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Review Article

Pediatric Ulcer, Diagnosis and Management of Patients at High Risk Groups

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Abstract

Present article describes a pediatric ulcer and its associating complications in pediatric groups. Peptic ulcer has multiple causes of occurrence, but *Helicobacter pylori* infection is the main reason. This bacterium invades stomach or duodenum mucosal lining secretion of more acid and choking of enzyme activity. It shows relatively infrequent occurrence in children. Ulcers located at the end of the stomach (where the duodenum is attached) cause swelling and scarring, which can narrow or close the intestinal opening. Disease has certain biomarkers which are used to establish presence of serum antibodies in patients that also display state of tissue damage and recurrence. *Helicobacter pylori transmit* from human to human and colonize very fast inside the stomach mucosa and generate serum antibody response. This article explains serological, microscopic and clinical examination of peptic ulcer. Both therapeutic and drug monitoring are essentially required for it's effective treatment

Keyword: Peptic Ulcer, *Helicobacter Pylori,* Stomach or Duodenum, Damage, Mucous Membranes, Risk Factor, Diagnosis, Therapeutics

Introduction

Peptic ulcer disease is an infection of stomach or duodenum caused by *Helicobacter pylori* (HP). This is reported in pediatric age groups worldwide. A peptic ulcer is an injury or a round or oval shape open sore in the lining of the stomach mucous membranes or duodenum [1]. These show relatively infrequent occurrence in children. Peptic ulcer induces production and secretion of acid from stomach and digestive enzymes. Ulcers develop when the normal defense and repair mechanisms of the lining of the stomach or duodenum becomes weaker. In true sense, mucous lining is more likely to be damaged by acid secreted from stomach. Ulcers in the stomach and duodenum are typically secondary to systemic illnesses or drugs in young children; secondary ulcers do not recur. In contrast, duodenal ulcers in older children and adolescents have a relapsing course that is increasingly recognized to be related to coexisting, chronic, active antral gastritis and *Helicobacter pylori* infection [2].

In a state of delayed or no treatment ulcers penetrate into the lining of the stomach or duodenum the first part of the small intestine. If ulcer transfers into the stomach, then it is called as gastric ulcer. Similarly, ulcer in duodenum it's called a duodenal ulcer. It happens in any age group, but children those who intake more coffee, tea, soda and fast and use caffeine, have more chances of peptic ulcer. Without proper diagnosis and treatment, it is very hard to find relief. If timely treatment is not possible stomach or duodenal wall is eroded, blood vessels get damaged, results in bleeding. Sometimes a hole has worn through the wall of the stomach or duodenum, and bacteria and partially digested food can spill through the opening into the sterile abdominal cavity (peritoneum). Ulcers located at the end of the stomach (where the duodenum is attached) can cause swelling and scarring, which can narrow or close the intestinal opening.

Gastric cancer is associated with acquired chronic inflammation in the stomach, its starts with infection by *Helicobacter pylori* [3]. This is one of the top causes of deaths occurring worldwide. It is an inflammation-associated cancer with a multistep carcinogenesis. The process consists of *H. pylori* infection, ongoing inflammation, development of metaplastic epithelia and genetic instability eventuating in gastric cancer. The organism can be transmitted from human to human with evidence of colonization, appearance of gastritis, and serum antibody response. Antimicrobial therapy is used for eradication of *Helicobacter pylori* colonization and mitigation of symptoms [4].

Causes

Helicobacter pylori is a Gram-negative, bacillus it causes the pathogenesis of certain gastroduodenal diseases, e.g. non-ulcer dyspepsia (NUD), chronic inflammation, ulcers, etc [1]. Peptic ulcer is characterized by its recurrent nature as *Heli-*

cobacter pylori, causes hemorrhagic bleeding due to severity of infection and heavy presence of pathogen after its rapid colonization [5]. Though, it has not been fully established that *Helicobacter pylori* infection and recurrent abdominal pain has some relationship (Figure 1) [6].

