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Peptic ulcer disease in children

Ranjan Dohil* MBBCh, MRCP (UK)
Assistant Clinical Professor of Pediatrics
University of California at San Diego, San Diego, CA, USA

Eric Hassall MBChB, FRCP(C)
Associate Professor of Pediatrics, University of British Columbia
Division of Gastroenterology, British Columbia Children's Hospital, Vancouver, BC, Canada

A peptic ulcer in a child looks the same as it does in an adult, and many of the aetiologies of peptic ulcer disease in children are similar to those in adults. However, there are many differences between children and adults, especially in the areas of clinical presentation, the prevalences of different types of ulcer disease, and the prevalence of complications of ulcer disease. Therefore the approach to diagnosis and management in children is often at variance with that in adults. One important example is the approach to suspected *Helicobacter pylori* (*H. pylori*) disease in children, in which consensus groups have advised a considerably different approach in children. While the chapter deals with the full range of peptic ulcer disease in children, the focus is on those aspects in which there are differences between adults and children.

Key words: ulcer; *H. pylori*; gastritis; gastropathy; stomach; duodenum; paediatric; endoscopy.

The focus in this chapter is on aspects of peptic ulcer disease in children that differ from those in adults, as those which are common to children and adults are addressed in other chapters. The major differences between peptic ulcer disease in children and adults lie in the prevalence and presentation in children. Because of these important differences, the approach to suspected peptic ulcer disease in children often differs from that in adults: for example, specific guidelines have been drawn up by consensus groups to address the approach to suspected *Helicobacter pylori* (*H. pylori*) disease in children.

Conceptually it is useful to categorize peptic ulcer disease into *primary* and *secondary* (Table 1). In this approach, secondary ulcers are those associated with or occurring in the presence of systemic underlying disease, whereas primary ulcers do not do so; included, however in the primary category are those few disorders known to cause acid hypersecretion.

While the categorization is based on aetiology, there are other general qualities that are consistent with this approach. For example, primary peptic ulcers are usually chronic, with fibrinopurulent debris overlying active inflammatory infiltrate, granulation tissue and fibrosis.[1] In contrast, secondary peptic ulcers are usually more acute in onset, often induced by physiological stress or drug ingestion, and are not generally

*Current address: Joint Program in Pediatric Gastroenterology and Nutrition, UCSD Medical Center, San Diego, CA, USA.

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Table 1. Causes of peptic ulcers in children.

Primary peptic ulcers	Secondary peptic ulcers
H. pylori-associated	Crohn's disease
H. pylori-negative/'Idiopathic'	'Stress'
Hypersecretory states:	Neonatal ulcers
Zollinger–Ellison syndrome	Traumatic gastropathy
G-Cell hyperplasia/hyperfunction	Aspirin and other NSAIDs
Systemic mastocytosis	Other drugs:
Cystic fibrosis	Valproic acid
Short bowel syndrome	Dexamethasone
Hyperparathyroidism	Chemotherapy
	Alcohol
	Potassium chloride
	Allergic gastritis and eosinophilic gastritis
	Cytomegalovirus
	Graft-versus-host disease
	Uraemic gastropathy
	Henoch–Schönlein gastritis
	Corrosive gastropathy
	Coeliac disease
	Hepatic cirrhosis
	Bile gastropathy
	Autoimmune disease
	Exercise induced
	Sickle cell disease
	Other granulomatous gastritides:
	Foreign body reaction
	Idiopathic
	Sarcoidosis
	Histiocytosis X
	Tuberculosis
	Phlegmonous gastritis and emphysematous gastritis
	Other infections:
	Helicobacter heilmanii
	Herpes simplex
	Influenza A
	Syphilis
	Candida albicans
	Histoplasmosis
	Mucormycosis
	Anisakiasis
	Radiation gastropathy

fibrotic. Primary peptic ulcers are more often duodenal, whereas secondary ulcers are more often gastric than duodenal. In the section on secondary ulcers, many conditions are included that are often, but not necessarily always, accompanied by erosions or ulcers, even where these are often not the predominant endoscopic feature. In this article, the term 'ulcer disease' is used fairly loosely, but many conditions described herein display erosions rather than ulcers, some having both.

