbers and their values in relation to other numbers</td>
</tr>
<tr>
<td>VAS (Visual Analogue Scale)</td>
<td>Variety of VAS scales. Some with numbers, word descriptors and some with faces</td>
<td>&gt;8 years old</td>
<td>Reliable and valid in both adults and children. Useful with children who have conquered the concept of ordination which occurs around ages 8-10 years</td>
</tr>
</tbody>
</table>

Table 1. Pain rating scales

uses six categories of assessment, facial expression, cry, breathing patterns, arm movement, leg movement and state of arousal. Multidimensional tools that include behavioral observation and quantification of physiologic parameters include the CRIES (crying, requires oxygen to maintain saturation greater than 95%, increased vital signs, expression, sleeplessness) developed for postoperative pain; and the SUN (Scale for use in newborns). The PIPP is a seven indicator measure that includes behavioral, physiologic and contextual indicators.
Toddlers and preschoolers

Toddlers and pre-schoolers may not understand the word pain but can report “hurt” “owies” ‘boo boo” or “ouch”. Clinician should determine what words these children use to describe pain and apply these words in assessment of pain. Structured questioning or standardized pain assessment tools should be utilized to evaluate pain. The Oucher scale is valid for children aged 3 to 12 years. It combines pictures with a vertical Visual Analog Scale (VAS) and is available with photographs of Caucasian, African American and Hispanic children. The CHEOPS (Children’s Hospital of Eastern Ontario Pain Score) is designed to assess pain in non-verbal children and is a 13 point behavioral scale that has been validated for children 1-5 years of age. A more recently developed behavioral tool is the FLACC (Faces, Legs, Activity, Cry and Consolability Scale) which incorporates five categories of pain behavior and has gained appeal in the measurement of pain for children who cannot report pain.

School age children and adolescents

School age children can communicate pain in more abstract terms and can respond to direct questioning regarding their pain. Many of the self-report tools used with school age children are applicable for adolescents. These include the FACES scales, Oucher, Poker Chip Tool, numeric rating scale (Fig.2) and the Visual Analog Scale.

Children with cognitive impairment

Pain may be more difficult to assess in children with cognitive impairment. The appearance of insensitivity to pain in patients with cognitive impairments may be the result of an inability to express pain and the failure of caretakers to recognize their pain signals. There are behavioral scales to measure pain intensity for children who are unable to communicate due to cognitive impairment.

Evaluating behavior and physiologic changes

Behavior of children should be interpreted cautiously as sometimes watching television, playing or sleeping may be strategies for coping with pain. They may become irritable, angry, sad, depressed, withdrawn and/or exhibit aggressive behavior when in pain. Children may also deny pain to avoid suspected undesirable events and prolonging the hospital stay. Physiologic changes such as increased heart rate, blood pressure, increased respirations, decreased oxygen saturation, dilation of pupils, flushing or pallor may be seen in early onset of acute pain. However these changes subside with continuing or chronic pain.

Secure parents’ involvement

Parents are often the primary source of information regarding their children’s pain. Children may feel more comfortable expressing their pain when their parents are present.
Parents are able to identify behaviors children exhibit when in pain and predict the intensity of the child’s response to pain. Parents also can be a supportive presence in helping the child to cope with pain more effectively. In one study, 99% of children state that “having their parent present provided the most comfort when in pain”.

**Take the cause of pain into account**

The pathology of pain may provide clues to the expected intensity and type of pain. For example, pain associated with vaso-occlusive crises in sickle cell disease is often severe. Sore throat pain may range from mild to severe. Since pain perception is always subjective, pain assessment tools should be used to gauge intensity of pain.

**Take action**

The reason to assess pain is to be able to relieve or minimize it by using analgesic/adjuvant drugs and nonpharmacologic methods. An important point to remember is that regardless of the treatment used to relieve the pain, it is essential to monitor and evaluate the effectiveness of the interventions.

**Integrative pain management**

State-of-the-art pain management in the 21st century demands that along with pharmacological management, supportive techniques and non pharmacological measures should be used in approach to the management of a child’s pain and suffering.

**Pharmacologic pain management**

The current standard for the management of pain in children consists of four concepts: “by the ladder”, “by the clock”, “by the mouth”, and “by the child”. This means that pain management in children should follow the World Health Organization Analgesic Stepladder, be administered on a scheduled basis, be given by the least invasive route, and be tailored to the individual child’s circumstance and needs (McGrath, 1996).

1. **By the ladder**

   The WHO Analgesic Stepladder is a multi-step approach to treating pain, and is a guide for initiating analgesic drugs and dosages that correspond to the patient’s reported level of pain. The ladder starts with non-opioid oral drugs for mild pain and progresses to strong opioids, adjuvants and invasive therapies for severe and/or intractable pain (Fig.3). It is important to keep in mind that the potency of analgesia should be matched to the child’s reported level of pain. For example, if children report severe pain, they should be started on a potent opioid such as morphine. It would be inappropriate to start a child with severe pain on ibuprofen or a weak opioid and progress up the ladder from that point.

2. **By the clock**

   One of the most common causes of undermedication of children with analgesic drugs is the use of PRN (pro re nata or “as needed”) dosing schedules. The goal of pain management is to optimize pain relief while minimizing undesirable side effects. When analgesics are administered on a scheduled basis a steady therapeutic state is achieved, providing consistent pain relief, and allowing for tolerance to side effects to develop. When a PRN schedule is used, analgesia is frequently administered in a random pattern. This results in brief periods of pain relief followed by potentially long periods of pain with increasing undesirable side effects. PRN dosing has been found to be ineffective as the only method of pain management, but can be appropriate when used to provide extra doses of a regularly scheduled analgesia to treat ‘breakthrough’ pain (i.e., episode of intense or severe pain).
3. By the mouth

The route used to administer medication to children must be carefully considered. Generally, the least invasive route should be used to administer analgesic medications.

Routes of administration

**Oral/Sublingual** : Children who are able to swallow tablets can achieve excellent pain control with oral medications, and this route should be the first choice for administration of analgesic medication.

When changing from parenteral administration to oral administration of opioid analgesics, health care providers must calculate the appropriate dosage adjustment to maintain equal analgesic strength to the parenteral dose to assure adequate pain control.

**Rectal** : Many drugs are available as rectal suppositories, however absorption of drugs by the rectal route can be inconsistent. The rectal route is also contraindicated in children with neutropenia or thrombocytopenia because of the risk of infection or bleeding. Generally, children find the administration of suppositories uncomfortable and invasive. It is not a preferred route if there are other less invasive routes available.

**Transdermal/Topical** : For children who cannot take oral medications and have no intravenous access, this route is an acceptable alternative and provides excellent pain control. EMLA® (prilocaine/lidocaine) or other topical agents, should be used to anesthetize the site prior to inserting the subcutaneous needle or cannula, making the procedure virtually painless.

**Intramuscular** : The intramuscular route should be avoided in administering analgesic medication to a child. Children instinctively fear ‘shots’ and will not report pain if they believe they will be given an injection as a result.

**Intravenous** : Oral analgesic medications should be given for as long as the child is able and willing to take them, and as long as the pain can be

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**Fig. 3. Therapeutic ladder for pain management.**
adequately controlled. However, for children with analgesic dose requirements that exceed reasonable oral dosing, or for whom oral medications are not tolerated, the intravenous route is the most appropriate.

Epidural/Caudal/Intrathecal: When high doses of systemic opioids are ineffective in relieving pain or are causing intolerable side effects (severe constipation, myoclonus, excessive nausea/vomiting), administration of analgesics via the epidural or intrathecal route will often relieve pain. Decisions regarding patient eligibility, level of catheter placement, and appropriate drugs and doses should be made in consultation with an anesthesiologist and according to institutional policies.

4. By the child

The needs of the individual child must be taken into account when determining dosages of pain medications. There is not a standard dose that will work for all children. The goal is to provide each child with the dose of analgesic medication that prevents recurrence of pain prior to the next dose, keeping the child pain-free.

Analgesic drugs

Oral dextrose in neonates: Behavioral pain responses to venepuncture and other painful procedures can be relieved by oral dextrose as a nonpharmacologic, safe and effective method. Analgesia elicited by sweet solutions is probably mediated by the release of endogenous opioids. So using dextrose solution in neonates is a useful, feasible, and nonexpensive method of inducing analgesia for painful peripheral venepuncture.

Nonopioids: Frequently used nonopioids include paracetamol (acetaminophen) and ibuprofen. Non-steroidal anti-inflammatory drugs (NSAIDs) (Table 2) have analgesic, anti-pyretic and anti-inflammatory activity. NSAIDs act peripherally to provide their analgesic effect by interfering with the synthesis of prostaglandin, through the inhibition of cyclooxygenase (COX). There are two isoenzymes of COX; COX-1 and COX-2. By selectively inhibiting the COX-2 isoform, prostaglandin pathways are influenced, decreasing pain and inflammation and avoiding the toxicities of the inhibition of COX-1. Most NSAIDs are non selective inhibitors of COX. There is limited pediatric data for dosing and side effects of the selective COX-2 inhibitors. The side effects of nonselective NSAIDs include decreased platelet aggregation, gastric irritation, and the potential for renal toxicity with long term use. Children with low platelet counts or who are neutropenic should be monitored carefully when taking nonselective NSAIDs for pain relief.

Opioids: Opioids bind with certain receptors (Mu, Kappa, and Delta) in the CNS and peripheral tissues to provide analgesic effects. Mu receptors are located in the CNS and provide central analgesia, but also play a role in the development of respiratory depression, physical dependence and withdrawal symptoms. Kappa receptors are located in greatest concentration in the cerebral cortex and substantia gelatinosa of the dorsal horn. Kappa receptors are responsible for analgesia at the level of the spinal cord and the brain, but have less of a role in physical dependence and withdrawal. Delta receptors are concentrated in the substantia gelatinosa of the dorsal horn and have a primary effect upon spinal and supraspinal analgesia.

Mu-agonist drugs are the most commonly used class of opioids and include drugs such as...
Morphine, fentanyl and codeine. The analgesic effect of these drugs has no ceiling and dosing is limited only by the presence of unmanageable side effects.

Morphine is the standard opioid to which others are compared and remains a valuable drug for the treatment of acute, severe pain. Peak effect after IV bolus is 15 min. Duration of action is between 2 and 3 hours. Both liver and kidney are responsible for morphine elimination. The liver mainly metabolizes it. One of the principal metabolites, M6G, is also a potent opioid agonist and may accumulate in renal failure.

**Administration:** Dilute in 5% glucose or 0.9% saline. Stop or reduce infusion each day and restart when first signs of discomfort appear. Failure to assess daily will result in overdosage and difficulty in weaning patient from ventilation.

Meperidine (Pethidine) also falls into the class of Mu-agonists. However, meperidine has fallen out of favor as an analgesic drug, due to its short duration of action and the accumulation of a toxic metabolite normeperidine, which causes undesirable CNS side effects, including seizures, at low doses of the drug.

Depending on the opioid, they can be given orally, rectally, as subcutaneous or intravenous infusions, intramuscularly, transdermally and directly into the CNS via epidural/caudal/intrathecal injection.

Adverse effects: The most common side effects of opioid analgesia in children are constipation, sedation, pruritis and nausea/vomiting. Respiratory depression, although the most frequently cited concern of health care providers, is a relatively rare occurrence. In the event mild respiratory suppression occurs it is easily managed by awakening the child, giving oxygen, and decreasing further opioid doses by 25%. In the event of severe respiratory depression, the American Pain Society (1999) recommends using naloxone in small doses for children < 40 kg. They recommend a dose of 0.5 mcg/kg IV every two minutes until respirations improve.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>10 to 15 mg/kg dose q 4 hour PO to a max of 650mg dose</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10 to 15 mg/kg dose q 6 to 8 hour PO to a max of 650mg dose</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>10 mg/kg dose to a max single dose of 800 mg q 6 to 8 hour PO</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>1 to 1.5 mg/kg dose to a max single dose of 75 mg q 8 to 12 hours</td>
</tr>
<tr>
<td>Naproxen</td>
<td>5 to 7.5 mg/kg dose to a max of 500 mg dose q 12 hour PO</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.5 to 1 mg/kg as single dose IM to a max of 60 mg, followed by 0.5 mg/kg IV q 6 hour to a max single dose of 30 mg. Max duration is 5 days (useful in short term pain management) Limited data on use of oral Ketorolac in children.</td>
</tr>
</tbody>
</table>

Table 2. Nonsteroidal anti-inflammatory drugs used for pain
All opioids have the potential for tolerance, physical dependence and addiction. The phenomenon of drug tolerance must be separated from the fear of addiction in order to appropriately use opioid therapy. Tolerance refers to the progressive decline in analgesic potency and the need to increase doses of the opioid to achieve the same analgesic effect over time. Tolerance also occurs to the side effects of opioids with long term administration, particularly sedation and respiratory depression. Tolerance is easily managed by increasing the dose of the opioid, adding appropriate adjuvants, or switching to another opioid drug. Cross tolerance between opioids is incomplete; therefore, the dose for the new opioid should be reduced up to 50% of the equianalgesic dose and re-titrated from there for adequate pain relief (Table 3).

**Patient-controlled analgesia**

Patient-controlled analgesia (PCA) permits patients to self-administer small doses of opioid analgesics intravenously or subcutaneously at frequent intervals. PCA is a portable, computerized syringe-system connected to a patient’s intravenous line that allows self-administration of medication for pain relief. PCA allows the child to push a hand-held button that attaches to and activates the machine. The medication used in the PCA machine is usually one of several narcotics commonly used in children. Child is monitored by his or her nurse, by intensivist and sometimes with electronic monitors that measure heart rate or rhythm, breathing rate and/or oxygen “saturation.” Adjustments can be made in the dose and sometimes the type of narcotic used so that child can be made as comfortable as possible (Table 4). Among the many safety features designed into PCA machines is a “lockout” period. The “lockout” is programmed to prevent one dose from being given right after the previous dose. Generally speaking, children six years of age or older are candidates for PCA. Children younger than that are less likely to push the button. PCA is used in the management of moderate-to-severe, pain often in postoperative, burn, sickle cell and cancer pain. PCA allows the patient to assume control of analgesic administration without the need for nursing intervention, eliminating administration delays. Although there are theoretical risks to giving a child narcotics by PCA or any other route, PCA has been safely used in children and has become fairly routine at most children’s hospitals.

