Peptic ulcer disease in children

Peter B Sullivan

Abstract

Peptic ulcer disease is uncommon in children with an estimated frequency of 1 case in 3000 hospital admissions. In children, peptic ulcer disease is usually classified as either primary or secondary depending on the underlying pathology. *Helicobacter pylori* infection of the stomach is the commonest cause of primary peptic ulcers. Other causes of primary ulcers include those caused by rare conditions of acid hypersecretion such as Zollinger–Ellison syndrome; G-Cell hyperplasia; systemic mastocytosis; short bowel syndrome; and hyperparathyroidism. Secondary ulcers occur more often in younger children. They have a worse prognosis and are usually associated with physiological stress and systemic illness such as sepsis, head trauma, burns, sickle cell disease, type I diabetes, systemic lupus erythematosus and drug therapy. Upper gastrointestinal endoscopy is the investigation of choice for children with suspected peptic ulcer disease. Triple therapy given twice daily with a proton-pump inhibitor plus two antibiotics (e.g. Metronidazole plus Amoxicillin or Amoxicillin plus Clarithromycin) for two weeks will eradicate *H. pylori* and heal ulcers in the majority of cases.

Keywords child; duodenal ulcer; gastric ulcer; *Helicobacter pylori*; peptic ulcer

Introduction

Peptic ulcer disease is uncommon in children. Understanding of the aetiology, the investigation and treatment of this condition has changed markedly in recent years. The advent of paediatric endoscopy in the mid 1970s allowed visualization of peptic ulcers, whereas previously they had only been seen indirectly on barium contrast studies. Similarly, the advent of H_2 receptor blockers also in the mid 1970s and of proton-pumps inhibitors in the late 1980s revolutionized treatment. The one factor more than any other which led to a complete re-evaluation of the understanding of the origins of peptic ulcer disease, however, was the discovery of *Helicobacter pylori* infection of the stomach in the early 1980s. The discovery of *H. pylori* switched the understanding of the aetiology of peptic ulcer disease from that of an acid driven disease to an infectious disease. Interestingly, as far back as 1915, Gerdine and Helmholz demonstrated that ulcers in children sometimes occur in restricted geographical regions, a fact which even at that time nearly 100 years ago suggested that epidemic infectious causes might be concerned with the aetiology of peptic ulcer disease.

Peter B Sullivan *MA MD FRCP FRCPCH is Reader in Paediatric Gastroenterology and Head of the University of Oxford, Department of Paediatrics, Children's Hospital, Oxford Radcliffe Hospital, Oxford OX3 9DU, UK. Conflicts of interest: none.*

Classification

Peptic ulcer disease in children is usually classified as either primary or secondary depending on the underlying pathology. Primary ulcers include those caused by rare conditions of acid hypersecretion such as Zollinger–Ellison syndrome; G-Cell hyperplasia; systemic mastocytosis; short bowel syndrome; and hyperparathyroidism. The very much more common cause of primary ulcers, however, is *H. pylori* infection of the stomach. Primary ulcers usually occur in children older than 10 years of age, are usually chronic and situated in the duodenum.

Secondary ulcers occur more often in younger children are usually acute and can occur in either the stomach or duodenum. In neonates and infants the vast majority of ulcers are secondary ulcers and they are usually gastric. Secondary ulcers are associated with physiological stress and systemic illness, such as sepsis, head trauma, burns, sickle cell disease, type I diabetes, systemic lupus erythematosus and drugs (e.g. non-steroidal anti-inflammatory drugs, corticosteroids, sodium valproate, theophylline).

There has been a noticeable change in peptic ulcer disease in Western countries in the last decade; the proportion of *H. pylori*-positive ulcers has declined with an increase in the prevalence of *H. pylori*-negative ulcers. In a pooled analysis of six clinical trials of 2900 patients, 27% of duodenal ulcers were found not to be associated with *H. pylori* or NSAID. A systematic review of 16,080 patients over a period of 10 years indicated that the mean prevalence of *H. pylori* in those adults with endoscopy-proven duodenal ulcer was 81.2% with confidence intervals of 80.6–81.8%. Interestingly, this high prevalence fell to 77% when only cases occurring in the last 5 years are examined. Whether gastric acid hypersecretion is implicated in the development of non-NSAID, non-*H. pylori* ulcer is still controversial.

Pathophysiology

Peptic ulcer is diagnosed at endoscopy where there is a mucosal break of 5 mm or larger covered with fibrin. Mucosal breaks smaller than 5 mm are called erosions. An erosion is a mucosal break that does not penetrate the muscularis mucosa whereas an ulcer extends through the muscularis mucosa in the sub-mucosa.