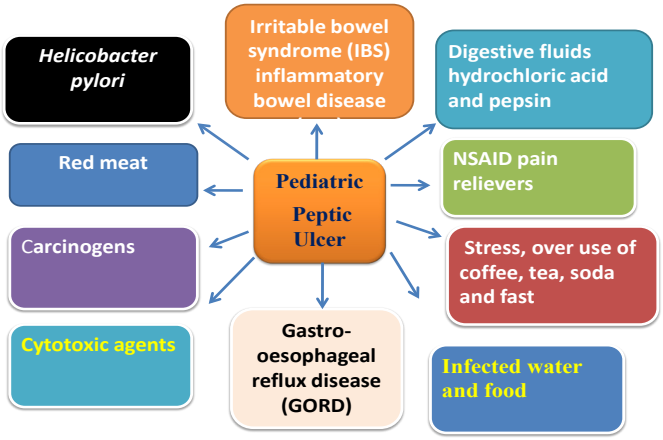

Figure 1: Showing Various Causes of Pediatric Peptic Ulcer

Children whose parents have peptic ulcers are more likely to have ulcers especially if their parents are infected with *Helicobacter pylori*. These bacteria make substances that weaken the protective mucus in child's stomach. The stomach can't always fully defend itself against strong digestive fluids. These include hydrochloric acid and pepsin. This may cause ulcers to form. This makes it more likely to get damaged from acid and pepsin. Exposure to second hand smoke is another risk factor for ulcers in children. It also slows the healing process of ulcers and causes ulcers to come back (Figure 1).

It has been seen that the regular use of NSAIDs causes gastrointestinal problems and bleeding in some children. In both adults and children over use of non-steroidal anti-inflammatory drugs (NSAIDs) aspirin, ibuprofen, and naproxen sodium make the stomach vulnerable to the harmful effects of the digestive fluids' hydrochloric acid and pepsin. These remain at the high risk of peptic ulcers. Among strong causes of peptic ulcer are heavy drinking, smoking and acidity. If any infant or child intake more coffee, tea, soda and fast and use caffeine, chances of peptic ulcer get increased. Caffeine forces the stomach to release more acid. This may make the pain of an existing ulcer worse. However, it does not cause ulcers. Emotional stress is no longer thought to cause ulcers. But people with ulcers often say that their stress increases ulcer pain. Physical stress may increase the risk for ulcers, especially in the stomach. Children after severe burns, injuries, and illnesses display stress ulcers (Figure 1).

Ulcerative colitis is less prevalent in pediatric groups [7]. Though, it is seen mostly in adolescence or early adulthood, but it may occur at any age. Diffuse inflammation of the mucosa of the colon and rectum is a sign of ulcerative colitis. Later on, disease symptoms are seen in form of bloody diarrhea [8]. Another infection known as inflammatory bowel disease (IBD) is also diagnosed in children less than 18 years of age [9]. It is characterized by idiopathic, lifelong, and progressive intestinal inflammatory conditions like ulcerative colitis [10]. For effective therapeutic drug monitoring is essentially required for both diseases [11]. There is need to know prognostic factors in ulcerative colitis (UC), it will help in improving patient management and to reduce complications (Figure 1) [12].

Signs & Symptoms

If someone is feeling sudden, sharp, lasting belly pain, bloody or black bowel movements, bloody vomit or vomit, all these are signs of a peptic ulcer. Other internal problems are deep, and breaks are seen in stomach or duodenal wall from where heavy bleeding occurs because of blood vessel breakage. Bleeding also occurs from obstructions formed as ulcer blocks the path of food from going through the intestines. All above sign and symptoms clear indicate peptic ulcer evoking and child needs a medical help. An ulcer can wear a hole through the wall of the stomach or duodenum. Bacteria and partially digested food can spill through the opening into the abdominal cavity (peritoneum). This is a serious condition called peritonitis. This is inflammation of the abdominal cavity and wall.

More specifically infants with pyloric stenosis feel hungry and provided full meals, but they vomit forcefully (projectile vomiting) shortly after eating. Due to vomiting infants face problem of dehydration that results in severe weight loss in infants. Some infants have a yellowish discoloration of the skin and the whites of the eyes (jaundice) at this point. Hypertrophic pylocric stenosis occurs to the thickening (hypertrophy) of stomach wall that creates a partial blockage (obstruction) that interferes with the passage of stomach contents into the small intestine. The pylorus is the muscular sphincter located where the stomach joins the first part of the small intestine (duodenum). Normally, the pylorus contracts to keep food in the stomach for digestion and relaxes to let the food out into the intestine. For reasons that doctors do not fully understand, the pylorus becomes thickened and sometimes closes off (called stenosis), blocking material from leaving the stomach. This blockage usually occurs in the first month or two of life.