**Newer analgesic agents**

**Central α₂-adrenoceptor agonist**

Since the first report of clonidine, an α₂ adrenoceptor agonist, the indications for this class of drugs have continued to expand. In December 1999, dexmedetomidine was approved as the most recent agent in this group and was introduced into clinical practice as a short-term sedative (<24 hours).

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α₂-adrenoceptor agonism. The mechanism of action is unique and differs from those of currently used sedative agents, including clonidine. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation and analgesia. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidney; decreased intraocular pressure and decreased insulin release from the pancreas. In general, presynaptic activation of the
### Table 3. Opioid used for relief of pain

<table>
<thead>
<tr>
<th>Equi-analgesic drug</th>
<th>Equianalgesic Dose (parenteral)</th>
<th>Starting dose intravenous</th>
<th>Intravenous oral ratio</th>
<th>Onset</th>
<th>Duration</th>
<th>Max. dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>bolus dose: 50–100 μg/kg every 2–4 hr continuous infusion: 10–30 μg/kg/h</td>
<td>1:3</td>
<td>1-2 hr</td>
<td>4-6 hr</td>
<td>60 mg/dose</td>
<td>Advantages: Rapid onset action minimal respiratory depression orally Disadvantages: Nausea, vomiting, constipation, respiratory depression, hypotension, CNS depression</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100–250 μg</td>
<td>bolus dose: 1–3 μg/kg (slowly over 3–5 min fast bolus may cause thorax rigidity) continuous infusion: 1–2 μg/kg/h</td>
<td>1:1 (intravenous to transdermal)</td>
<td>1-2 min</td>
<td>20-30 min</td>
<td>3mcg/kg/dose</td>
<td>Advantages: Rapid onset if given IV, short duration, potent analgesic Disadvantages: Respiratory depression, apnea may precede alteration of consciousness chest wall rigidity if given too rapidly.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>bolus dose 15–20 μg/kg every 4 hr continuous infusion: 5 μg/kg/hr</td>
<td>1:5</td>
<td>almost immediately</td>
<td>2-4 hour</td>
<td>5 mg/dose</td>
<td>Advantages: Rapid onset if given IV; less sedating and fewer systemic side effects than morphine; less pruritis than morphine Disadvantages: Respiratory depression, CNS depression, sedation</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100 mg</td>
<td>bolus dose: 1 mg/kg every 3–4 hr continuous infusion: 0.25 mg/kg/h</td>
<td>1:1</td>
<td>4-6 hrs</td>
<td></td>
<td></td>
<td>Advantages: Less respiratory depression and sedation</td>
</tr>
</tbody>
</table>
α₂-adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α₂-adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation and anxiolysis. Dexmedetomidine combines all these effects, thus avoiding some of the effects of multiagent therapies. Side effects consist of mild to moderate cardiovascular depression, with slight decreases in blood pressure and heart rate. It is available in the United States, not yet available in India.

Non-pharmacologic approaches to pain

- Although analgesics are the mainstay of pain relief, most pain is best treated with a combination of drug (analgesic) and non-drug approaches.
- Non-drug approaches to pain management can enhance comfort, promote sleep and enhance the quality of life.

Non-pharmacologic interventions should routinely be used. Although these strategies alone are frequently insufficient for moderate to severe pain, they are usually helpful in conjunction with pharmacological therapy. Such strategies are shown in Table 5.

**Nonpharmacologic interventions may be provided, based on training, by:** Physicians, nurses, physical, occupational, recreation, art, music, child-life or other therapists, social workers, religious or spiritual leaders, clinical psychologists and others.
Points to Remember

- Pain management is an important aspect of medical management of all neonates and children that every pediatrician should be familiar with.

- Failure to assess pain is a critical factor leading to under treatment. Assessment and documentation should be done at regular intervals after initiation of treatment, at each new report of pain, after pharmacologic or nonpharmacologic intervention, at an appropriate interval (e.g., 15-30 minutes after parenteral therapy, 1 hour after oral administration).

- When there is uncertainty about the presence or amount of pain even after using assessment strategies as with infants or young children, a diagnostic trial of analgesics is appropriate. Most patients can be managed by the pediatrician in outpatient department or wards.

- For postoperative pain, management with intravenous agents is required with proper monitoring of respiratory and cardiovascular status, preferably in intensive care setting.

- A consultation with pain specialist (anesthesiologist) is necessary only in situations of intractable or chronic pain not responding to usual medications.

References

ASSESSMENT OF VISION IN A CHILD

* Sumana Datta
** Rakhi Bandyopadhyay
*** Himadri Datta

Abstract: Early recognition of any visual impairment is very important because significant visual impairment has a serious impact on all areas of development including cognition, language, social, gross and fine motor abilities. Vision assessment is an integral aspect of examination of a pediatric patient and it is possible to assess vision, at any age, using age-appropriate vision screening methods.

Keywords: Vision, Screening, Child.

Normal visual development and functions

In normal visual development, a child starts by observing the mother’s face. The developing infant brain is very plastic and vulnerable to environmental stimulation. Early stimulation with a clear retinal image to each eye and proper eye alignment is required for the development of binocular motor fusion, high grade stereopsis and excellent visual acuity of each eye. Strabismus or blurred retinal image (mono-ocular or binocular) in early infancy will disrupt normal visual development and lead to anatomical and functional changes to the visual centers in the brain. This is known as amblyopia. Children are susceptible to develop amblyopia between birth and 7 to 8 years of age. The earlier the onset of abnormal stimulation, the greater the visual deficit. The critical period for visual development is during the first 3 months of life. By 9 years of age, the visual system is mature enough to be resistant to the effects of abnormal visual stimuli.

Visual milestones

• The pupillary light reflex is present at 30 weeks of gestation.
• Blink is present by 2 to 5 months.
• Fixation starts to develop by 2 months and is well developed by 6 months.
• Optokinetic nystagmus (OKN) is present at birth. The pursuit movement has a directional bias, with the temporal to nasal pursuit being better than nasal to temporal. This is present till 2 to 4 months of age, after which, this bias is no longer present.
• Accommodation develops by about 4 months of age.
• Stereopsis is present by 3 to 7 months.
• At birth, 67% of neonates are exotropic, 1% esotropic and 30% are straight. Ocular alignment is stabilized by 2 months.
• Foveal maturation is complete by 4 months.
• Optic nerve myelination is complete by 7 months to 2 years.
Normal visual acuity in a child

Visual acuity at birth is quite poor, being 20/400 to 20/800. It reaches adult levels by about 18 to 24 month, when tested by the fixation preference method.

Key points for measuring a child’s vision

- The first step will be to create rapport with the child, to make him comfortable.
- The examination room should be a child-friendly one, with a lot of age appropriate toys.
- Talking to the parent before the examination, will often make the child more receptive to the examination.
- The format of examination should be more like a game in which the child is encouraged to participate.
- Small children perform better when seated on mother’s lap.
- Occlusion, during vision testing, in a small child may be facilitated by asking the parent to cover each eye, taking care not to allow the child to peek between fingers or press too firmly.
- If the child is crying or hungry it is better to postpone the examination for sometime.
- To attract the child’s attention, an interesting object like a torch light or a brightly coloured toy can be used. Large objects with high contrast forms activate the visual pathways more effectively than light without form.

Pediatric vision screening includes eliciting a detailed history thorough examination as appropriate for the age of the patient, referral for a comprehensive eye check-up, when indicated.

I. History

Birth history should include date of birth, consanguinity among parents, gestational age, history of prematurity, birth weight, any significant antenatal, intranatal, postnatal or perinatal complications, hospitalization and attainment of developmental milestones.

Chief complaint and reason for eye evaluation. Ocular history including prior eye diseases and treatments, family history of ocular diseases and relevant systemic illnesses should be sought.

II. Vision screening examination

A. Neonates:

Vision assessment in neonates consists of:

1. External examination to rule out congenital structural abnormalities.
2. Pupillary reflex to assess for poor or unequal reaction to light
3. Red reflex test and Bruckner test

The Red reflex test is performed by looking at each eye of the patient, with a direct ophthalmoscope set at zero, from a distance of 18 inches, to assess the clarity of the ocular media. The examiner needs to answer three questions:

(a) Is there a red reflex from each eye?
(b) Are the red reflexes from each eye equal?
(c) Is the quality of the red reflex normal for the individual baby? (taking into account the skin tone and race or ethnicity)

If the answer to any of these three questions is no, then the red reflex is abnormal.

The Bruckner test is performed in a dimly lit room, with the examiner at a distance of
30 inches (0.75m) from the child. The examiner overlaps both the pupils simultaneously, creating a binocular red reflex using the largest circular light of the ophthalmoscope, usually set at zero. Normally the red reflex from each eye should be of the same colour and brightness. Abnormalities include:

(a) asymmetrical reflexes, where one reflex is duller or brighter

(b) different colour of the red reflex, including a white reflex, a partially or totally obscured reflex, or crescents present in the reflex. Asymmetrical red reflexes can be seen in anisometropia and strabismus. An altered red reflex can be due to retinoblastoma, cataract or vitreous haemorrhage. Crescents in the red reflex may signify presence of refractive errors.

A widening of lid fissures in a neonate, when the room lights are extinguished indicates presence of, at least light perception.

The visual acuity in neonates is quite poor, in the range of 20/400, fixation is not developed and ocular alignment is not stabilized.

**B. Infants:**

In an infant aged between 3 to 6 months the following tests can be done to assess vision

1. Ability of a cooperative infant to fix and follow a target with both eyes
2. Red reflex
3. External examination
4. Pupillary examination

In an infant aged between 6 to 12 months the following tests can be done to assess vision

1. Ability to fix and follow a target, with each eye
2. Alternate occlusion
3. Corneal light reflex
4. Red reflex
5. External examination
6. Pupillary examination

**Fixation**

Fixation develops by 2 to 3 months. This progressively improves and by 6 months of age, an infant should clearly fixate and follow an object.

Fixation is tested by the use of a bright coloured toy or light, though infants find the human face a much more compelling target. If fixation is present, the infant looks directly at the target, visually locks on the target and accurately follows the moving target. Usually at age 6 months and thereafter, fixation is described as central, steady and maintained or as uncentral, unsteady and unmaintained. “Central” refers to the corneal light reflex from a fixation light falling at the centre of the pupil. “Steady” refers to absence of nystagmus or oscillations. “Maintained” refers to the ability to keep the eye fixed on the target, when either eye is covered. Central fixation indicates foveal vision usually in the range of 20/100 or better. If fixation is not central, it means that the fovea is not fixating and the patient is viewing from an extrafoveal part of the retina. This is called eccentric fixation. If eccentric fixation is present, it indicates a visual acuity of 20/200 or less. Patients with eccentric fixation appear to be looking to the side and not at the fixation target. They have poor smooth pursuit or following movements and do not accurately follow a moving object.

Fixation preference is a term used, when, with both eyes open, the patient preferentially uses one eye for fixation. That eye is the dominant
eye and the other eye becomes the non dominant eye. Presence of a strong fixation preference indicates amblyopia in the non dominant eye.

**Fixation preference test**: This is done by alternately occluding each eye and observing the infant’s behavior. If the infant vigorously objects to occlusion of one eye and the uncovered eye shows wandering movements, then there is a possibility of poor vision in the uncovered eye.

**Induced tropia test or Vertical prism test**: This test is designed specifically to assess fixation preference and to diagnose amblyopia in preverbal children. A 10-diopter prism with base down or base up is placed before one eye while the patient looks at an appropriate target. The prism is then shifted to the other eye. The test assumes that the patient will always prefer to fix with the eye without the prism, since the prism induces a vertical squint and consequent decline in visual acuity. If the acuity is the same in both eyes, alternating fixation will be seen, as the prism is moved from one eye to the other.

If the patient has strong fixation preference, he will continue to fix with the preferred eye, even when the prism is placed in front of it. This signifies amblyopia in the non preferred eye.

- Infants with large angle esotropia and tight medial rectus muscles have difficulty bringing the eyes to the primary position, so the eyes stay adducted. These infants are unable to abduct. They use the right eye to view things to the left and the left eye to view things to the right. This is known as cross fixation. Presence of cross fixation usually signifies equal vision.

- In presence of squint, fixation preference can be quantified by briefly covering the nonsquinting (preferred) eye to force fixation to the squinted eye. The cover is then removed from the preferred eye and it is observed for how long the nonpreferred eye is able to maintain fixation before fixation switches to the preferred eye. If it is immediate, then there is a strong fixation preference and the squinted eye is amblyopic. If fixation is maintained for 5 seconds or through a blink or through a following movement, the vision in the nonpreferred eye is probably equal to the preferred eye.