Peptic ulceration of the stomach or duodenum, either primary or secondary, is almost always accompanied by abnormalities of the gastric mucosa, either a gastritis or a gastropathy. These issues are discussed more fully elsewhere.[2,3] There are many gastropathies and gastritides that are not accompanied by peptic ulceration, and these too are discussed in other sources.[2]

Before discussing specific entities in the categories of primary and secondary ulcer diseases, consideration of the ways in which children present clinically may give an important paediatric perspective.

Clinical presentation

In the paediatric age group, abdominal pain is a very common reason for seeking medical advice and is the most common presenting symptom of peptic ulcer disease. Nevertheless, peptic disorders (oesophagitis, gastritis, gastropathy and duodenitis), account for fewer than 5% of children presenting with abdominal pain, even in a subspeciality practice. Peptic disorders overall, including peptic ulcer disease, are far less prevalent in paediatrics than in a practice of adult gastroenterology.

Symptoms of peptic disorders may be similar, and in children aged 8–10 years or older, they may be similar to those seen in adults. While epigastric pain or discomfort that is meal exacerbated or awakens the child from sleep is often a symptom of peptic ulcer disease in children, it may also be a presenting symptom of more common disorders such as non-ulcer dyspepsia and constipation. Most primary peptic ulcers in children occur between the ages of 8 and 17 years (mean 12 years)[4–6], while secondary ulcer disease occurs at all ages. Younger children may not be able to localize the pain to the epigastrium and may present with anorexia and irritability, especially with meals.

Other presenting symptoms include anorexia, nausea, early satiety, recurrent vomiting and anaemia. Weight loss occurs less often. Gastrointestinal bleeding may occur with longstanding antecedent epigastric pain or other symptoms, but painless bleeding may be the only manifestation of ulcer disease. Up to 25% of children with duodenal ulcers have this 'silent' presentation, approximately 25% presenting with bleeding and antecedent pain, and the rest with abdominal pain or recurrent vomiting.[5,7] On physical examination, epigastric tenderness is an unreliable sign of gastritis or ulcer disease.

Symptoms of gastritis or peptic ulcer can be mimicked by oesophagitis, gallbladder or liver disease, pneumonia, pancreatitis and giardiasis. Pain that is truly localized to the epigastrium is relatively uncommon in children and always requires investigation, as does upper gastrointestinal tract bleeding with or without pain. Although presenting symptoms may lead to the suspicion that peptic disease is present, gastritis, duodenitis and peptic ulcer are not clinical diagnoses but endoscopic and biopsy diagnoses. Suspicion also may mislead; for example, a child with haematemesis following aspirin or non-steroidal anti-inflammatory drug (NSAID) ingestion may well have bled from undiagnosed oesophageal varices or *H. pylori*-associated ulcer rather than an NSAID ulcer.

PRIMARY PEPTIC ULCER DISEASE

While there is a paucity of prevalence figures in children, it is clear that peptic ulcer disease is much less common in children than adults. For example, in our own unit in a tertiary children's hospital, with a referral population of some 3 million, we diagnose only about 4–6 new primary ulcers per year. Of these, duodenal ulcers are much more prevalent than gastric ulcers; in our experience over a 14-year period, all ulcers being diagnosed endoscopically and excluding NSAID-related ulcers, duodenal ulcers were approximately 20–30 times more prevalent than gastric ulcers.

Far and away the most common primary peptic ulcers are *H. pylori* related, although a significant minority are *H. pylori*-negative or 'idiopathic'. Very few are caused by conditions known to cause acid hypersecretion (Table 1).

Helicobacter pylori-associated ulcer disease

A discussion of *H. pylori*-associated peptic ulcer disease is incomplete without an account of *H. pylori* gastritis and related conditions, given more fully elsewhere.[2,8]

In the paediatric literature, the most common types of *H. pylori* gastritis are diffuse antral gastritis and non-ulcer pangastritis, but since paediatric reports seldom refer to corpus histology, this may simply reflect a sampling bias. In occasional children, the authors have seen focal intestinal metaplasia in corpus and in antral biopsies. However, the types of gastritis which predispose to gastric adenocarcinoma are not described in children; these gastritides are multifocal atrophic gastritis and progressive intestinalizing pangastritis. To date, there are no data on the relationship between *H. pylori*, intestinal metaplasia and gastric cancer in children, and the age of acquisition of *H. pylori* does not appear to be a marker for an increased risk of gastric carcinoma.[9–11]