Studies of the location of peptic ulcer disease in children indicate that in about a third of cases were gastric ulcers are predominantly in the antrum and only infrequently on the greater curve whereas three-quarters are in the duodenum (usually in the duodenal bulb). In a minority of cases both gastric and duodenal ulcers may be found present. Incidence of peptic ulcer disease varies in different geographical regions. In Japan, for instance, in a large case series of 283 children in whom 732 endoscopies were performed because of gastrointestinal symptoms: 100 had duodenal ulcers and 43 gastric ulcers representing nearly 20% of all endoscopies. These findings contrast with the much lower levels (1.8–5%) of peptic ulcer disease in children reported in North America, Australia and Europe.

The prevalence of non-*H. pylori*, non-NSAIDS peptic ulcer disease has also been studied in Israel and out of the 622 upper endoscopy reports, a total of 11 (1.8%) children with mucosal ulceration were found with gastric ulceration in three (27%) cases, and ulceration of the duodenal bulb in 10 (91%) cases (two children had ulcers in both the stomach and duodenal bulb). Notably, *H. pylori* infection was only detected in three

(27%) children with duodenal ulcer. Gastritis was more severe, however, in patients with *H. pylori* infection/duodenal ulcer compared with *H. pylori*-negative/duodenal ulcer group.

This finding is in line with those from other studies on the pathology of *H. pylori* infection in children which have also shown that the heavier the colonization of the gastric mucosa with *H. pylori* the more severe is the histological lesion. Although this association is well-known also in adults, there are some distinctly different features of *H. pylori* infection in children when compared with adults. Oxyntic gastritis is more common in children and neutrophil polymorphs, which are generally present in adults, are scanty or even absent in children. This may be related to differences in the immune response in children and/or less protracted exposure to the organism together with absence of other noxious factors including use of tobacco, ethanol and anti-inflammatory drugs. Conversely, lymphonodular hyperplasia (LNH) is much more prominent in children than in adults and has been reported in between 50 and 90% of cases. These nodules vary in size from 2 to 4 mm and are covered with a smooth, non-ulcerated mucosa which produces a typical 'cobblestone' appearance. The finding of such a nodular antrum on endoscopy is highly predictive of *H. pylori* infection in children. The large study from Japan, for example, found *H. pylori* in 28.8% of those with non-nodular gastritis and in 98.5% of those with nodular gastritis. Children have much more reactive lymphoid tissue than adults and LNH represents an immunological response of the gastric mucosa to local antigenic stimulation by *H. pylori*. Eradication of *H. pylori* is followed by the complete resolution of the inflammatory process and the disappearance of micronodules, but this may take several months.

Clinical features

Symptoms in children with suspected peptic ulcer disease commonly include epigastric pain, a relationship of pain with eating, a positive family history, vomiting and bleeding and are crucial factors for the diagnosis of peptic ulcer disease in childhood. Other presenting symptoms include, early satiety or anorexia, nausea, recurrent vomiting and anaemia. Weight loss may also occur.

Abdominal pain is the most common symptom and it is usually dull and vague but may be poorly localized or localized to the epigastric or (in pre-school children) to the periumbilical region. Unequivocal epigastric pain is relatively uncommon in children and should always prompt further investigation. The classical 'adult' history of pain that wakens and is exacerbated by food and relieved by fasting is not elicited that often in children but does help distinguish organic from functional abdominal pain.

Recurrent vomiting caused by peptic ulcer disease is more commonly found in young children and may be associated with poor growth.

Peptic ulcer disease may also present with gastrointestinal bleeding (e.g. haematemesis or melaena). Upper gastrointestinal tract bleeding with or without pain requires investigation. Bleeding may occur against a background of chronic epigastric pain or other symptoms, but painless bleeding may be the only manifestation of ulcer disease. Up to one quarter of children with duodenal ulcers have this 'silent' presentation, a further 25% presenting with bleeding and antecedent pain, and the remainder with abdominal pain or recurrent vomiting.

Family clustering

A positive family history of peptic ulcer disease is common with between one quarter and two-thirds of children with a peptic ulcer also having a first degree relative with peptic ulcer disease. This may be accounted for to some extent by *H. pylori* infection which is known to cluster within families and other close knit communities. A higher frequency of *H. pylori* infection is found in spouses and offspring of *H. pylori*-infected adult cases. This high frequency in spouses suggests that genetic factors are less important than environmental ones. A crucial question is whether members of a family are colonized by the same strain of *H. pylori*. Although there is evidence that the same strain of *H. pylori* can be isolated from individuals within a particular family, the picture is complicated by the fact that, in other studies, different strains have also be isolated from several family members. Strain identification using DNA digest patterns has shown young siblings to be colonized by different strains, although individuals can harbour more than one strain of *H. pylori* simultaneously. Clonal variants of *H. pylori* have been shown to cluster in some families with a history of duodenal ulcer disease. Family members are known to harbour strains of *H. pylori* with the same DNA fingerprints.

Differential diagnosis

The differential diagnosis of peptic ulcer disease is extensive as the symptoms of peptic ulcer disease can be mimicked by oesophagitis, eosinophilic gastritis, Crohn's disease, gall bladder disease, pneumonia, pancreatitis or functional dyspepsia.