**C. Preschool age**:

From 1 year age till the time the child is able to cooperate for subjective visual acuity chart testing, he is tested by the same methods used to test infants. A child of 1-2 years of age can be tested by using small candy beads, measuring 1 to 2 mm in size, placed on the examiners palm at a distance of 33 cm. If the child can pick up the beads, it signifies that he/she has a visual acuity of at least 6/24 or 20/60. Although young children can not read letters, by the age of 2.5 to 3 years over 85% of children are able to match letters and by 3 years most children can do so. Cardiff cards using vanishing optotypes of pictures of familiar objects like a car, a fish or a bus have been used to test vision in a child, not cooperative enough for standard visual acuity testing. In Cardiff cards the optotypes or pictures are such that they vanish instead of becoming blurred. Between 3 to 4 years, the format for testing for visual acuity should be:

1. Visual acuity
2. Corneal reflex/cover-uncover test
3. Red reflex
4. External examination
5. Pupil examination

**Visual acuity testing**

- This should be done using standard charts at the earliest age that is possible. Patients should be encouraged to learn optotype – equivalent tests at the earliest possible age.
• The standard distance is 20 feet (6 meters), but testing at 10 feet (3 meters) is more successful in some children. Near vision is assessed at a distance of 40 cm.

• It should be measured in each eye separately.

• Preferably, at each visit, the same viewing distance and lighting conditions are to be used.

• In increasing order of difficulty, the tests are (Fig. 1)
  – Lea symbols
  – Allen picture test
  – HOTV
  – Sheridan- Gardner test
  – Cambridge single and crowding cards
  – Tumbling E
  – Snellen numbers
  – Snellen letters

• Testing visual acuity with isolated letters or figures may show falsely increased visual acuity. Hence crowded optotypes or linear visual acuity (a row of optotypes) should be used wherever possible. This is because single letters are easier to identify than letters arranged in groups (crowded optotypes) or in lines (row of optotypes).

• Pointing to one letter in a line of letters with a finger makes the task easier and should therefore be avoided. Pointing to the line, which is to be read is acceptable, as it helps the child know which line to read.

Fig 1. Visual acuity tests
• Patients should not be allowed to lean forward during examination.

• Young children are quick to memorise letters presented to them during examination. Charts having different letters may have to be used for visual acuity examination, in such cases.

• Visual acuity must be measured at distance and near using tests with same optotypes.

• When testing vision, it is critical to ensure monocular testing. The occluded eye should be completely covered. Children should not use their own hand as an occluder and if an occluding paddle is used, the child should not hold it.

• Only in cases of nystagmus, visual acuity is recorded first with both eyes open, as binocular vision is often better than unioocular vision and placing an occluder during monocular vision testing can lead to worsening of nystagmus with decline in visual acuity. Monocular vision testing in nystagmus, may require blurring of the contralateral eye with a high plus lens (+4.00 to +5.00 Dioptres).

• At the age of 3 to 4 years, visual acuity of 20/50 or worse or 2 lines of difference between the eyes is an indication for referral.

School age child: At around 5 years

All tests for vision are, as in the age 3 and 4 years. The indications for referral is a visual acuity of 20/40 or worse or a 2 line difference in visual acuity testing has to be repeated between two eyes, every 1 to 2 years after the age of 5 years All tests remain the same as above. The indication for referral is a visual acuity of 20/30 or worse or a 2 line difference between the two eyes.

Points to Remember

• **Vision assessment is an integral part of examination of the child and early recognition of visual impairment is very important.**

• **While diagnosing visual impairment, it is mandatory to consider normal visual milestones.**

• **Age appropriate vision screening methods have to be chosen.**

Bibliography


**NEWS AND NOTES**

“THE SECOND NATIONAL ASSEMBLY ON PEDIATRIC EMERGENCY MEDICINE”

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Venue: NIMHANS, Bangalore

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Diagnostic Pitfalls in a Child with Fever

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Abstract: Fever is the most common symptom for which a physician is consulted. Appropriate diagnosis is needed for proper management. A systematic approach is required to achieve this. Pitfalls can occur in various situations like documentation of fever, identifying severity of the underlying illness, interpretation of symptoms, clinical examination, ordering and interpretation of laboratory tests, treatment etc. Pitfalls in any of these steps may lead to prolonged morbidity and related sequelae.

Keywords: Fever, Diagnostic pitfalls, History, Clinical examination.

Documentation of Fever

It is not unusual to meet this common question in clinical practice that the head of a younger child remains warmer than the rest of the body. Parents notice it by putting the hand on the forehead. Evening rise of body temperature (normal circadian rhythm) is also commonly mistaken as the fever. Many a times, these children do receive various medicines including antipyretics, antimalarials, antibiotics and occasionally antituberculous drugs with or without laboratory investigations. Documentation of fever is almost always lacking in these children. Very often, measurement of body temperature is found within normal range in this group. In young children as the thermoregulation system is not mature, the body temperature may be higher in the hot environment (summer). It is very common in neonates and is termed as dehydration fever. Over wrapping the infants in winter season, after exercise or heavy meal in older children may show mild elevation of body temperature which should not be mistaken for fever. Various methods and devices are available for measuring body temperature. They should be used appropriately as per standard recommendations to document fever so that diagnostic pitfalls can be avoided.

Identification of Serious Illnesses

Once fever is documented, it is very essential for the clinician to identify any serious underlying disease. At the time of presentation, apparently the child may not be looking serious. Still on detailed history and thorough clinical examination, there may be subtle signs indicating impending serious illnesses like congestive heart failure, shock, CNS infections, septicemia, etc. If such conditions are not identified in time, the patient may become seriously ill within a short time which at times may be fatal. One should always check for the following symptoms and signs suggesting serious illnesses. They should never be missed.
Changes in sensorium, drowsiness, signs of meningeal irritation, bulging fontanelle, suggesting intracranial infection.

Disproportionate tachycardia, tachypnea, delayed capillary refill, reduced urine output, core-skin temperature difference > 3°F indicating impending shock

Fever in a neonate

Membrane over the tonsils in a case of diphtheria

Tachypnoea, chest retractions, stridor, grunting suggesting respiratory distress

Purpuric, petechial or ecchymotic skin lesions indicating meningococcemia, DHF or septicemia

Known immunodeficiency status, V-P shunt, cardiac disease, etc.

Pattern of fever

In the present era of self medication with liberal use of antipyretics and irrational use of antibiotics, typical pattern of fever is hardly seen. Fever with rigors need not be malaria always. Fever in malaria is erratic and often does not follow the typical pattern described in textbooks, especially in infants and young children. Fever with rigors may be due to malaria, UTI, bacterial endocarditis, pneumonia, brucellosis, deep seated abscesses, etc. Low grade fever with evening rise described in the past for tuberculosis and certain malignancies, does not hold good in children. Gradually improving/decreasing fever by 3 to 4 days suggests self limiting viral infection, while bacterial infections peak by that time. Certain conditions have biphasic pattern of fever. It can be viral or due to infections known to have secondary immune phase like dengue haemorrhagic fever (DHF) and leptospirosis. In these situations, one should wait for certain days before announcing the cure. At times, second phase (immune phase) may be serious and can endanger the life in conditions like DHF and leptospirosis. Parents should be informed to watch for danger signs so that timely management can be life saving. Unless the physician is aware of this phenomenon, it is interpreted as relapse of the disease or development of some complications and patient is mismanaged. In malignant hyperthermia, the child suddenly develops high grade fever (> 105°F), tachycardia, tachypnea, hypoxemia, cyanosis and acidosis on exposure to certain drugs or on induction of anaesthesia before surgery. Very often, it is misdiagnosed as pyrogen induced fever or septicemia. Unless it is recognised and managed promptly with injection dantrolene and supportive care, it can be fatal. A single isolated fever spike should not be mistaken for an infectious disease. Such a spike is common with infusion of blood products, drugs, procedures or manipulation of a catheter on a colonized or infected body surface. Exposure to very high environmental temperature (in summer) and development of hyperpyrexia along with absence of sweating is sufficient to diagnose heat stroke. It should not be mistaken for CNS infection or cerebral malaria especially with changes in sensorium. Fever with absence of sweating may be due to diabetes insipidus, ectodermal dysplasia.

Nowadays, fever pattern per se is not very characteristic of any specific condition. Still proper documentation of fever and observing its clinical characteristics with consideration of drugs received by the child, can provide very useful information, avoiding pitfalls in the diagnosis.

Accompanying symptoms

Generally, specific symptoms help in localizing the site of infection such as cough and cold in respiratory infection, diarrhoea and
vomiting in GI tract infection, etc. Widespread involvement of a system (upper and lower respiratory tract) or multiple systems (Respiratory and GI tract) is indicative of viral infection, whereas localization of infection is characteristic of bacterial infection.\textsuperscript{1,2,4,6} Malaria and enteric fever are known for odd presentations, especially in infants and young children. Respiratory tract involvement with cough and wheezing, dysentery and urticaria are known presentations of malaria.\textsuperscript{9-13} Uncommonly, cough, wheezing and crepitations may be prominent features in a case of enteric fever. Initially, they are treated as respiratory tract infections and the diagnosis of typhoid or malaria may be late, sometimes with complications.

**Fever without localizing symptoms**

It is always difficult to diagnose the cause of fever in the absence of any accompanying symptoms especially in the first week. Thus UTI often presents without any symptom referable to urinary tract and pneumonia without cough. Malaria, viral infection, UTI and typhoid fever are common conditions presenting with fever without any localizing symptoms. Careful evaluation of progress of the patient is mandatory in such cases and early investigations may be justified for conditions like malaria and UTI.\textsuperscript{1-4,6,14,15}

**Non specific symptoms**

Headache, bodyache, vomiting, anorexia and irritability may be non specific symptoms associated with fever. Such symptoms are often worst at peak of fever and disappear with fall of fever. These symptoms should not be mistaken for CNS and hepatic infections,\textsuperscript{1} otherwise the patient may be submitted for unnecessary investigations. Persistence of these symptoms needs further workup. Refusal of feeds in neonates and infant may indicate serious infection and may not localize to any system. Sometimes it may be the only symptom in small infants and should therefore never be ignored.

**Thorough clinical examination**\textsuperscript{1,6,14}

Lack of detailed history and thorough physical examination is perhaps the most common diagnostic pitfalls in a case of fever. Daily observations regarding progress of symptoms and head to toe clinical examination should be recorded. Even a minor point noticed by parents or physician should be noted. It may not be important on the spot, but with evolving disease process, it may prove to be an important pointer for a specific condition. Regular unbiased evaluation at certain intervals in a case of longer duration of fever is quite rewarding. Development of skin rashes, bleeding spots, not moving limb in a case of osteomyelitis or congenital syphilis, bony tenderness in a case of leukemia, noticing an abscess over perianal region or covered areas are examples which are noted on thorough clinical examination. Per rectal examination is important from this point of view. Examination of throat and otoscopic examination of ears are commonly lacking in office practice. Localized inflammed, enlarged tonsils or granular pharyngitis with tender tonsillar lymph nodes are result of bacterial infection. Faucial membrane denotes possibility of diphtheria so also unilateral blood stained nasal discharge. Ophthalmic examination of eyes should be routine in a case of fever. Methodical systemic examination contributes a lot in a case of fever by excluding certain conditions and strengthening the possibility of others.

**Pitfalls in laboratory investigations**\textsuperscript{1,4}

Relevant history and thorough physical examination should form the basis of probable diagnosis. Laboratory tests should be performed at appropriate time with reference to clinical diagnosis. It helps to reach the diagnosis and
further planning of management. Irrational investigations does not only waste the money but also misguides in the diagnosis. In this era of plethora of investigations in the market, its injudicious use has become the biggest pitfall in the diagnosis.

In the office practice, in a case of fever, once the serious conditions are ruled out, there is no reason to rush for laboratory investigations. In most cases of fever, viral infection becomes obvious and bacterial infection gets localized in 3 to 4 days. Persistent fever beyond day 4 without localizing signs deserves laboratory investigations. Complete blood count, peripheral blood smear examination, urine routine and culture study and chest x-ray are justified in these patients. In suspected serious conditions like CNS infection, meningococcemia, shock, cerebral malaria and fever in a neonate or immunodeficiency of the child, reluctance to do investigations or delay in performing investigations may prove to be great blunder. In this group, earliest investigations and appropriate, prompt action may make the outcome favourable. In children with no definitive diagnosis beyond day 4, blood culture is an important test. The sample for blood culture should be collected before antibiotic therapy is commenced. CSF examination is mandatory in every suspected case of meningitis and also in neonates and young infants without localization. Treating the patient of meningitis with antibiotics without CSF examination is not only a pitfall in diagnosis, but also is responsible for complications like hydrocephalus, brain abscess, etc. due to incomplete and inadequate treatment. In a case of prolonged fever, while performing various tests, available materials should be sent for culture like bone marrow, CSF, ascitic fluid, pleural fluid, lymph node biopsy, etc. In a case with strong clinical possibility of miliary tuberculosis and negative x-ray chest picture, CT scan study of thorax may confirm the diagnosis.

**Pitfalls in a child who has received medicines**

Antipyretic is indicated in a child with moderate to high grade fever and also in febrile child who is irritable and uncomfortable due to fever. Paracetamol should be the preferred antipyretic in dose of 15 mg/kg/dose on basis of need. It can be repeated at interval of 4 to 6 hours if fever develops. It should not be used round the clock just not to allow the rise of body temperature. The practice of using multiple antipyretics either singly or in combination round the clock is the most practical diagnostic pitfall in a case of fever. Antipyretics mask the developing symptoms and diagnosis may be late as in a case of rheumatic fever. It also gives false security to the parents and the treating physician and the disease may evolve with complications like development of subdural empyema or a brain abscess in a case of bacterial meningitis. Use of very potent antipyretics like nimesulide may hide serious underlying infection. Empirical use of antibiotics, antimalarials, antituberculous drugs and other medicines without proper investigations is a very common trend in practice. When the fever persists inspite of multiple medicines, it becomes the great challenge for the physician to reach the diagnosis and to plan for further management as the results of various investigations are modified. Sometimes, we never come to know what exactly it was. Vaccine preventable diseases are less likely in adequately immunized children, though no vaccine offers complete protection in all the vaccinees. In a vaccinated child, the disease may have atypical or incomplete manifestations or shift of age to develop the disease. Steroids should never be used in undiagnosed fever. It may modify the disease totally and we may fail to diagnose the condition. It may aggravate existing infection or suppress features of leukemia, temporarily resulting in poor prognosis.
When the cause of fever is not available inspite of detailed history, clinical examination and investigations in older children and adolescents, think of fictitious fever. We should look for details of social background, friends circle of the child and other circumstances which may give the clue for fictitious fever. We should not forget to take the help of our psychiatric colleagues in these circumstances.