The severity and depth of *H. pylori* gastritis are variable, but in general, inflammation is most intense in the antrum, followed by the cardia, and least in the body.[12] In our own patients, antral gastritis scores were higher in those with *H. pylori*-associated duodenal ulcer than in those without ulcers, and virtually absent in those with *H. pylori*-negative ulcer disease.[4,13] Although normal gastric histology has been reported in children infected with *H. pylori*[14], 'normal' and 'gastritis' were not quantitatively defined, and few biopsies were taken per patient for histology.

In *H. pylori* infection, endoscopy may show normal gastric mucosa or reveal erythema, erosions, ulcers and, especially in children, antral nodularity.[4,15] It is our experience that when *H. pylori* gastritis is associated with duodenal ulcer in children, a striking diffuse nodularity of the antrum always is present; when *H. pylori* causes gastritis alone, this nodularity is seen in only about 50–60% of cases.[4] We have not seen this nodularity in cases of true non-*H. pylori* duodenal ulcer disease, nor in any of the some 5000 upper gastrointestinal endoscopies at which neither ulcer disease nor *H. pylori* were present over the last 14 years; in our experience, about 20% of duodenal ulcer disease in children is non-*H. pylori*-associated.[13] Nodularity is sometimes not visible on first examination of the antrum, but once biopsies have been taken, oozing blood acts as a vital stain, making visible a confluent carpet of nodules (Figure 1); the term recently coined for this is 'haematochromoendoscopy'. Thickened mucosal folds may occasionally occur in the body and antrum.[16,17] We have found that duodenal ulcers in children are often difficult to visualize at endoscopy without the use of intravenous glucagon just prior to examination of the duodenal bulb.

The absence of endoscopic abnormalities in some 50% of children with *H. pylori* infection[4], and the patchy nature of the infection and of gastric mucosa-associated lymphoid tumour (MALT) lymphomas, emphasizes the need to take biopsies from the gastric antrum, body and cardia as an integral part of diagnostic endoscopy.[12,18–20] Consensus guidelines for an approach to the diagnosis and treatment of *H. pylori* are given in detail elsewhere[21] and summarized below.

Helicobacter-negative or 'idiopathic' ulcer disease

H. pylori-negative duodenal ulcer is an important entity in children, presenting in about 15–20% of children with duodenal ulcers who have not taken NSAIDs and have

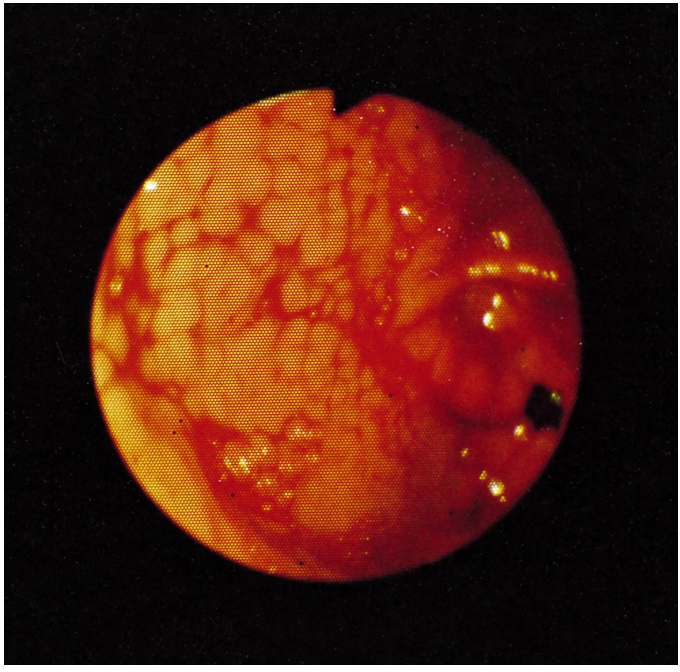

Figure 1. Endoscopic view showing the gastric antrum in a 12-year-old with *H. pylori* infection, with the pylorus in the distance. Once biopsies have been taken, oozing blood acts as a vital stain, making visible a confluent carpet of nodules ('haematochromoendoscopy'). This is a typical appearance, but it is not diagnostic of current *H. pylori* infection since the nodules may remain for months or years after the successful eradication of *H. pylori*. Nodules are not present in the corpus or fundus in *H. pylori* infection.