The most common sign is a gnawing or burning pain in the abdomen between the breastbone and the navel. The pain often occurs between meals and in the early morning. The typical symptoms of peptic ulcer are gnawing pain, burning pain, aching, soreness, and feeling of hunger. The burning pain in the stomach is often felt between the breastbone and the belly button (navel). Children also feel pain more between meals, in the early morning, or at night. It may last from a few minutes to a few hours. Less common peptic ulcer symptoms include belching, nausea, vomiting, poor appetite, burping or hiccupping a lot, weight loss, feeding problems, blood in vomit or bowel movements, which may look dark red or black. Child faces weight loss, feeling tired and weak, anemic, bloating, belching, nausea and vomiting, vomit with blood in it, poor appetite, weight loss, tiredness and weakness, red or maroon stool or black, tarry stool,

Risks

The greatest risk factor for gastric and duodenal ulcers is an *H. pylori* infection. *H. pylori* infection more likely is seen who are living in overcrowded conditions, or sharing a bed, genetics (children with Hispanic and African-American backgrounds have a higher risk).

Children who regularly take aspirin or NSAID pain relievers

are also at risk for ulcers. In rare cases, other medical conditions can cause ulcers in children. Some medical conditions also can play a role in ulcers. For example, illnesses that make it hard for the body to heal (such as serious burns from a fire) increase a child's risk of ulcers. This is also true for infants who become septic (very ill with a bacterial infection). In otherwise healthy kids, peptic ulcers are very unusual.

Patients remain at risk of inflammatory bowel disease, pattern changes at the follow-up, need of surgery and cumulative risk for colectomy [13]. At present incidences of pediatric-onset ulcerative colitis (UC) is rising. Children those who come in the grip of acute severe ulcerative colitis (ASUC) need hospital care [14]. The incidence of pediatric-onset ulcerative colitis (UC) is rising. Predicting those at risk at an early stage helps stratify patients into those who may require second line therapy or early surgical treatment. Traditionally, risk scores have used a combination of clinical, radiological and biochemical parameters; established indices include the 'Travis' and 'Ho' scores [14].

Diagnosis

For starting an appropriate treatment of peptic ulcer, a correct diagnosis is highly essential for starting treatment. Clinicians ask for complete medical history and physical examination of affected child. For diagnosis of patients following methods are followed

X-ray examination of Upper GI gastrointestinal tract

An x-ray examination is performed with swallowed contrast material to outline the GI tract. These X-rays of the esophagus, stomach, and duodenum let the doctor get a close look at the gastrointestinal tract. Liquid barium is provided to drink to the patient while getting the X-ray. The ulcerative part is outlined on the X-ray film. It also help to visualize organs in the upper part of your child's digestive system. For this test, your child will swallow barium. This is a silvery, white, chalky liquid that coats the inside of your child's organs. This helps them show up on an X-ray better. Then the provider will take an X-ray of these organs (Table 1).

Table 1: Diagnostic Methods Used for Detection of Pediatric Peptic Ulcer

Technique use	Biomarker	Accuracy	Sensitivity	Specificity
ELISA	IgG1 and IgG3 subclasses against heat stable *H. pylori* antigens.	99.9% accurate.	0.0001 mg/mL 0.1 to 1 fmole or 0.01 ng to 0.1 ng	Very high specificity
Upper gastrointestinal (GI) endoscopy and biopsy	Cellular and tissue damage changes	98.8%. more accurate	55% sensitivity	High specificity
Biochemical	Stimulated serum gastrin/ pepsinogen I levels	98.0%. more accurate	96%	High specificity
Medical and family history.	Current and past illnesses.	Moderate	Moderate	Non specific
Blood test	Antibodies/proteins produced naturally	98.8%. more accurate	85% sensitivity	High specificity
Urea breath test	Swallow a pill, liquid or pudding that contains tagged carbon molecules	measures the amount of CO2 in an exhalation before and after ingesting a urea-containing solution more accurate	High specificity	High specificity
Stool test ((PCR) test	Polymerase chain reaction (PCR) test	Identify mutations that may be resistant to antibiotics used to treat *H. pylori*, more accurate	High specificity	High specificity
Stool antigen test	Stool antigens	Proteins (antigens) associated with *H. pylori* infection in the stool more accurate	High specificity	High specificity