Points to Remember

- **Fever is the most common symptom in daily pediatric practice.**
- **Pitfalls can occur starting from the stage of documentation of fever.**
- **A detailed history and thorough clinical examination are mandatory for reaching the diagnosis.**
- **Sound analysis and interpretation of history, physical examination and basic investigations is the key of diagnosis in most cases of fever. Pitfalls in any of these may lead to a disaster.**

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VESICOURETERIC REFLEX - WHAT’S NEW?

* Dipti Devi

Abstract: Vesicoureteric reflux is one of the most common anomalies of the urinary tract. Despite considerable experience of pediatric surgeons and nephrologists worldwide, there is lack of unanimity in its approach till now. There is lack of evidence based data because of paucity of well conducted studies. It was regarded as an important and preventable cause of renal parenchymal damage. Therapeutic approaches changed over time from surgical to conservative approach concentrating on aggressive investigation after UTI for early diagnosis. During the past decade, there is considerable debate on the clinical significance and current approach of VUR. The previous accepted dogma of ascent of bacteria from the bladder to the kidney in presence of VUR is now changing. It is now regarded as a marker of congenital hypodysplasia, voiding dysfunction and predisposition to UTI. It may be the time to retreat from the aggressive diagnostic approach after UTI. Prompt treatment of UTI and individualized approach with less invasive investigation in the high risk group may be most appropriate in this preconsensus era. DMSA has been suggested as the preferred imaging to evaluate children with UTI rather than USG and VUCG.

Keywords: VUR, Renal damage, UTI, VUCG, DMSA.

Vesicoureteric reflux (VUR) is the abnormal retrograde flow of urine from the bladder into the ureter. Historically, since its recognition in 1930s, VUR generated considerable interest amongst pediatricians, pediatric nephrologists and urologists worldwide. Many conclusions have been evolving regarding its etiology, clinical significance and management. Recently, there is emerging evidence from current literature to recommend a change and to reduce investigations of children with UTI to diagnose VUR.

Prevalence

Prevalence of primary VUR in healthy pediatric population is less than 2%, though the incidence may vary according to age of screening as VUR often resolves over time.1 On the contrary, a high number of VUR is detected after evaluation of 20-30% of UTI, 9-11% of antenatal hydronephrosis, 32% of siblings, 66% of offsprings, 25% of ESRD2 and following screening of VATER syndrome, urodynamic problems and failure to thrive.

Evolving therapeutic approach

During early years of its recognition, enthusiastic surgical approach led to many adverse effects including secondary incontinence.3 The International Reflux Study
led to the hypothesis that VUR is a risk factor for upper UTI and renal scarring following infection.\textsuperscript{4,5} Until the 1980s, the recommendations were to manage infants of any grade and older children with grade 1-4 VUR with long term antibiotic prophylaxis. Open surgical management was recommended for new scar/progression, fall in GFR, hypertension, recurrent breakthrough infections in spite of prophylaxis, grade 5 VUR in older child, non compliant group or any grade persisting as same after 1-2 years or beyond puberty specifically in a female child. Studies on early markers of parenchymal loss like C-reactive protein and renin angiotensin system are under way. Endoscopic injection of subureteric material was introduced in 1981 by Matouschek and since then it gained popularity as an alternative to open surgery and antibiotic prophylaxis.\textsuperscript{6} Recently US Food and Drug administration approved dextranomer hyaluronic acid copolymer for endoscopic injection in VUR\textsuperscript{7} avoiding surgery and antibiotic prophylaxis. However, a recent Cochrane review questioned the superiority of surgery or prophylaxis over no treatment at all.\textsuperscript{8,9} There is little evidence based recommendation of management of VUR.\textsuperscript{10}

Data from studies on fetal hydronephrosis documented congenital renal damage in the absence of UTI.\textsuperscript{2} Non functioning renal units were mostly hypo-dysplastic kidneys. Antibiotic prophylaxis or early surgery did not prevent renal damage in these children. The degree of renal dysplasia did not correlate well with severity of reflux. More recently following experimental gene knock out models, it is proposed that dysregulation of normal nephrourologic developmental programme results in VUR associated hypo-dysplasia. Ureteric bud originating from aberrant site, contact the sparse mesenchyme resulting in hypo-dysplasia (Fig. 1). Renal hypodysplasia is characterized by small kidneys with global parenchymal reduction or massively distended cystic kidneys with loss of corticomedullary differentiation usually in boys associated with severe VUR.

In the early 1970s, Burger and Smith demonstrated familial occurrence of VUR.\textsuperscript{2} A broad range of inherited patterns including autosomal dominance with incomplete penetrance, autosomal recessive, X-linked and even multifactorial inheritance has been found. In the last decade, in vitro (organ culture) and in vivo (knock out animal) studies on developing kidneys generated hypothesis regarding molecular control of nephrourogenesis enabling identification of hundreds of molecules including growth/ survival factors, cell adhesion molecules and transcription factors. Pronephros and mesonephros produce transcription factors like Lim-1, Pax-2, Eya-1 and Foxc-1. These factors are activated in the intermediate mesoderm to activate formation of metanephrogenic mesenchyme. This mesenchyme secretes Gdnf (glial derived neurotrophic factor) to induce the nearby Wolffian duct through its receptor c-Ret and co-receptor Gfr-1á to give out the ureteric bud which invades the metanephric blastema and continues on dichotomous branching and elongation till repressed. Renal agenesis results from knock out mice for lim-1, Pax-2, Eya-1, UP111a and blocking antibodies to Gdnf. Knock out mice for Foxc-1 and Spry1 results in additional ureters and addition of Gdnf to ectopic ureter. In the HoxB7/Ret transgenic mice, kidneys are small and cystic with short dilated ureters and VUR. Many other proteins are identified including Emx-2, Hgf, c-Met, Bmp-2, Bmp-4, Tgf-á, Fgf, Cfl-1, Wnt-4 etc (Fig. 2). In a recent study, 17% of children with renal hypodysplasia and Chronic Renal Insufficiency (CRI) are associated with renal syndromal gene mutation or variants. Several syndromes have an identified gene like Renal coloboma syndrome (OMIM 120330, Pax-2), Branchio-oto-renal syndrome (BOR, OMIM 113650, Eya-1), Townes-Brocks syndrome...
(TBS, OMIM 107480, SALL-1) and hypoparathyroidism-sensorineural deafness and renal disease syndrome (HDR, OMIM 146255, GATA3). Feather et al., identified a locus on chromosome 1p13 and some other congenital anomalies of kidney and urinary tract (CAKUT)-associated locus on 13q12-22 responsible for familial VUR. But the human gene responsible for VUR is yet to be found.

The high intravesical pressure that accompanies different forms of dysfunctional voiding with VUR is a risk factor of intrarenal reflux and renal damage. There is considerable debate over several years about the imaging strategies after UTI. Conventional IVU (intravenous urography) takes months or years to detect scar following UTI. Ultrasound (US) is an excellent modality for structural renal and bladder abnormality. However it is neither sensitive nor specific for detecting VUR. 74% of reflux is associated with normal US and 28% of them is grade 3 or more. Indirect signs like increased residual volume increases the sensitivity to 85%. The sensitivity of US for scarring compared to DMSA is 37% vs 100% and specificity 65% vs 99%. DMSA can diagnose acute pyelonephritis if done during acute stage. However detection of acquired scar takes around 6 months. A plain abdominal radiography may provide information regarding small calculi, spinal or sacral anomalies, bowel dilatation and stool retention. Voiding cysto urethrography (VCUG) provides fine anatomical details of bladder and urethra. But the results can be affected by size and position of catheter, rate of bladder filling, height of column of contrast media, state of hydration, volume/
temperature/concentration of contrast medium and overestimation if done in acute stage. Its limitations are radiation exposure to gonads, need for catheterization and possibility of infection. However with a prophylactic protocol, symptomatic post procedure UTI is only 1.7%. Recently digital and pulsed fluoroscopy enable reduction in radiation exposure and reliable documentation. However, VUR may be intermittent requiring unacceptable cyclic VCUG. It may be avoided by use of RNC (radionuclide cystography) and VUS (voiding urosonography). RNC provides less radiation exposure and continuous monitoring but poor anatomy. VCUG and direct RNC provide information during filling phase, while indirect RNC provide information during micturition phase with greater sensitivity for VUR. So, indirect RNC was recommended by some experts in toilet trained children.\textsuperscript{11} Contrast enhanced voiding urosonography (VUS) with microbubble containing contrast medium provides cyclic procedure with better yield, less radiation exposure though less anatomy, less accurate grading and longer examination time. Recent Gadolinium enhanced dynamic magnetic resonance urography allows no radiation, superior in discriminating acute pyelonephritic lesions and permanent damage in acute stages, better anatomy than US and IVU with angiographic and functional informations. It is expensive, not widely available and time consuming. In future, it might replace other imaging modalities.\textsuperscript{11}

\textbf{Fig 2. Candidate genes for vesico-ureteric reflux and urinary tract malformation and their genomic loci in mice.}
The guidelines of the American Academy of Pediatrics for symptomatic first UTI below 2 years include combination of US and early VCUG or RNC. Swedish and UK guidelines are same with addition of DMSA. These guidelines cannot explain the changing trends of knowledge of VUR. Recently it has been suggested that DMSA may replace VCUG as the first investigation based on the fact that a normal DMSA excludes VUR of clinical significance. But it is not accepted by all. Only 58% of experts advocate its use. Some centers recommend DMSA 6 months after UTI in all patients with VUR or with at least two febrile UTI or one UTI with delayed antibiotic. Usually the preferred procedure in centers with a legitimate academic interest is a combination of US and DMSA and following an abnormal report or recurrent UTI a VCUG or RNC. Many clinically oriented pediatric nephrologists use VCUG or RNC as first line and DMSA is used only in VUR or recurrent UTI. Guidelines for older children differ between centers and are not evidence based. US and DMSA are usually used and VCUG or preferably RNC is used only in abnormal imaging or antenatal HDN or familial VUR. All with recurrent UTI are advised for VCUG. However the benefit of diagnosing VUR after UTI is under debate now.

Recent studies state that detection and treatment of VUR is not crucial for preventing renal scarring. VUR is present in only 30% of febrile UTI and is most often of low grade. In a recent study, high procalcitonin level is able to predict high grade VUR with 92% sensitivity and 44% specificity thus avoiding VCUG. In a recent review article, Stephen D. Marks, et al suggest an acceptable protocol for UTI as follows:

1. Identify whether febrile or afebrile UTI
2. Non-febrile UTI do not need any imaging
3. Febrile UTI is divided as with or without high risk features
4. Low risk children need no imaging
5. High risk children should be investigated.

![Fig. 3. Investigation after febrile UTI in high risk group]

US
↓
without dilatation
↓
<3yrs
↓
DMSA
IRC=

>3yrs
↓
MAG3+IRCT= indirect radioisotope cystography
DMSA
↓
abnormal bladder/ureteric dilatation
↓
Diuretic MAG3
↓
MAG3+VCUG

MAG= Mercapto-acetyl-triglycine renography
VCUG= Voiding cystourethrography
High risk group

• Recurrent infection
• Clinical signs such as poor urinary stream or palpable kidneys
• Unusual organisms (non E. Coli)
• Bacteremia /septicemia
• Prolonged clinical course/ no response to antibiotic within 24-48 hrs
• Unusual clinical presentation as older boy
• Abnormal antenatal US

VUR is found in 32% of siblings, greater than grade 3 in only 2% and renal abnormalities in only 3% of them. Young asymptomatic sibling should be investigated with VCUG or RNC. US may be a reliable alternative to VCUG in older sibling more than 5 years .However studies of control group are needed to determine the benefit of screening of asymptomatic sibling . A high suspicion of UTI and immediate treatment should be advised.

Wider use of antenatal US resulted in finding of renal pelvic dilatation in 4.5% of pregnancies. Congenital lesions are 14%. Focal scars develop in 19% with VUR grade 4 or 5. Postnatal US after first week avoid false negative results. Recently, VCUG performed only in abnormal US findings restricted the number of VCUG by 50 % and diagnose low grade VUR in 74% with resolution at 24 months in most cases. A high index of suspicion and immediate treatment of UTI should be advised.

Conclusion

Review of literatures suggests that VUR is genetically heterogenous and is a marker of disorders like primary renal lesions, altered bladder functions or predisposition to UTI. It can be concluded that primary lesions should be distinguished from secondary lesions. An early DMSA following UTI, can solve it. A normal DMSA after the first UTI can exclude VUR of clinical significance. Contrary to the previous belief, there is evidence that progressive reflux nephropathy (RN) might occur in older children with abnormal initial DMSA. Following acute pyelonephritis, scarring is independent of VUR. Also serious doubts exist on the relevance of prophylaxis or surgery of VUR.

As there is little evidence based material to rely upon, a flexible and individualized approach is probably the best one in this preconsensus era. An early DMSA following acute pyelonephritis can identify children at risk. However early identification of renal damage on outcome is still not clear. So, less invasive and less radiation load techniques should be used till evidence based recommendations from well designed studies are available.

Points to Remember

• It is important to differentiate congenital from acquired scarring. An early DMSA following UTI can solve it.
• The most efficient steps as clearly advocated now, are to treat UTI early and effectively and consider risk factors for acquired scarring.