Investigation

Oesophagogastroduodenoscopy has replaced barium meal as the investigation of choice for children with suspected peptic ulcer disease and a three-fold increase in the diagnosis of peptic ulcer disease was seen after the introduction of endoscopy. Children previously suspected to have a peptic ulcer by barium study should undergo endoscopy if their symptoms persist or recur. Endoscopy allows for direct visualization of the mucosa for the localization of any bleeding and also or the identification (LNH) and diagnosis of *H. pylori* infection. Gastric mucosal histology can help differentiate suspected peptic ulcer disease from other aetiologies such as Crohn's disease or eosinophilic enteropathy.

The [C^{13}] urea breath test is not an appropriate alternative to endoscopy for the initial diagnosis of *H. pylori* in children because of the wide differential diagnosis involved. The [C^{13}] urea breath, however, is more appropriate than repeat endoscopy to confirm eradication of *H. pylori*.

In non-*H. pylori* peptic ulcer disease a fasting plasma gastrin level should be obtained to exclude one of the rare G-cell disorders Zollinger–Ellison syndrome.

Treatment

The treatment of peptic ulcer disease is the treatment of the underlying cause. Non-*H. pylori* ulcer disease can be treated effectively with acid-suppression. Receptors for histamine are located on the acid-producing parietal cells and blocking histamine 2 receptors (e.g. with Ranitidine) suppresses gastric acid secretion. Proton-pump inhibitors (PPIs) are more potent at acid-suppression than histamine 2 receptor blockers and they block

acid secretion at the level of the H^+/K^+ ATPase in the gastric parietal cell. PPIs such as Omeprazole or Lansoprazole are also bacteriostatic against *H. pylori* and are used in treatment although used alone they are unable to eradicate *H. pylori*. There is evidence (largely from children treated for gastro-oesophageal reflux) that PPI therapy is safe in children for up to 11 years.

In terms of the treatment of *H. pylori* infection, three sets of published paediatric evidence based guidelines based on input from 90 experts in 20 countries are available from the Canadian Association of Gastroenterology (2004), the North American Society for Pediatric Gastroenterology (2000) and the European Taskforce on *Helicobacter pylori* infection (2000) and they are remarkably in agreement. Where *H. pylori* infection is the cause of peptic ulceration the current recommendation for children is triple therapy given twice daily with an acid suppressant (proton-pump inhibitor) plus two antibiotics (e.g. Metronidazole plus Amoxicillin or Amoxicillin plus Clarithromycin) for two weeks. Acid-suppression may be continued to two weeks after the antibiotics. An increasing prevalence of resistance of *H. pylori* to Metronidazole and Clarithromycin has been noted in children and this may result in treatment failure. Depending on patterns of antibiotic resistance, other therapeutic agents may be used and include bismuth subcitrate or, in children over 12 years, Tetracycline. Compliance with treatment is the single biggest determent of successful eradication.

In addition to its important role in diagnosis, endoscopy is also valuable for the treatment of bleeding peptic ulcers. Injection of adrenaline (epinephrine) is the most popular therapeutic method for dealing with high risk bleeding peptic ulcer but available evidence shows that addition of a second endoscopic procedure such as electro-coagulation or 'haemoclip' reduces further the bleeding rate, the need for emergency surgery and also mortality.

The use of therapeutic endoscopy and the discovery of *H. pylori* have changed surgical approaches to peptic ulcer treatment considerably. At one time (when the aetiology of peptic ulcer disease was believed to be gastric hypersecretion) surgical treatment for peptic ulcer disease was designed to control gastric secretion and vagotomy and pyloroplasty was the treatment of choice. Now surgery is reserved predominantly for the treatment of acute ulcer bleeding.

Prognosis

In the pre-*H. pylori* era, long-term follow-up of children with peptic ulcer disease indicated that less than one third of cases became free of symptoms for a prolonged period of time without recourse to surgery and nearly half continued to have pain despite treatment with H2 antagonists. Triple therapy (proton-pump inhibitor plus two antibiotics for two weeks) has been shown to eradicate *H. pylori* and lead to ulcer healing in between 65% and over 90% of cases.

Mortality rates are low in older children with primary ulceration and *H. pylori* infection and highest in infants and children with serious systemic illness who have secondary ulceration particularly when this is associated with haemorrhage and perforation. ◆

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Practice points

- Peptic ulcer disease is uncommon in children.
- Peptic ulcer disease in children is usually classified as either primary or secondary depending on the underlying pathology.
- *Helicobacter pylori* infection of the stomach is the commonest cause of primary peptic ulcers.
- Oesophagogastroduodenoscopy is the investigation of choice for children with suspected peptic ulcer disease.
- Triple therapy given twice daily with a proton-pump inhibitor plus two antibiotics (e.g. Metronidazole plus Amoxicillin or Amoxicillin plus Clarithromycin) for two weeks will eradicate *H. pylori* and heal ulcers in the majority of cases.