Endoscopy

A test that uses an endoscope to examine the inside of part of the digestive tract. Tissue samples from inside the digestive tract may also be taken for examination. For diagnosis of peptic ulcer endoscopy is used. It is imaging tests in which a flexible viewing tube is inserted through the child's mouth and down the esophagus into the stomach and first part of the duodenum. A small tissue is removed and collected for biopsy to determine whether an ulcer is caused by *Helicobacter pylori* bacteria. Stool tests and breath tests can also be done to detect Helicobacter pylori. If more complications or perforations are seen doctor perform as x-rays, computed

tomography (CT), or magnetic resonance imaging (MRI). Abdominal ultrasonography is used to find a small lump (about the size of an olive) in the infant's abdomen (the enlarged pylorus). Occasionally, if the infant is observed after feeding and before forcefully vomiting, a wavelike contraction across the abdomen called a peristaltic wave can be seen. Most commonly, however, the doctor does abdominal ultrasonography to confirm the diagnosis. Surgery is done to remove out bulge or any perforation. Blood, stool, breath, and stomach tissue tests are followed to investigate the presence of *H. pylori* (Table 1).

Serological tests

Presence of *Helicobacter pylori* in patient's serum sample can be established by using IgG, IgA and IgM antibodies against *H. pylori* by an ELISA technique. Presence of *H. pylori* is also confirmed by culture or microscopy, and comparison in controls [15]. *Campylobacter jejuni* and total antibodies against cytomegalovirus (CMV) showed a greater similarity between *H. pylori* and C. jejuni [14]. Serum is examined by ELISA method to evaluate anti-*H. pylori* IgG, IgM and IgA antibodies. But this serologic examination is not much enough to diagnose and see the condition of affected area in stomach and duodenum. Hence, gastroscopy is done to understand the aetiology [16]. In addition, *endoscopic* are also correlated with *H. pylori* phenotype related with GU than with DU (Cag A or Vac A) [5]. Similarly, anti-CagA determinations cannot replace endoscopy though it is a valuable diagnostic tool for detection of *H. pylori* [17]. Further, presence of serum immunoglobulin G (IgG) antibody to *H pylori* is determined in serum samples using the high-molecular-weight cell-associated protein *H pylori* enzyme immunoassay (Table 1) [18].

Helicobacter pylori infected children display recurrent abdominal pain and gastritis. These are diagnosed by using serologic tests, biopsies for culture, histologic analysis, and CLO test. *H pylori* is also detected by polymerase chain reaction [18]. Blood, stool, or breath tests are performed to detect for signs of blood loss, inflammation, and the presence of *H. pylori* in the stool (Table 1).

Serologic markers of *H. pylori* infection

This disease can be marked biochemical markers that are an increase in fasting and in meal-stimulated serum gastrin levels. In the past an elevated pepsinogen I levels were considered as genetic marker for risk of developing duodenal ulcer disease Serologic markers of *H. pylori* infection can serve as potential predictors for the development of gastric cancer. Serologic markers of *H. pylori* infection can serve as potential predictors for the development of gastric cancer [19]. Serum or urinary *H. pylori* antibodies, cytotoxin-associated gene A antibodies, pepsinogen and microRNAs were reported to be associated with precancerous lesions or gastric cancer (Table 1) [20].

One possible reason for the varying outcomes of *H. pylori* infection is related to differences in the virulence of *H. pylori* strains in addition to host, environmental and dietary factors. The identification of risk markers for classifying *H. pylori* infected patients into highland low-risk groups is highly desirable for personalized prevention. Serologic markers of *H. pylori* infection can serve as potential predictors of the development of gastric cancer. The significance of virulence factors in Helicobacter pylori [21]. Subjects infected with cagA-positive *H. pylori* do not always produce serum CagA antibodies, even in east Asian countries. CagA seropositivity was significantly associated with gastric cancer, even in east Asian countries, in a metaanalysis. Serum CagA antibody titers can differ according to the ELISA kit used. Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach (Table 1) [21].