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Anticholinergics for prolonged non-specific cough in children

Children with non-specific cough, (non-productive cough in the absence of identifiable chest disease) are commonly treated with a variety of medications for control of cough symptoms. This review examined the effect of inhaled anti-cholinergic drugs in children with non-specific cough. Currently there is no evidence to support the use of inhaled anti-cholinergics as no randomised-controlled trials of inhaled anti-cholinergic medications in the management of prolonged non-specific cough in children were found.


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EARLY DIAGNOSIS AND MANAGEMENT OF LEARNING DISABILITIES

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Abstract: Learning disabilities are a heterogeneous group of disorders manifesting as difficulty in reading, writing, reasoning and mathematical abilities. It is presumed to be due to a dysfunction in central nervous system. Prevalence rates range from 10% to 17.5%. It is a life long disorder. Diagnosis of affected children should be before second grade for better outcome. A comprehensive psycho educational assessment is required for making a diagnosis. Management involves a good program based on phonological principles.

Management of co-morbid conditions helps in dealing with this condition more effectively. ADHD is commonly associated with learning disabilities and hence management of this is essential.

Keywords: Learning disabilities, Diagnosis, Management, Co morbid conditions.

Learning disabilities (LD) are neurological disorders that result in a difficulty in the emotional development. Children with learning disabilities are usually of average or above average intelligence with a discrepancy between ability and achievement. These children are quite frequently misunderstood and labeled as lazy, stupid or retarded which may be completely unfair to them.

There are several definitions of LD. A widely accepted definition is given below.

Learning disability is a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning or mathematical abilities. These disorders are intrinsic to the individual and are presumed to be due to a dysfunction of the central nervous system. Even though a learning disability may occur concomitantly with other disabling conditions (e.g., sensory impairment, mental retardation, social emotional disturbance) or environmental influences (e.g., cultural differences, insufficient / inappropriate instruction), it is not the direct result of those conditions or influences.

Learning impairments may vary in severity, from mild to severe and is differentiated as just reading difficulty or reading associated difficulty in spelling and written expression or associated with mathematic difficulty. The learning problems significantly interfere with academic achievement or activities of daily living that require reading, mathematical or writing skills. Besides the integral difficulty in learning it is seen that the family, school, socio cultural milieu, and education play a significant influence in the ultimate outcome of learning in children. Therefore, learning disability is diagnosed when the individual’s achievement on individually administered, standardized tests in reading,
mathematics or written expression is substantially below that expected for age, schooling and level of intelligence.

At this point it is interesting to note that there are different terminologies used to describe different learning disabilities. Dyslexia refers to disorder of reading, dysgraphia means disorder of writing and dyscalculia is a disorder in mathematics. Frequently a child may have a combination of one or more difficulties. Rarely do they occur in isolation.

Dyslexia is one of several distinct learning disabilities. It is a specific language-based disorder of constitutional origin characterized by difficulties in single word decoding, usually reflecting insufficient phonological processing abilities. These difficulties in single word decoding are often unexpected in relation to age and other cognitive and academic abilities; they are not the result of generalized developmental disability or sensory impairment. Dyslexia manifest by variable difficulty with different forms of language, often including, in addition to problems in reading, a conspicuous problem with acquiring proficiency in writing and spelling. Dysgraphia is a neurological-based writing disability in which a person has difficulty expressing thoughts on paper and with writing associated with unreadable penmanship and problems in gripping and manipulating a pencil. Dyscalculia is yet another term which refers to a mathematical disability in which a person has unusual difficulty solving arithmetic problems and grasping math concepts manifesting as difficulty in mathematical operations such as addition, subtraction, multiplication, division, with poor retention and retrieval of math concepts.

Nonverbal learning disabilities refer to developmental disorders of motor function (developmental coordination disorder), Visuo-spatial processing, mathematics (dyscalculia), memory, prefrontal executive function, and social-emotional cognition and behavioral function.

**Prevalence LD**

The prevalence figure of LD depends upon the definition and varies from study to study. Dyslexia is perhaps the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 5 to 10% to 17.5%. Previously, it was believed that dyslexia affected boys primarily, however, more recent data indicate similar numbers of affected boys and girls. Prevalence rates for reading disorder are estimated at 4% of school-age children, with a range of 2-10%.

**Neurobiological basis of learning disabilities**

Causative factors in learning disabilities include genetic which can be chromosomal or inherited conditions; intrauterine factors like maternal malnutrition, exposure to irradiation, TORCH infections, substance abuse; disorders of cerebral dysgenesis and inborn errors of metabolism; perinatal causes like placental insufficiency, prematurity, complications of labor and delivery; postnatal causes like CNS damage due to trauma, infections, malnutrition, resistance to thyroid hormones, abuse, neglect, toxin exposure, uncontrolled seizures and neurodegenerative disorders.

**The genetics of learning disabilities**

Twin studies, sibling analysis and family pedigree analysis have shown a genetic basis for learning disabilities. For example, twin studies have shown that if one twin has reading disability, the probability of its occurrence in the other twin is 68% for monozygotic twins and 40% for dizygotic twins. Familial transmission is known to occur. For example, if there is family
Table 1. Clues to early diagnosis of learning disorders

**Delayed language**
- Problems with the sound of words (trouble rhyming words, confusion of words that sound alike)
- Expressive language difficulties (mispronunciations, hesitations, word-finding difficulties)
- Difficulty naming (difficulty learning the letters of the alphabet and the names of numbers)
- Difficulty learning to associate sounds with letters
- History of reading and spelling difficulties in parents and siblings

**Reading**
- Difficulty decoding single words
- Particular difficulty reading nonsense or unfamiliar words
- Inaccurate and labored oral reading
- Slow reading
- Comprehension often superior to isolated decoding skills
- Poor spelling

**Language**
- Relatively poor performance on tests of word retrieval (name the pictured item)
- Relatively superior performance on tests of word recognition (point to the pictured item)
- Poor performance on tests of phonologic awareness

**Clues most specific to young children at risk of dyslexia**
- Difficulty with tests assessing knowledge of:
  - The names of letters
  - The ability to associate sounds with letters
  - Phonologic awareness

History of reading disabilities the probability of its occurrence is significantly increased. The relatives of children with learning disorders have a relatively high incidence of expressive language disorder. Linkage studies implicate loci on chromosomes 6 and 15 in reading disability.\(^{13-15}\)

Additional findings of the strong heritability of phonologic awareness suggest “that it may be the main proximal cause of most genetically-based deficits in word recognition, and thus it may be the most appropriate focus for diagnosis and remediation”.\(^{16}\)

**Signs of learning disability**

Learning difficulties in children present in a variety of ways (Table 1). The earliest pointer to a child with learning disability may be language delay. Other signs in preschool children are delay in learning the alphabets, difficulty in rhyming words, difficulty in letter sound associations, mispronunciations, and delay in learning numbers. In the primary school, there may be delay in learning to read, slow and hesitant reading characterized by word substitutions, omissions, guessing of words and poor comprehension. This may be accompanied
by writing difficulties. Handwriting may be illegible, messy with reversals and inconsistencies in the formation, sizing and spacing of letters. Handwriting is slow and laborious with spelling errors. This may be accompanied by poor performance in arithmetic, computations and difficulty in solving word problems. Other signs may be fine motor incoordination, visuospatial difficulties and behavior, memory and attention dysfunctions varying from mild to severe. During adolescence, the presenting features may be behavioral problems such as aggression, truancy, school refusal, psychosomatic complaints and symptoms of stress and anxiety accompanied by poor scholastic achievement.

### Assessment of learning disability

When learning disability is suspected, the child is referred for complete physical, neurological and neuropsychological assessments. In general, most children do not exhibit any neurological impairment except for soft neurological signs.

Neurological examination should include assessments of head growth, motor skills across a number of areas like conceptual level (praxis), comprehension of pantomimes and emblems (e.g., thumbs-up sign), finger movement skills (rapidity, ability to isolate individual finger movements, ability to prehend). An evaluation should be made for subtle or soft signs. There is no single examination for eliciting subtle signs, but a number of overlapping examinations are performed such as lateral preferences, stressed gaits, gait steadiness, sustentation postures/stations, finger to nose, tongue protrusion, maintaining eye closure, balance, hopping, and timed coordination. Assessments should be made for visual and hearing impairments.

Neuropsychological assessments include a variety of tests of abilities and functions in the domains of cognitive/intellectual, language, visual-perceptual, academic, motor, sensory and emotional/behavioral. A correlation is then drawn between a profile of strengths and weaknesses and known brain functions.

### Neuropsychological testing

Standardized tests are administered by a clinical psychologist. Intellectual functioning can be measured yielding an intelligence quotient (IQ). Commonly used tests are Bayley Scales of Infant Development, Weschsler Preschool and Primary Scale of Intelligence – Revised, Weschsler Intelligence Scale for Children – IV, Weschsler Adult Intelligence Scale, Binet-Kamat Intelligence Scale, Peabody Picture Vocabulary Test which can overcome the language barrier for the children with communication difficulties. Copying geometric figures, Goodenough Draw-a-Person Test, Kohs Block Design and geometric puzzles may be used as screening tests for visual-motor coordination. Assessments of adaptive functioning can be done with Vineland Adaptive Behavior Scales. Specific tests to detect specific learning disabilities are available.

### Neuropsychiatric disturbances in LD

Difficulties in psychosocial adjustment appear to be the major social-emotional

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**Table 2. DSM IV classification**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>315.0</td>
<td>Reading disorder</td>
</tr>
<tr>
<td>315.1</td>
<td>Mathematics disorder</td>
</tr>
<tr>
<td>315.2</td>
<td>Disorder of written language</td>
</tr>
<tr>
<td>315.31</td>
<td>Expressive language disorder</td>
</tr>
<tr>
<td>315.32</td>
<td>Mixed expressive-Receptive language disorder</td>
</tr>
<tr>
<td>315.39</td>
<td>Phonological disorder</td>
</tr>
<tr>
<td>315.4</td>
<td>Developmental coordination disorder</td>
</tr>
</tbody>
</table>
Management

All the available facts and diagnostic studies are assembled and reviewed in the management of a child with learning disabilities. A set of diagnoses and diagnostic formulations are generated (Table 2 and 3). It is important to take into account the child’s areas of strengths and areas of weaknesses. The strengths have to be capitalized on and the weaknesses have to be supported or strengthened. An individualized treatment plan is developed. Treatment should be multimodal and judiciously utilize medical intervention, psychopharmacological treatment, behavioral management and educational and remedial teaching. Parent support groups and advocacy organizations have a very important role to play. A multidisciplinary approach has to be taken to provide the most effective and efficient therapeutic care. The team would ideally comprise of developmental pediatrician, neuropsychiatrist, psychologist, remedial

<table>
<thead>
<tr>
<th>Table 3. ICD -10 Classification of Disorders of Psychological Development (WHO)</th>
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</thead>
<tbody>
<tr>
<td>F80   Specific developmental disorders of speech and language</td>
</tr>
<tr>
<td>F80.0 Specific speech articulation disorder</td>
</tr>
<tr>
<td>F80.1 Expressive language disorder</td>
</tr>
<tr>
<td>F80.2 Receptive language disorder</td>
</tr>
<tr>
<td>F81   Specific developmental disorders of scholastic skills</td>
</tr>
<tr>
<td>F81.0 Specific reading disorder</td>
</tr>
<tr>
<td>F81.1 Specific spelling disorder</td>
</tr>
<tr>
<td>F81.2 Specific disorder of arithmetical skills</td>
</tr>
<tr>
<td>F81.3 Mixed disorder of scholastic skills</td>
</tr>
<tr>
<td>F81.8 Other developmental disorders of scholastic skills</td>
</tr>
<tr>
<td>F81.9 Developmental disorder of scholastic skills, unspecified</td>
</tr>
<tr>
<td>F82   Specific developmental disorder of motor function</td>
</tr>
<tr>
<td>F83   Mixed specific developmental disorders</td>
</tr>
</tbody>
</table>

manifestations of learning disabilities. Children with LD experience less acceptance, lower popularity, more peer rejection and increased neglect by peers than do normally achieving children or low-achieving peers.

It has been estimated that 30-70% of children with LD will experience ongoing comorbid symptoms of attention-deficit/ hyperactivity disorder (ADHD) as they enter into adulthood. Both LD and ADHD have a high degree of comorbidity with other neuropsychiatric disorders like depression, conduct disorder, anxiety disorder, substance abuse, Tourette syndrome, tic disorders and other stereotypic movement disorders and sleep disorders. These facts stress the need for screening, early detection, recognition, comprehensive assessments and early intervention or even incorporate prevention strategies and thus improve the quality of life of the affected individuals.
teachers, physiotherapist, occupational therapist, speech and language therapist and the school. Other professionals may need to be consulted depending on the nature of the problem.

Remedial education is the focus of management. This has to be individualized and tailored to each child keeping in mind the child’s various strengths and weaknesses.

Children identified as dyslexic receive systematic and highly structured instructions in basic phonologic skills required for decoding and reading. Reading proficiency depends on phonological processing and awareness and understanding of the alphabetical principle. Instructions are provided either individually or in small groups of 2:1 or 3:1 and include phonology, morphology, syntax, semantics or pragmatic use of language. Along with knowledge of phonics, a rapid sight word vocabulary is essential to efficient reading. Difficulties in handwriting and maths are tackled simultaneously with instructions in phonology. Drills, rehearsals, practice and repetitions are required to consolidate the learning.

A large body of evidence has been reviewed by the National Reading Panel commissioned by the NICHD, USA…that concluded that, direct and systematic phonologic awareness and phonics instruction produced significant effects in dyslexic children as well as children in kindergarten or first-grade who are found to be at-risk for reading disability.