no serological or histological evidence of *H. pylori* infection.[13] The disorder has features different from those of *H. pylori*-associated ulcer disease: whereas children with *H. pylori*-associated duodenal ulcers have a nodular antrum and impressive histological gastritis, those who are *H. pylori* negative by histology and serology have no nodularity and a virtual absence of histological gastritis.

While genetic and psychological factors probably play a role[22], the disorder is currently regarded as 'idiopathic', but more data in this area are required. Of interest is that, in the authors' small series, all of the children with *H. pylori*-negative duodenal ulcers were Caucasian. It is possible that acid hypersecretion may be one factor in some children with *Helicobacter*-positive or negative ulcer disease[23], but there is a considerable overlap in acid secretion between children with ulcers and those without.[24] It has been our experience that a higher proportion of ulcers in children presenting with bleeding are *H. pylori* negative.

Hypersecretory states

Zollinger–Ellison syndrome and antral G-cell hyperplasia of hyperfunction are very rare in children.[25,26] In addition to the typical pancreatic gastrinomas, Zollinger–Ellison syndrome has been reported in children with solitary extrapancreatic gastrinomas in the stomach, liver and kidney.[25,27,28] Compared with adult disease, malignant gastrinomas in children are slow growing, and in one series, long-term outcome was

improved in those children who underwent total gastrectomy when all the gastrin-producing tumour could not be excised.[25,28]

Antral G-cell hyperplasia or pseudo-Zollinger–Ellison syndrome is characterized by hyperchlorhydia, peptic ulceration and an exaggerated post-prandial gastrin response, but no response to secretin stimulation.[26] It has been documented in infants and children, and may respond to surgical antrectomy[26,29]; one infant with severe peptic disease responded to omeprazole therapy.[30]

Systemic mastocytosis, a disease in which mast cells accumulate in the skin, bone marrow, liver, spleen and gastrointestinal tract, is associated with acid hypersecretion. Eighty per cent of adult patients had gastrointestinal symptoms such as abdominal pain and diarrhoea; dyspeptic symptoms often were associated with duodenal erosion or ulcers.[31]

Other conditions associated with acid hypersecretion include short bowel syndrome[32,33], hyperparathyroidism[34,35] and cystic fibrosis. Gastric acid hypersecretion is a transient phenomenon that can occur after massive short bowel resection (greater than two-thirds) in both infants and adults[32,33], and can result in peptic ulceration. Hypergastrinaemia often is present and may be caused by a reduced level of intestinal gastrin inhibitory factor[32]; gastrin levels may remain elevated long after basal acid secretion has returned to normal.[33]

In cystic fibrosis (CF), post mortem studies suggest a high prevalence of peptic ulcer disease, but this probably reflects terminal stress ulceration.[36] The incidence of peptic ulcer disease in living children with CF is unknown; although it is described in both black and white children with CF, an increased incidence has been reported in blacks.[37,38] This may be the result of genetic differences between CF in different ethnic groups.[37] Increased basal and pentagastrin-stimulated gastric acid secretion was noted in 75% of children with CF compared with age-matched controls.[39] In addition, poor buffering of acid in the duodenum may be a contributing factor. In our experience, peptic disease of the stomach and duodenum is uncommon in CF. This may be because many children with CF receive antibiotics often, which may remove *H. pylori* as a factor, and many receive acid-suppressing agents on an ongoing basis. In contrast, peptic disease of the oesophagus is common in CF.[40]

Chronic varioliform gastritis

Also known as chronic erosive gastritis, this is an uncommon disorder of unknown aetiology[41] that has been reported in a few children.[41–44] Most striking endoscopically are the innumerable prominent nodules in the fundus and proximal body of stomach; in children, the antrum is less often involved. Typically, the gastric rugae are irregularly thickened, with nodules located on the crests of the folds. The nodules sometimes have an umbilicated central crater or erosion. We have observed variable degrees of collagen deposition with active inflammation and gland atrophy in adolescents.[45]

SECONDARY PEPTIC ULCER DISEASE

This usually occurs in association with an identifiable ulcerogenic circumstance or agent (other than *H. pylori*, that is). In contrast to primary peptic ulcer disease, ulcers are more often acute and are more prevalent in the stomach than in the duodenum. Many of the conditions in this category have an erosive or haemorrhagic gastropathy;

the latter term refers to the presence of subepithelial haemorrhage, and in the disorders described, is often accompanied by mucosal breaks, i.e. erosions or ulcers.