The best studied virulence factor of *H. pylori* is the cytotoxin-associated gene A (Cag A) protein [22]. The prevalence of Helicobacter pylori antibodies was significantly higher in patients with gastric cancer than in control subjects. Patients with low *H. pylori* antibody titers and mucosal atrophy comprised an extremely high-risk population for gastric cancer. It is important that *H. pylori* antibody titers varied greatly depending on the test kit used. Therefore, it is preferable to develop a domestic ELISA kit by using local *H. pylori* strains (Table 1).

Serum PG was identified as a marker of the gastric mucosal status including atrophy and inflammation. The combination of *H. pylori* serology and measurements of serum PG I levels and the PG I/II ratio can be applied for gastric cancer screening. Serum CagA antibodies, the status of PG and miRNA levels might be suitable for delineating the high-risk population for gastric cancer in Japanese population. Japanese national health insurance system approved *H. pylori* eradication therapy for all patients with '*H. pylori* related chronic gastritis [22]. However, the risk of gastric cancer exists even after curing *H. pylori* infection. The risk of developing gastric cancer in patients cured of *H. pylori* infection was 0.3% per year in Japan (Table 1) [23].

Humoral immune response to Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a Gram-negative, curved bacillus it causes pathogenesis in gastroduodenic region e.g. non-ulcer dyspepsia (NUD), chronic inflammation, ulcers, etc [1]. In response to Helicobacter pylori infection in children, body raises systemic humoral immune response to secreted antigens. These children show the recurrent abdominal pain (RAP) that also indicates chronic gastritis. Most of infected children diagnosed displayed increased levels IgG1 and IgG3 subclasses against heat stable *H. pylori* antigens. Contrary to this, IgG antibody levels to *H. pylori*, were found significantly different from the 10-14% seropositive rate of asymptomatic children [15].

Management of patients at high risk groups

For the management of *Helicobacter pylori* infection in children triple therapy with amoxicillin and clarithromycin is recommended as the first-line therapy of *H. pylori* infection. test-and-treat" strategy is followed for *H. pylori* infection for asymptomatic children to protect against the development of gastric cancer. In *Helicobacter pylori* specific germline mutations are seen and its infected patients show higher risks for gastric cancer related to a number of other familial genetic diseases [3].

Patients with atrophic gastritis, intestinal metaplasia, and epithelial dysplasia of the stomach remain at increased risk for gastric cancer. High grade dysplasia is main reason of disparity in patients because it is a premalignant condition [24]. There are certain factors which increase the chances

of gastric cancer i.e. exposure to biomass smoke, daily consumption of processed meat, and poverty are main risk factors. Persons those who consume hot dogs, red meat they show intestinal-type gastric cancer [25]. Vegetarians those who daily consume green vegetables show higher protection against gastric cancer. Exposure to biomass smoke was associated with evidence of oxidative stress and DNA damage increases the chances of lung associated diseases with gastric problems [25]. The down regulation of circMAN1A2 could inhibit the proliferation, migration and invasion of gastric cancer cells [26]. Gastric microbiome, other than Helicobacter pylori, plays a role in the tumorigenesis of gastric cancer (GC) [27].

Inoculation of viruses in damaged stomach mucosal lining increased the severity of gastric cancer. Entry of virus (oncogenic viruses) is just like a double-edged sword and it is an important issue [28]. Several countries have started Helicobacter pylori eradication strategy and included it into national gastric cancer eradication program. In Japan a national plan is launched to prevent chronic gastritis. *Helicobacter pylori (H. pylori)* eradication reduces gastric cancer risk. The findings strongly support the promotion of *H. pylori* eradication strategy for all age groups in high-incidence countries [29]. Vaccination against *H. pylori* would reduce the cost of eradication therapies and lower gastric cancer incidence. But this is still a challenge. An effective vaccine should have an adequate route of delivery, appropriate bacterial antigens and effective and safe adjuvants [30].