The panel also concludes that the outcome is better in younger children, response is best when instructions in phonic awareness are delivered in small groups of 2:1 or 3:1, and also that more frequent instruction i.e., 4-5 days/week is more effective. Although the older, reading-disabled children respond with improved word reading to similar intensive, direct and explicit instruction, they are less responsive and gains are not as marked and more intensive work for a longer period is required. The role of the school and parents is very crucial in the successful remediation of a child with learning difficulties. The school has to be actively involved in the entire process of identification, assessment and remediation. An Individualized Education Program or IEP is drawn up that specifies current difficulties and describes the educational program that has been designed to meet that child’s unique needs. Measurable short and long term goals are set and reevaluated annually to ensure achievement. Goals may be academic, address social or behavioral needs, relate to physical needs or address other educational needs. Parents, regular class teachers, special educator and psychologist are members of the IEP team. The National Reading Panel also recommends that teachers trained specifically in teaching dyslexic children are more effective.

The management of dyslexia in students in secondary school is based on accommodation rather than remediation. Accommodations are alterations in the way tasks are presented that allow children with learning disabilities to complete the same assignments as other students. Common accommodations are preferential seating of the child, providing extra time for completion of tests, tape recorded lessons and allowing verbal responses and frequent breaks. Individual tutoring or small-group instruction may be required in mathematics and/or written language if these disorders are also present. Students with LD in higher classes also need specific tutoring in study skills, organization of notes, time and material, and specific memory strategies. Use of assistive technology such as calculators, spell checkers, word processors and computers help in making the task easier and make it possible for learning disabled students to achieve success.
Parent counseling, education and support is essential to develop a supportive home environment and a consistent home/school program. Affected children may also need other interventions such as pharmacological treatment if there is an associated ADHD or other co-morbid conditions, social skills training for deficits in social cognition and behavioral management.

**Facilities available for children with LD**

Children evaluated fully and diagnosed as Learning Disabled by a registered psychologist can avail of many facilities. The psychologist has to make the recommendations suitable for the child and these recommendations are then forwarded to the relevant board of education through the school. Many educational boards recognize the difficulties faced by these children and are sympathetic to their plight.

1. Second language exemptions are provided for children with dyslexia
2. Extra time for board examinations is available
3. Provision of scribes for children with dysgraphia
4. Use of calculators in the examinations for children with dyscalculia

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The address: National Institute of Open Schooling, www.nos.org

**Conclusion**

Learning disabilities are life long disorders. The diagnosis of affected children should be before second grade for better outcome. It is also advisable to identify children at – risk and enroll them into a reading program. Management of co-morbid conditions helps in dealing with this condition more effectively. It is also essential to develop good teachers trained in various methodologies to handle such children. Milder cases can be managed in the regular classrooms with slight modifications and accommodations. The moderate and severe cases need smaller group instruction. Awareness of the facilities available for such children is not very well known and should be propagated by schools, pediatricians and other professionals.

**Points to Remember**

- **Delayed language development in infancy is a risk factor and such children should be indexed for follow up for learning problems.**
- **Diagnosis by second grade is important for good outcome.**
- **All high risk infants should be screened for learning difficulties.**

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INTRAVENOUS IMMUNOGLOBULIN (IVIG) IN PEDIATRIC PRACTICE

*Jeeson C Unni

Abstract: Intravenous Immune globulin (IVIG) is an intravenous solution composed of heterogenous human immnoglobulin G. Peak serum concentrations occur immediately after intravenous injection and is dose related. IVIG is indicated to provide immediate passive immunity or as replacement therapy for patients with antibody deficiencies. Common indications are primary immunodeficiency, Kawasaki disease, Gullain Barre syndrome and idiopathic thrombo cytopenic purpura. IVIG should be used cautiously in children with history of hypersensitivity to human immunoglobulin and those with severe hypogammaglobulinemia or risk for thrombotic events. Live virus vaccines to be delayed until 3 months after IVIG administration. Most adverse reactions associated with IVIG are mild and transient.

Keywords: Intravenous Immunoglobulin, Indications, Contraindication, Adverse reactions.

Gamma globulins were first introduced as a therapeutic modality in 1952 by Robert A. Good, who injected gamma globulins by the intramuscular route to treat patients with X-linked agammaglobulinemia. IVIG has been available for use for past 22 years. The indications for its use expanded to include a variety of autoimmune and inflammatory diseases. Its safety improved as newer, highly purified IVIGs and methods to improve viral safety became available. However, of late, concerns related to the availability of commercial IVIG have made it mandatory that we have a re-look into its use in pediatric practice.

Description

Intravenous immune globulin (IVIG) is an intravenous solution composed primarily of heterogenous human IgG, with trace amounts of IgA and IgM. IVIG is collected from the venous blood of donors. All samples undergo HIV and HBV testing. The amount of each IgG subclass is similar to that of human plasma, although the titers against specific antigens vary among manufacturers. Also, the IVIG products differ in the preparation method, viral inactivation steps, stabilizing agent, osmolality and IgA content. Thus, all the IGIV products are not the same.

The currently available IVIG are the 4th generation preparations containing intact immunoglobulin that is 99% monomeric IgG, low anti-complement activity, having undergone...
‘complete’ viral inactivation and is available as ready to use liquid formulation with a shelf life of 2 years when stored at room temperature.

**Pharmacokinetics**

IVIG is administered intravenously. Peak serum concentrations occur immediately after IV injection and are dose-related. Following infusion, IVIG products show a biphasic decay curve. The initial phase is characterized by an immediate post-infusion peak in serum IgG and is followed by rapid decay due to equilibration between the plasma and extravascular fluid compartments. The second phase is characterized by a slower and constant rate of decay.

Within 24 hours, up to 30% of a dose may be removed by catabolism and distribution. Data concerning distribution are scant, but IVIG appears to be distributed throughout intravascular (60%) and extravascular (40%) spaces, crosses the placenta (in increasing amounts after 30 weeks of gestation), and may be excreted into milk. The exact fate of IVIG is not well defined, but the serum half-life is that of immune globulin (IgG), approximately 21-29 days. Great inter-patient variability exists for the half-life of IgG. Fever, infection or high IgG concentrations appear to coincide with a shortened half-life whereas immunodeficiency appears to be associated with a longer half-life of IgG. For example, the apparent half-life of IgG is approximately 40 days (range, 23-84 days) in immunosuppressed patients. As there are significant differences in the half-life of IgG among patients with primary immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection varies among patients and has not been established by controlled clinical studies.

Though a large number of studies on the pharmacokinetics of IVIG are available in the literature, there is a lack of information on IVIG clearance or area under the curve parameters and target serum IgG concentrations. It has been suggested that more studies need to be done to characterise the pharmacokinetic properties of IVIG in a range of patient populations.1

**Indications**

IVIG is used to provide immediate passive immunity after suspected exposure to an organism for which no active immunization exists or if there is inadequate time to develop active immunity and as replacement therapy for patients with antibody deficiencies. These are extremely rare conditions. IVIG also has been used successfully to treat Kawasaki disease,2 Guillain-Barre Syndrome (GBS)3,4 and idiopathic thrombocytopenic purpura (ITP).5 Life threatening conditions like Kawasaki disease, Guillain-Barre Syndrome and active bleeding in ITP with very low counts are the only absolute indications for its use in these times of limited availability.

**Off label uses of IVIG**: Although IVIG is beneficial in CMV infection prophylaxis, its role in AIDS has not been determined. It has also been used in autoimmune hemolytic anemia (AIHA), immune-mediated neutropenia, neonatal alloimmune thrombocytopenia, thrombocytopenia (refractory to platelet transfusions), solid organ transplantation, pediatric intractable epilepsy, polymyositis, systemic lupus erythematosus, systemic vasculitic syndromes, juvenile idiopathic arthritis (JIA), etc.

**Mechanism of action and dosage**

1. **Primary immunodeficiency** (e.g., agammaglobulinemia or hypogammaglobulinemia):
The passive immunity imparted by IVIG, in these conditions, is capable of attenuating or preventing infectious diseases and deleterious reactions from toxins. Protection is conferred against mycoplasmal, parasitic, bacterial and viral infections.

A dose of 300-600 mg/kg (3-6 ml/kg) IV once every 3-4 weeks is recommended at an initial infusion rate of 1mg/kg/minute (max 8 mg/kg/minute). The required frequency of administration and amount of IVIG vary from patient to patient and at different times in the same patient depending on the serum IgG levels at a given time and presence of infection as mentioned earlier. The child’s IVIG requirement needs to be adjusted according to clinical response and trough concentrations. A target IgG trough concentration (i.e., prior to the next infusion) of at least 5 g/L has been proposed in the literature. However, no randomized clinical trial data are available to validate this recommendation. Studies have shown that children with hypogammaglobulinemia who are receiving replacement treatment grow normally and have an infection rate similar to that of non-immunodeficient children.¹

In March 2000, the FDA established the efficacy criterion for approval of IVIG products as no more than 1 serious infection per patient per year. A serious infection is defined as pneumonia, bacteremia or sepsis, osteomyelitis or septic arthritis, visceral abscesses, or bacterial or viral meningitis.

2. Kawasaki disease: Mechanism of action of IVIG in Kawasaki disease is not well understood but is probably related to its ability to inactivate anti-self antibodies. IVIG must be administered within 10 days of illness and preferably within 6 days of illness. Very early IVIG may further reduce coronary artery lesion (CAL). IVIG with aspirin could reduce the percentage of CAL at 6 weeks from 25% to 5%. Study from PGI Chandigarh concluded that significant myocardial dysfunction and coronary artery changes due to KD were uncommon in their cohort due to administration of IVIG during the acute phase of the illness.⁸ Late administration of IVIG is a risk factor for giant aneurysm formation.⁹ Multiple doses are less efficacious. The recommended dose of IVIG in Kawasaki disease is 2g/kg IV infusion over 12 hours and this dose has shown significant decrease in the number of new CALs than with the lower dose.² However, IVIG could be given as two doses (1 gm/kg/day x 2) if there is a feasibility problem in administration.

10-20% of patients have persistent or recurrent fever for more than 36 hours after initial dose of IVIG. Some clinicians advocate re-treatment with IVIG or administration of pulsed steroids in children with persistent and recurrent fever or worsening echocardiography.¹⁰¹¹ If IVIG is repeated at this point it is recommended that full dose aspirin is continued and IVIG be given at 1g/kg as a single dose. These cases, referred to as “nonresponders to IVIG”, or “initial treatment failure”, or “IVIG resistance”, or “the re-treatment group”, could be at greatest risk of developing CAL.

Atypical Kawasaki disease (10% of cases) must also be treated with full complement of IVIG and aspirin, if echocardiogram is abnormal or borderline normal or if higher number of risk factors are present.

3. Guillain-Barre Syndrome (GBS): Mechanism of action of IVIG in GBS is also not well understood but is probably related, as with Kawasaki disease, to the beneficial effect it exerts by the anti-idiotypic suppression of autoantibodies.¹²

No randomized studies performed in children have been published. One small (n=7)
study evaluated the use of IVIG in children and compared the results to an earlier study of plasma exchange (n=8) done at the same institution. They concluded that IVIG is the preferred therapy and it is certainly considerably easier to use than plasma exchange. It seems that the adult studies may be extrapolated to children and in adults also IVIG is as effective as plasma exchange. However, some investigators have suggested that the course and prognosis may be more favorable for children with Guillain-Barre syndrome than for adults. The recommended dose of IVIG in GBS is 400mg/Kg per day for 5 days.

4. Idiopathic thrombocytopenic purpura (ITP): Despite more than 22-year experience of therapeutic benefit, the relevant molecular and cellular targets of IVIG in autoimmune disease remains unclear. Effectiveness in ITP is not well understood. It was felt that it probably interferes with macrophage Fc-receptor-mediated phagocytosis. And more recently activation of Fc gamma receptors on CD11c+ dendritic cells has been suggested as the molecular target of IVIG in acute resolution of murine ITP. The end effect is that IVIG blocks reticuloendothelial Fc-receptors, decreases antibody synthesis, protects platelets and megakaryocytes from platelet antibodies and clears persistent viral infection by infusion of specific antibody.

However, it is well known that IVIG treatment provides only a temporary response (transient rise in platelet count), so it is mainly of benefit in acute ITP. The effect usually lasts for only a few weeks, although platelet stabilization for up to 1 year after administration has been reported. Treatment of ITP with IVIG appears to be more effective in children than in adults. In chronic ITP it may be used when a temporary rise in platelets is desired or during pregnancy because the risk to the baby is less than with other treatments.

The following are the guidelines suggested by American Society of Hematology. Platelet count <10,000, symptoms of either
- Minor purpura - IVIG, Steroids, +/- hospitalization
- ‘Wet’ purpura - IVIG, high dose steroids
- Life-threatening bleeding – IVIG with steroids and hospitalization

If platelet count is 10,000-20,000
- Minor purpura - +/- IVIG, oral steroids
- ‘Wet’ purpura - +/- IVIG, steroids
- life-threatening bleeding - IVIG with high dose of steroids + hospitalisation

If platelet count is 20,000-50,000
- Minor purpura - +/- IVIG, oral steroids
- ‘Wet’ purpura - +/- IVIG, steroids
- Life-threatening bleeding - IVIG, high-dose steroids and hospitalization

Therefore, IVIG may be reserved for use in ITP if the platelet count is less than 20,000/cumm and there is wet purpura or life threatening bleeding and even in minor purpura if platelet count is less than 10,000/cumm.

Total dose of IVIG for immunomodulation is 2g/kg divided over 2-5 days to be given as IV infusion. Two days of the 5 day therapy may suffice if platelet count reaches 30-50,000 after the second dose. The course may be repeated every 3-6 week, if needed. High-dose regimen (1000 mg/kg for 1-2 days) is not recommended for child with expanded fluid volume or where fluid volume is a concern. Doses should be based on ideal body weight and not total body weight.
Patients with hepatic impairment: Specific guidelines are not available; probably none is needed.