Crohn's disease

Gastroduodenal involvement is relatively common in paediatric Crohn's disease.[46] Such symptoms as may occur are similar to those of acid-peptic disease and of delayed gastric emptying, haematemesis and melena occurring less frequently.[47–50] Endoscopic and/or histological evidence of Crohn's disease of the stomach may occur in the absence of upper gastrointestinal symptoms and sometimes precede the occurrence of diagnostic features in the ileum and colon. Not infrequently, gastroscopic or histological findings will result in a change of diagnosis from ulcerative colitis to Crohn's disease.

In our own experience, about one-third of patients with Crohn's disease who underwent upper gastrointestinal tract endoscopy had histological evidence of gastritis[46]; only one-third of these had endoscopic features of a loss of vascular pattern, mucosal swelling, aphthous ulcers or luminal narrowing. Although most gastroduodenal ulceration in Crohn's disease is shallow, we have also seen deep ulcers in the duodenum, which can mimic peptic ulcer disease. For both the endoscopic and histological findings, the antrum is the most common repository of disease, but granulomas are also present in the corpus and cardia.

'Stress' ulceration

This usually occurs within 24 hours of the onset of critical illness in which physiological stress is present, for example shock, hypoxaemia, acidosis, sepsis, burns, head injury, encephalopathy, major surgery and multiple organ system failure.[51–54]

Stress erosions are typically asymptomatic and multiple. When they do present, they do so with overt upper gastrointestinal haemorrhage, perforation being uncommon. Early lesions predominate in the fundus and proximal body, later spreading to the antrum to produce a diffuse erosive and haemorrhagic appearance. Antral involvement alone is uncommon.

Neonatal ulcers

Gastric mucosal disorders are seldom identified in the newborn, even in sick preterm infants. This is perhaps in part because endoscopy is seldom indicated, or because of a greater reluctance to perform endoscopy in babies. Nevertheless, a high prevalence of haemorrhagic gastropathy has been reported in sick neonates in an intensive care unit who had no upper gastrointestinal symptoms or signs, undergoing endoscopy as part of a research protocol.[55] Thus, for the most part, neonatal gastropathies are simply stress lesions in this age group, but with a greater predilection to haemorrhage and perforation.[56] However, haemorrhagic gastropathy has also been reported in otherwise healthy full-term infants[57], presenting with severe upper gastrointestinal tract haemorrhage, and in one case as antenatal haemorrhage.[58]

Traumatic gastropathy

Also known as prolapse gastropathy[59,60], this is caused by forceful retching or vomiting that produces typical subepithelial haemorrhages in the fundus and proximal body of

the stomach. Mallory–Weiss tears (acute erosions) in the gastro-oesophageal junction zone may also occur. Although both prolapse gastropathy and tears tend to resolve quickly, they can result in significant blood loss. By a similar mechanism of trauma, linear erosions may occur in the herniated gastric mucosa of patients with large hiatal hernias, resulting in the anaemia of chronic blood loss.[61] Suction through nasogastric tubes, the ingestion of foreign bodies, and endoscopic procedures such as diathermy[62,63] are common causes of subepithelial haemorrhage and focal erosion. The metal in ingested foreign bodies may occasionally cause gastritis.[62]

Aspirin and other NSAIDs

Although even one dose of aspirin may cause petechial haemorrhages in the stomach within a few hours and erosions within 24 hours[64], early lesions usually are of little clinical significance and are not predictive of clinically significant ulcer formation.[65] Nevertheless, in severe erosive gastritis caused by NSAIDs, ulcers will bleed and/or perforate. Lesions resulting from NSAIDs are more commonly gastric than duodenal, occurring more typically in the gastric antrum than in the body.