Treatment

For killing of *H. pylori*, a combination of metronidazole or amoxicillin with colloidal bismuth subcitrate or bismuth subsalicylate is provided to the children [31]. It results in 70% mortality in *H. pylori*. These also cut down inflammation of gastric mucosa, stops further histologic damage. It also diminishes the chances of risk of peptic ulcers and gastric cancer. Standard triple therapy, bismuth-based quadruple therapy, and the sequential therapy treatment are recommended for treatment of ulcers [32]. Even after strong chemopreventive strategies pathogen saves itself due to resistance and recurs again. It is happening currently in high-risk populations [33]. More specifically, proton-pump inhibitors or antisecretory drugs are provide to patients facing ulcers due to NSAIDs. These patients need careful differential diagnosis and adequate treatments [33].

Most *H. pylori*-related ulcers can be cured. Complete medication by using antibiotics for 2 weeks and an acid suppressor (antacid) for 2 months or longer provide an early relief. The ulcer may take 8 weeks to heal, but the pain usually goes away after a few days or a week. These medicines kill bacteria. Children who are infected with Helicobacter pylori are given antibiotics to eliminate the bacteria and a proton pump inhibitor to reduce stomach acid. In such cases H2-blockers are provided which reduce the formation of amount of acid in the stomach. They do this by blocking histamine, which causes acid to be released. In addition, proton pump inhibitors are provided which obstruct production of acid in stomach. Drugs that reduce acid include proton pump inhibitors, histamine-2 (H2) blockers, and antacids. Mucosal protective drugs protect the stomach's mucous lining from the acidic damage [19].

If infant those facing severe vomiting, then children is evaluated for diagnosing problem of dehydration and loss of electrolytes. It is also a symptom of metabolic alkalosis. Clinicians provide intravenous fluids for maintaining electrolyte balance and remove off problem of dehydration. Besides, blockage in duodenum is removed by surgery so that breast milk enters the small intestine easily. This surgery is pyloromyotomy, and relatively minor.

Surgical and clinical post-operative care

H. pylori infection increases the risk for stomach cancer later in life. When treating *H. pylori*, these medications or procedures are often used in combination with antibiotics. In most cases, anti-ulcer medicines heal ulcers quickly and effectively, and eradication of *H. pylori* prevents most ulcers from recurring. If infection does not end after long chemotherapeutic treatment or medication, then only options is surgical operation. The most common problems which are restored by surgery is reduction of acid secretion by cutting the vague nerve as it transmits message from brain to stomach, it is known as vagotomy. Surgical removal of lower part of stomach (antrum), which produces a hormone that stimulates the stomach to secrete digestive juices, is also done. Sometimes a surgeon may also remove an adjacent part of the stomach that secretes pepsin and acid. A vagotomy is usually done in conjunction with an antrectomy. Surgery is done to remove obstructions in duodenum and small intestine (pylorus) so that food contents pass more freely from the stomach. It is also known as pyloroplasty.

Lifestyle changes

For quick healing of peptic ulcer change in life style mainly food habits are highly important. Hence, people should long term use of spicy, fatty, or acidic foods. Smoking of cigarettes is highly harmful for children. Smoking slows down the healing process of ulcers and causes ulcers to come back. Alcohol consumption is also irritating to the lining of the GI tract. There are a number of different treatment options for gastric and duodenal ulcers. In the past, physicians advised parents to avoid feeding their children with ulcers spicy, fatty, or acidic foods. However, a bland diet is now known to be ineffective for treating or avoiding ulcers. No particular diet is helpful for most children with ulcers [34-37].

Conclusion

H. pylori infection is the main causative agent of peptic ulcer and other complications. This bacterium causes a chronic infection of the stomach. This disease can be marked by biochemical markers mainly meal-stimulated serum gastrin levels in fasting and non-fasting state. Children those who use regularly aspirin or NSAID pain relievers are also at risk for ulcers. Some medical conditions also can play a role in ulcers. There was found a close relationship between *H. pylori* infection and occurrence of gastric cancer risk in patients. There is a high incidence of peptic ulcer and gastric cancer in many Asian, European and African countries with different risk groups with variable serological immunoglobulin levels. There is an immense need to identify high risk groups on the basis of cellular, genetic, molecular and immunological examination for timely therapeutics and management of disease. Both triple therapy and surgical procedures and clinical care should be allowed to all high-risk group patients.

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