Patients with renal impairment: Reduction in dose, concentration, and/or rate of administration is recommended. Though there is no prospective study available, these measures should reduce the risk of ARF in at-risk patients. FDA recommends that the product may be reconstituted or diluted in such a manner so as to produce both the minimum concentration and rate of infusion practicable.

**Administration**

Initial infusion should start slowly and increase rate gradually if tolerated. Administer by a separate infusion line. Do not mix with other medications or fluids. Visually inspect product for particulate matter and discoloration prior to administration whenever solution and container permit. Discard any unused portions.

**Contraindications and warnings**

IVIG is only for intravenous administration. IVIG should be used cautiously in patients with a history of human immunoglobulin hypersensitivity. Patients with agammaglobulinemia or severe hypogammaglobulinemia are at an increased risk of developing immune-mediated adverse reactions to the initial infusion if they have not received immune globulin IV (IVIG) in the preceding 8 weeks or if they have never received immunoglobulins. Contraindicated in patients with selective IgA deficiency who possess antibody to IgA as they are likely to have anaphylactic or immune-mediated adverse reactions to pooled immunoglobulin products such as IVIG. This occurs even if a product contains low amounts of IgA. No complications to the fetus have been reported, but IVIG has not been well studied in pregnant women. IVIG should be given to a pregnant woman only if clearly needed.

Caution should be used while prescribing an infusion of IVIG in patients with a history of cardiac disease or thromboembolic disease because of risk of thrombotic events following administration. Children with heart failure, previous thromboembolic events, immobilization, diabetes mellitus, hypertension or known or suspected hyperviscosity (presence of cryoglobulins, fasting chylomicronemia, hypertriglyceridemia, or monoclonal gammopathies) may be at risk for thrombotic events. It is strongly recommended that in patients at risk for thromboembolic events that the infusion concentration be no more than 5% and the infusion rate should be initiated no faster than 0.5 ml/kg/hour and advanced slowly only if well tolerated to a maximum of 4 ml/kg/hour.

To reduce the risk of acute renal failure, caution should be undertaken in patients at increased risk (e.g., patients with any degree of renal impairment or renal disease, diabetes mellitus, dehydration or hypovolemia, sepsis, paraproteinemia or concomitant nephrotoxic drug therapy) and periodic monitoring of renal function tests must be done. Measurement of blood glucose must be done with a glucose-specific method if a patient takes a parenteral product that contains maltose.

**Drug interaction**

Live virus vaccines should be delayed until 3 months after IVIG administration and it may be necessary to revaccinate persons who receive IVIG shortly after live virus vaccination. IVIG should not be administered concomitantly with measles/mumps/rubella vaccines, MMR rotavirus vaccine; or varicella virus vaccine live. Tetanus toxoid may be given at the same time as immune globulin, but at a different injection site. Administration of immunoglobulins and hepatitis A vaccine, inactivated at the same time may be necessary for patients who need post-exposure prophylaxis or combined
CSF pleocytosis (several thousand cells per cubic mm) and elevated CSF protein (several hundred mg/dl) is often seen. The symptoms have resolved without sequelae within several days after IVIG discontinuation.

Acute renal failure, renal dysfunction, osmotic nephrosis, and death have been reported in patients receiving immune globulin IV (IVIG). Increases in BUN (azotemia) and creatinine have been observed as soon as 1-2 days after infusion of IVIG. Patients may experience sudden weight gain, edema, decreased urine output, or shortness of breath. Progression to oliguria and anuria requiring dialysis has been observed; although, some patients have spontaneously recovered following cessation of treatment. Preliminary evidence points to IVIG products containing sucrose as presenting a greater risk for this complication.

**Conclusion**

IVIG is recommended for specific conditions only in pediatric practice. It needs to be used judiciously due to the limited supply of the drug in the market. It is safe for use if certain principles of administration are followed. Slow infusion rate and good hydration may prevent renal failure, thromboembolic events and aseptic meningitis. Slowing or stopping the infusion usually allows these symptoms to resolve. Pretreatment with oral antihistamines and analgesics may help to alleviate these symptoms.

Anaphylactic shock is rare and is more likely to occur in patients with agammaglobulinemia or severe hypogammaglobulinemia who have not received immune globulin IV (IVIG) within the preceding 8 weeks or who have never received IVIG. Anaphylactoid reactions can be manifest as fever, hypotension, chills, nausea, dizziness, flushing, and diaphoresis. Symptoms typically begin 30 minutes to 1 hour after initiation of the infusion and appear to be related to the infusion rate rather than the dose. Epinephrine for the treatment of any acute anaphylactoid reaction needs to be readily available.

In isolated cases and mostly with the use of high doses, administration of immune globulin IV (IVIG) has been associated with an aseptic meningitis syndrome. Aseptic meningitis syndrome usually begins within several hours to 2 days after IVIG administration. Symptoms, typical of aseptic meningitis, last for 3-5 days.

**Side effects**

An injection site reaction, characterized by erythema, pain, phlebitis, and eczematous reactions, has been noted. Most adverse reactions associated with IVIG are mild and transient and include flushing, hypertension or hypotension, malaise, back pain, myalgia, headache, nausea/vomiting, low-grade fever, chills, pruritus, urticaria, and rash. Slowing or stopping the infusion usually allows these symptoms to resolve. Pretreatment with oral antihistamines and analgesics may help to alleviate these symptoms.

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Points to Remember

- **IVIG in pediatric practice is generally safe**
It is recommended for certain specific conditions in pediatric practice

Newer modes of delivery such as subcutaneous immunoglobulin administration with less systemic reactions are being studied

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Diclofenac for pain relief in children

Diclofenac is commonly used for short-term pain relief in children, particularly around the time of surgery. There is good evidence that diclofenac is effective for pain relief in adults, and side effects such as stomach upset are well known. However, developmental differences mean that children may sometimes react differently to medicines than adults do. It is important to assess whether diclofenac is also effective in children, and to understand the type and frequency of adverse reactions that diclofenac causes in children. This review has found that, as with adults, diclofenac is effective for the relief of pain after an operation. If it is given at the time of an operation, it will halve the number of children needing extra pain relief. Diclofenac seems to be twice as effective as paracetamol (acetaminophen) for surgical pain, and this is also true for adults. Diclofenac appears to cause similar types of serious adverse reactions (such as bleeding of the stomach and allergic-type reactions), but these are rare and occur in fewer than 3 in 1000 children who take the drug. We had hoped to investigate whether diclofenac made children with asthma more wheezy, but there was not enough information for us to do this. The main conclusions of this review are that diclofenac is effective for relief of acute pain arising from operations in children, with a low risk of serious adverse reactions. Intramuscular injections of diclofenac should be avoided, due to risk of injection site problems. The main questions still to be answered are: What is the best dose to give and should diclofenac be avoided in children with asthma?

HAND-FOOT-AND-MOUTH DISEASE – AN OVERVIEW

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Abstract: Hand-foot-and-mouth disease (HFMD) is a viral illness with a distinct clinical presentation of oral and characteristic distal extremity lesions. Most commonly, the etiologic agents are coxsackieviruses, members of the Picornaviridae family. HFMD is more severe in infants and children than adults, but generally, the disease has a mild course. A brief prodrome of 12-36 hours duration is part of the usual presentation of HFMD. The lesions on the hands and feet are present for 5-10 days. The mucosal and cutaneous lesions heal spontaneously in 5-7 days. Usually, no medical care is necessary for HFMD. The topical application of anesthetics is beneficial. Patient Education includes good hygiene and avoidance of rupturing blisters.

Keywords: Hand-foot-and-mouth disease

Hand-foot-and-mouth disease (HFMD) is a viral illness with a distinct clinical presentation of oral and characteristic distal extremity lesions. Most commonly, the etiologic agents are coxsackieviruses, members of the Picornaviridae family.

Epidemiology and pathophysiology

Epidemic HFMD viral infections are usually caused by members of the Enterovirus genus, namely, coxsackievirus A16 or enterovirus 71. In addition, sporadic cases with coxsackievirus types A4-A7, A9, A10, B1-B3, and B5 have been reported. Infections usually occur as isolated events, but epidemics occur regularly. The incubation period averages 3-6 days. Coxsackievirus infection is highly contagious. During epidemics, the virus is spread from child to child and from mother to fetus. Transmission occurs by means of direct contact with nasal and/or oral secretions, fecal material, or aerosolized droplets in a fecal-oral or oral-oral route. Initial viral implantation in the buccal and ileal mucosa is followed by spread to lymph nodes within 24 hours. Viremia rapidly ensues, with spread to the oral mucosa and skin. By day 7, neutralizing antibody levels increase and the virus is eliminated.

Clinical

A brief prodrome of 12-36 hours duration is part of the usual presentation of HFMD, which consists of the following:

- Low-grade fever with an average temperature of 38.3°C and duration of 2-3 days
- Anorexia
- Malaise
- Abdominal pain
- Sore mouth
- Cough

The enanthem usually precedes the exanthem that is asymptomatic, but both may occur simultaneously. The lesions on the hands
and feet are present for 5-10 days, while the mucosal and cutaneous lesions heal spontaneously in 5-7 days.

HFMD is more severe in infants and children than adults, but generally, the disease has a mild course. Symptoms such as malaise, low-grade fever, and anorexia are often present. Occasionally, children have high fever, marked malaise, diarrhea, and arthralgias. Enteroviral infections may also cause myocarditis, pneumonia, meningoencephalitis, and even death. Infection in the first trimester may lead to spontaneous abortion or intrauterine growth retardation.

Oral lesions begin as erythematous macules that evolve into 2-3 mm vesicles on an erythematous base. The vesicles are rarely observed because they rapidly become ulcerated. They are painful and may interfere with eating. The total number of ulcers averages 5-10. The vesicles may involve the palate, buccal mucosa, gingiva, and tongue. The tongue is involved in 44% of the cases, and, in addition to the ulcers, the tongue may be edematous and tender.2

The lower lip has an ulcer with an erythematous halo. The tongue has an ulcer with an erythematous halo.

Cutaneous lesions are characteristic and are present in two-thirds of patients. Typically, the hands, feet, and buttocks are involved. The hands are involved more often than the feet, and the dorsal aspect of the hands and sides of the fingers are more commonly involved than the palmar surfaces. Each lesion begins as a 2-10 mm erythematous macule on which a central, gray, oval vesicle develops. The lesions are characteristically elliptical; their long axis parallels the skin lines.

• These lesions are asymptomatic and resolve in 3-7 days as a result of fluid resorption.

A typical cutaneous lesion has an elliptical vesicle surrounded by an erythematous halo. The long axis of the lesion is oriented along the skin lines.3

**Investigations**

Generally, no laboratory studies are necessary for hand-foot-and-mouth disease. Leukocyte counts are 4000-16,000/μL. Occasionally, atypical lymphocytes are present. The virus can be isolated from swabs of the vesicles or mucosal surfaces or from stool specimens and then inoculated into mice or cultured on viral tissue media. Neutralizing antibodies rapidly disappear; thus, they are usually detectable only in the acute phase. High levels of complement-fixing antibodies are present in the convalescent phase. Studies have illustrated the usefulness of a molecular assay using polymerase chain reaction primers to arrive at a rapid and specific diagnosis in order to distinguish between coxsackievirus A16 and enterovirus 71.4 This may hold promise in future outbreaks because infections with enterovirus 71 tend to be associated with more severe complications and fatalities. Classic histopathology findings of hand-foot-and-mouth disease include an intra-epidermal vesicle that contains neutrophils and eosinophilic cellular debris. The adjacent epidermis has reticular degeneration, that is, intercellular and intracellular edema. The dermis has a mixed infiltrate. Eosinophilic intranuclear inclusions are observed with electron microscopic studies.5

Neuropathology in fatal cases of enterovirus 71 infection have shown features of an acute encephalitis involving the brain stem and spinal cord.6

**Complications**

Dehydration occasionally occurs in children with hand-foot-and-mouth disease. Rarely,
complications of hand-foot-and-mouth disease include meningoencephalitis, myocarditis, pulmonary edema, and death.

**Prognosis**

The prognosis for hand-foot-and-mouth disease is excellent; except in large epidemics caused by human enterovirus 71 in which neurologic complications and death have been reported, especially in children.

**Treatment**

Usually, no medical care is necessary for hand-foot-and-mouth disease. The topical application of anesthetics is beneficial. Viscous lidocaine or diphenhydramine may be used to treat painful oral ulcers. Antipyretics may be used to manage fever, and analgesics may be used to treat arthralgias. Low-level laser therapy has also been shown to shorten the duration of painful oral ulcers.

**Patient education**

The virus that causes hand-foot-and-mouth disease may be present in the patient’s stool for 1 month. The patient’s exclusion from school is generally not required. Good hand-washing technique is necessary to reduce the potential spread of disease. To reduce viral spreading, the blisters should not be ruptured.

**Points to remember**

- Hand-foot-and-mouth disease (HFMD) is a viral illness with a distinct clinical presentation of oral and characteristic distal extremity lesions.
- Most commonly, the etiologic agents are coxsackieviruses, members of the Picornaviridae family.
- HFMD is more severe in infants and children than adults, but generally, the disease has a mild course.
- A brief prodrome of 12-36 hours duration is part of the usual presentation of HFMD. The lesions on the hands and feet are present for 5-10 days.
- The mucosal and cutaneous lesions heal spontaneously in 5-7 days.
- Usually, no medical care is necessary for HFMD. The topical application of anesthetics is beneficial.
- Patient Education includes good hygiene and avoidance of rupturing blisters.