In children, ulceration from NSAID ingestion is not nearly as prevalent as it is in adults, at least in part because the over-the-counter use of these drugs is not as common in children. When it does occur in children, haemorrhagic antral gastropathy and ulceration of the incisura (Figure 2) are the typical NSAID lesions. Occasionally, more extensive gastric involvement occurs, as does duodenal ulceration. Bleeding from

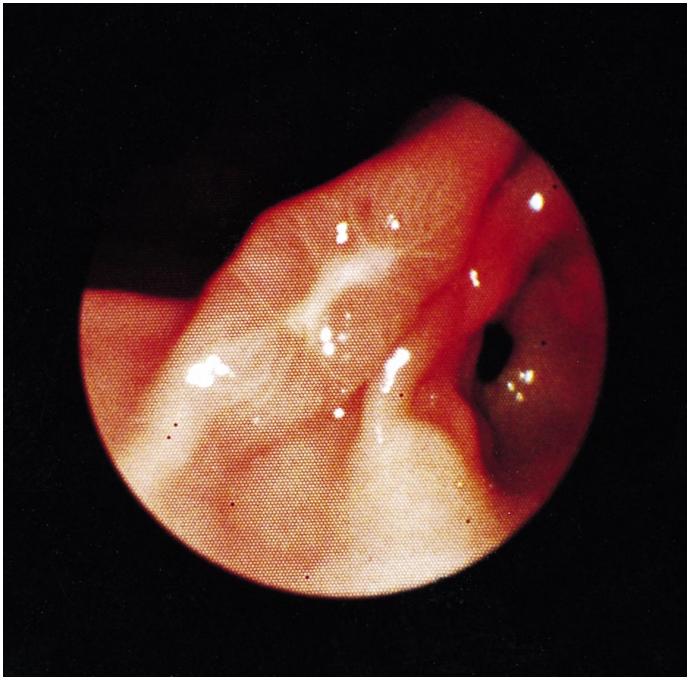

Figure 2. Endoscopic view showing an ulcer on the gastric incisura. This 4-year-old girl had taken two doses of aspirin for a febrile illness and presented with haematemesis. The incisura is a typical location for aspirin-induced ulceration in children.

such lesions following NSAID administration in children has been well documented.[66–70] In one study, 75% of children with juvenile rheumatoid arthritis who had taken one or more NSAIDs for over 2 months had endoscopic evidence of gastropathy, antral erosions or ulcers[68]; of these, 64% were suffering anaemia and abdominal pain.

There are no data in children on whether *H. pylori* eradication improves the rate of healing of peptic ulcers.

Other drugs

While many drugs may cause endoscopy-negative dyspepsia, erosive or haemorrhagic gastropathies have been described with valproic acid, chemotherapeutic agents, alcohol, potassium chloride and, very occasionally, high-dose corticosteroids.[71–79]

Allergic gastritis and eosinophilic gastritis

Allergic gastroenteritis and eosinophilic gastroenteritis are disorders that have some features in common but that manifest differently in clinical terms.[2] In both, the gastritis is part of a more generalized gastrointestinal involvement. Endoscopy may show normal mucosa, or erythema and a swollen mucosa, the findings usually being more marked in eosinophilic gastritis. Erosions have been described in children[80–83] and a refractory giant gastric ulcer in a young adult.[84] An eosinophilic gastritis has also been described as a manifestation of collagen vascular disease.[85]

Cytomegalovirus gastritis

On those rare occasions when cytomegalovirus (CMV) infection occurs in immune-competent children, it manifests as Ménétrier's disease. It is so rare in apparently immune-competent adults[86] that its finding suggests an occult malignancy or early immune deficiency.[87] Conversely, CMV infection is so common in immune-suppressed patients (such as those with AIDS or who have undergone a solid organ or bone marrow transplant) that it is in some cases difficult to know whether it is a pathogen or a commensal. However, if the highly distinctive pattern of injury is present, it is more likely that CMV is the cause.[88] The infection tends to occur in the gastric fundus and body, and may cause wall thickening, ulceration, haemorrhage and perforation.[89,90]

Graft-versus-host disease

Endoscopy is not routinely required for the diagnosis of graft-versus-host (GVHD), but when performed for the investigation of abdominal pain or bleeding, or to exclude opportunistic infection, the findings range from normal or subtle changes, even when most or all of the epithelium has been lost, to patchy erythema with erosions, to extensive mucosal sloughing, ulceration, fibrosis and perforation. More recently, the stomach has been shown to be an important area for the histological diagnosis of gastrointestinal GVHD even when diarrhoea is the main symptom and the small bowel is more damaged.[91,92] Chronic GVHD rarely involves the stomach.