**References**

DISORDERS OF CELLULAR MIGRATION AND NEURONAL ORGANIZATION

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Migrational disorders are disturbances of neuronal migration and cortical organization into gyri and sulci. This takes place between the 2nd and 5th month of intrauterine life. These disorders are heterotopias, lissencephaly (which includes agyria, pachygyria, polymicrogyria) and schizencephaly. They are developmental disorders with a strong association with TORCH infections. Phakomatosis and vascular malformations also come under this group.

Batches of neurons form between the 2nd and 5th month of intrauterine life and move out towards the peripheral cortex from the germinal matrix in the subependymal region of the ventricles. Each wave of neurons have to travel longer to a more superficial location in the cortex. They can be stopped anywhere along their journey. They can be immediately arrested and appear as nodular grey matter tissue subependymally or they may travel out further and stop subcortically. These abnormally located collections of normal neurons are called heterotopia.

Subependymal heterotopias are commonly seen in the region of the ventricular trigones, temporal and occipital horns. They may be single or multiple and lie along the wall of the lateral ventricle. Fig.1 shows a number of nodules along the lateral wall of the left lateral ventricle. When multiple like this they may be due to chromosomal mutations.

In Fig.2 there are bilateral bands of grey matter between the lateral ventricles and the cerebral cortex and separated from both by a layer of normal white matter. This is referred to as band heterotopia. On PET imaging using fluorine deoxyglucose, band heterotopia is found to have similar or even greater glucose uptake than normal cortex. This is in contrast to cortical dysplasia and other epileptogenic foci that show low uptake.

In schizencephaly there is a cleft extending from the ventricular surface through the cerebral parenchyma to the periphery of the brain. This cleft corresponds to the gap in which neurons failed to develop. It therefore follows that the wider the cleft, the more the neuronal loss and the more the neurological deficit. Likewise, prognosis is bleak if bilateral or in the frontal region. Fig.3 is an ultrasound picture of schizencephaly in a one year old with a closing fontanelle and a limited view. There is a black fluid space extending laterally from the ventricle. This is referred to as open-lip schizencephaly. The CSF cavity varies in size and may be quite large. Fig.4 shows schizencephaly as a large cystic lesion clearly communicating with the right lateral ventricle. In contrast, arachnoid cysts do not communicate with ventricles.
Fig. 1  Nodular heterotopia

Fig. 2  Band heterotopia

Fig. 3  Schizencephaly- US

Fig. 4  Schizencephaly- CT

Fig. 5  Pachygyria

Fig. 6  Cortical dysplasia- plain CT
When the cleft is very thin with no CSF cavity in between it is called closed-lip type and it is not possible to diagnose this with ultrasound. CT may demonstrate the cleft. MRI will give a more precise picture due to clearer white and grey matter differentiation. It will show that the cleft is lined totally or partially by cortical grey matter. This is the hallmark of schizencephaly. The lining grey matter is always abnormal with features of pachygyria or polygyria.

Lissencephaly consists of abnormal gyral formation. Therefore the brain is smooth without convolutions. It includes agyria, pachygyria and microgyria. In pachygyria, as the name suggests, the gyri are big or broad. In Fig.5 there are only two shallow sulci on the right, anterior to the sylvian fissure and only a few posteriorly. The grey matter is thick and the white matter is reduced. The border between gray and white matter is smooth and there is no arborization of the white matter into the grey matter that you can see on the left. If bilateral and total the cerebral contour is oval with a figure of 8 shape. The operculum does not develop and the Sylvian fissure is shallow. Note also the dilated occipital horn or colpocephaly that accompanies many congenital brain abnormalities.

Polymicrogyria, like pachygyria, has the same appearance except that the outer surfaces of the gyri have a nodular contour that is only seen in MRI.

Cortical dysplasia refers to localized disorganized neuronal tissue with abnormal neuronal cells. It is associated with refractory epilepsy. Fig.6 is a plain CT of cortical dysplasia showing brain tissue resembling a mass on the left side. Fig.7 is a contrast CT which confirms the absence of a mass as there is no enhancing lesion. There is a homogenous appearance. MRI will delineate the dysplastic brain better. Cortical thickening, reduced or no demarcation of the gray-white matter junction, hyperdensity of gray and subcortical white matter on T2-weighted images, hypodensity of subcortical white matter on T1-weighted images and atrophy of the white matter core are features of cortical dysplasia.

As you can see, imaging is useful in treatment and prognosis in these disorders that present with seizures and varying degrees of mental retardation.
LANGERHANS CELL HISTIOCYTOSIS

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Langerhans cell histiocytosis (LCH) is a group of idiopathic disorders characterized by the proliferation of specialized bone marrow-derived Langerhans cells (LCs) and mature eosinophils that primarily affects children.

Case study

A 2½ years old male child was admitted with the complaints of pain in the right hip and difficulty in walking for 6 months. He was a developmentally normal child born to 3rd degree consanguinous parents. Examination revealed a diffuse tender swelling in the right gluteal region. Cardiovascular system and respiratory system were within normal limits. Abdomen was soft and there was no hepatosplenomegaly. Central nervous system examination was normal except for a right sided antalgic gait. Complete blood count, renal function test, liver function test, coagulation profile, ESR, serum amylase and serum uric acid were within normal limits. HIV was non reactive and HbsAg was negative. Xray pelvis showed a large round osteolytic lesion of right ileum (Fig.1). Chest radiograph was normal. Skeletal survey was done in this child to rule out involvement of other bones.

which was normal. Ultrasonogram of abdomen showed mild hepatomegaly. Electrocardiogram and echocardiogram revealed a normal study. CT scan pelvis showed a large osteolytic lesion involving the right ileum 3.8×5.6 cm. Biopsy of the lesion was taken and sent for histopathology and immunohistochemistry. Section showed bony tissue with dense infiltrates composed of histiocytes, plenty of eosinophils, neutrophils and lymphocytes. A few histiocytes showed nuclear grooving (Fig.2). Immunohistochemistry of the lytic lesion was positive for S 100 and CD1a. A diagnosis of Langerhans cell histiocytosis (single organ involvement) was made and the child was started on vinblastine and prednisolone. The child is improving clinically as evidenced by improvement of gait and decreased intensity of pain and is on regular follow up.

Discussion

The term histiocytosis is an “umbrella” designation for a variety of proliferative disorders of dendritic cells or macrophages. Some, such as the rare “histiocytic” lymphomas, are clearly malignant, whereas others, such as reactive proliferations of macrophages in lymph nodes, are clearly benign. Between these two extremes is a small cluster of conditions characterized by proliferation of a special type of immature dendritic cell (DC) called the Langerhans cell. In most instances, these proliferations are monoclonal and therefore likely to be neoplastic in origin. The working group of the Histiocyte Society has divided histiocytic disorders into 3 different groups: (a) dendritic cell histiocytosis, (b) erythrophagocytic macrophage disorders and

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Fig. 1. Plain X-ray pelvis showed a large round osteolytic lesion of right ileum measuring 4 x 5 cm (white arrow).

Fig. 2. Section of the bony tissue showing dense infiltrates composed of histiocytes, plenty of eosinophils (black arrow), neutrophils and lymphocytes. A few histiocytes show nuclear grooving (white arrow).
(c) malignant histiocytosis. LCH belongs to group 1 and encompasses a number of diseases.¹ The cause of LCH is unknown. It may be triggered by an unusual reaction of the immune system from something commonly found in the environment. It is not a known infection or cancer. It is not known to be hereditary or communicable. The prevalence of these disorders is 1:50,000 in children younger than 15 years of age.² A male predominance has been reported.³ A langerhans cell is 15 to 25 mm in diameter with a central to slightly eccentric ovoid nucleus with an indendation or groove across the nucleus (nuclear grooving). The tumor cells in each are derived from dendritic cells and express HLA-DR, S-100, and CD1a. They have abundant, often vacuolated cytoplasm and vesicular nuclei containing linear grooves or folds. The presence of Birbeck granules in the cytoplasm is characteristic. Under the electron microscope, Birbeck granules have a pentalaminar, rodlike, tubular appearance and sometimes a dilated terminal end (tennis-racket appearance). As Birbeck granules are not seen in all tumor cells by electron microscopy, the detection of S-100 and CD1a expression by immuno-histochemical techniques aids in the diagnosis.⁴ Definitive diagnosis is made by presence of cell surface marker CD1a or presence of Bierbeck granules by electron microscopy.⁵ Even with multiple site involvement spontaneous remission has been reported.⁶ Some may develop life-long chronic problems, while others remain symptom free. The approaches to the treatment of extensive LCH, with or without organ dysfunction, have been almost as varied as the clinical manifestations of the disease. A single bone lesion tends to resolve spontaneously during a period of months to years. Biopsy of the lesion, necessary to confirm the diagnosis, may initiate healing with or without curettage. Criteria for additional treatment include intense pain and the threat of unacceptable deformity or disability.

Intralesional infiltration of corticosteroids is effective and convenient. Most patients have been treated with systemic chemotherapeutic agents due to the progressive nature of generalized LCH. Studies have demonstrated the efficacy of a variety of chemotherapeutic agents, either as monotherapy or in combination.

The case discussed here had a single organ involvement (iliac bone). Other bones and organs involvement were ruled out by skeletal survey and investigations mentioned above. The staining of the biopsy specimen showed Langerhans cells with the characteristic grooving in the nucleus. Electron microscopy examination for the presence of Birbeck granules could not be done in this case due to the lack of resources. S 100 and CD 1a positivity confirmed the diagnosis in this case. Though it was a single, it was big and lesion curettage was not warranted in a weight bearing bone due to the possibility of bone deformity. So chemotherapy was started as advised by hematologist. Though single bone involvement is a known feature of Langerhans cell histiocytosis it was in an unusual site in this case as skull bone is the most common site of involvement. A single Xray has changed the diagnosis of this child. LCH should always be kept in mind in any osteolytic lesion. Prompt diagnosis and management reduces morbidity and mortality of Langerhans cell histiocytosis and it is curable in most of the cases.

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CONGENITAL (PLASMODIUM VIVAX) MALARIA IN PRETERM NEONATE - A CASE REPORT OF ATYPICAL PRESENTATION

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Malaria is a major health problem in India and contributes to about 75% of total malaria cases from south Asia. Congenital malaria is a rare disease even in malaria endemic countries. Congenital malaria is defined as malarial parasites demonstrated in the peripheral smear of the newborn from 10-30 days after birth. Neonates can have malaria from mother through vertical transmission or either by mosquito bite or by blood transfusion. Maternal antibodies and placenta are the main barriers for fetal protection. Fetal red blood cells are resistant to malarial parasite. Congenital malaria with Plasmodium falciparum is reported in most of the cases as compared to Plasmodium vivax.

Case report

A 28-day-old male baby, delivered normally at 32-33 weeks of pregnancy with birth weight of 2250gms was admitted with history of fever and poor feeding for one day. On examination, baby weighed 2350 grams with temperature 102°F, respiratory rate 42 per minute, heart rate 164 per minute and blood pressure 70/40mm of Hg. There was no icterus, cyanosis, rash or edema. Liver was palpable 1cm below right costal margin and spleen was not palpable. Baby was put on antibiotics and intravenous fluids after taking samples for sepsis work up.

Investigations revealed a total count of 11900 cell/mm³ with neutrophils 20% out of which 16% were band forms, lymphocyte 73%, eosinophil 3%, monocytes 4%, PCV 31.9% and a platelet count of 45000. X-ray chest was normal. Blood and urine cultures were sterile. CSF study showed sugar 57mg, protein 108mg, cell count 4 lymphocytes with culture being negative. CRP was 6mg/dL. Peripheral smear revealed plasmodium vivax ring forms but there was no evidence of hemolysis. Renal function test were normal. Baby was given syrup chloroquine 10mg/kg immediately followed by 5mg/kg after 6 hours and 5mg/kg for once a day for next two days. Baby was discharged after negative blood, urine and CSF cultures and negative peripheral smear for P.vivax. Mother’s blood smear was also positive for P.vivax and hence treatment with chloroquine and primaquine was given. Repeat peripheral smear examination for mother and baby were negative after 7,14 and 28 days and platelet count of the neonate returned to normal.

Discussion

Malaria is reported to cause more than 300 million clinical cases and more than one million deaths each year worldwide. Malaria is still a major health problem in some parts of world including India. Even in hyper endemic countries congenital malaria is seen very
infrequently because of protection provided by maternal antibodies, placenta and fetal hemoglobin.3 In most cases, mother is infected during the first pregnancy. It leads to serious complications and congenital malaria in offspring.4

Malaria in newborn usually mimics sepsis with symptoms of fever, poor feeding, irritability, lethargy, etc obscuring the diagnosis of congenital malaria.5 Hence, one should keep malaria as one of the causes for fever. Confirmation of malaria is done by identification of parasite in thick and thin smears prepared with Giemsa stain and it might require repeat smear tests and a high index of suspicion. Baby also showed thrombocytopenia and ring forms of Plasmodium vivax. Thrombocytopenia can occur with this species of malarial parasite but it is one of the rare causes of platelet reduction and not many papers have reported this in their findings. Thrombocytopenia can be seen in both septicemia and malaria but baby and mother having P.vivax in peripheral smear, the response to antimalarials and all other lab reports negative for sepsis go against the diagnosis of sepsis.

Children with congenital malaria can present with irritability, feeding problems, hepatosplenomegaly, anemia and jaundice besides fever.3 A study from central India showed no infants developed parasitemia till six months of age whereas their mothers showed present of P.vivax or mixed infection in their placenta.6

It has been reported that young infants rarely present with typical clinical symptoms7 and even asymptomatic presentations have been described.8,9 This can be attributed to maternal IgG antibodies, which can alter clinical presentations in different congenital malaria cases.

Congenital malaria in premature babies is extremely rare especially with plasmodium vivax and very few cases are reported in literature.10 Malaria is a major contributing factor to early fetal losses, stillbirths and premature deliveries in endemic areas; hence early treatment can prevent most of these complications.

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