Uraemic gastropathy

In acute renal failure, gastropathy is caused by acute physiological stress, and perhaps high-dose steroids, rather than renal failure itself. In adults with chronic renal failure

(CRF) on haemodialysis, gastroduodenal lesions occur in up to 67% of patients, the predominant lesion being antral gastropathy in up to 50%. The presence and severity of gastroduodenal disease are not consistently related to the degree of hypergastrinaemia or to that of CRF.[93] Vascular ectasia in the stomach is an important cause of bleeding in CRF.[94]

Henoch–Schönlein gastritis

Endoscopy is seldom required for diagnosis of this condition, but when the diagnosis is uncertain, endoscopy may be helpful, showing a haemorrhagic and erosive picture typical of this disorder.[95,96] Although gastric mucosal biopsies are usually too superficial to show typical histological changes, they may show a leukoclastic vasculitis similar to that seen in the skin.[95]

Corrosive gastropathy

The most common ingestants affecting the stomach are acids, iron and strong alkalis, the latter predominantly involving the oesophagus but occasionally the stomach. When gastric injury does occur, the pre-pyloric area is particularly vulnerable[97,98], probably because of pylorospasm and the pooling of secretions. Endoscopic findings range from mild friability and erythema to necrosis, ulcers, exudates and haemorrhage, perforation being rare. Cicatrization is relatively rare and may take several months to become apparent.[99]

Coeliac disease

Duodenal ulceration has been reported in children with coeliac disease. In the last 14 years, we have seen one such case: a 20-month-old child who presented with anaemia, diarrhoea and poor growth. At endoscopy, she had numerous duodenal erosions; biopsies confirmed intestinal villous atrophy, and the child made an excellent recovery on a gluten-free diet. Similar findings in children with coeliac disease have been reported elsewhere, in addition to radiological evidence of post-bulbar duodenal stenosis.[100,101] Acute severe haemorrhage from gastric ulceration has been reported in an adult.[102]

Hepatic cirrhosis

The prevalence of peptic ulcer disease in cirrhotic patients may be higher than in the general population, but it does not seem to be related to the severity of the liver disease.[103] When peptic ulcer disease is present, it often is poorly responsive to H_2-blockers.[104] No difference has been noted in the prevalence of *H. pylori* between cirrhotics with and without peptic ulcers.

Bile gastropathy

Also known as alkaline gastropathy, or gastropathy caused by duodenogastric reflux, this entity is well documented in the post-operative stomach[105] and the intact stomach.[106] Typical endoscopic features include 'beefy' redness or erythema, and occasionally erosions. The main histological features are those of reactive gastropathy.[107] Fortunately, there are nowadays hardly any indications for partial gastrectomy in

children, and pyloroplasty in children[108] is seldom recognized as being attended by the above problems.

Autoimmune disease

In children and adults with connective tissue diseases, a mast cell gastritis and a combination of mast cell and eosinophilic gastritis have been described.[85,109] In a large group of children with insulin-dependent diabetes mellitus, half of the 7% who underwent upper gastrointestinal tract endoscopy had evidence of erosions and ulcers, none caused by *H. pylori*.[110]

Exercise-induced gastropathy/gastritis

This is well recognized in runners, usually presenting with blood loss anaemia with or without upper gastrointestinal tract symptoms. Erosive gastropathy has been described[111], as has non-erosive gastritis[112], the latter showing acute inflammation on biopsy.

Sickle cell disease

This condition has been associated with an increased incidence of duodenal, but not gastric, ulceration. In a recent case-controlled study, duodenal ulceration was reported in 9.8% of individuals with sickle cell anaemia who also had dyspeptic symptoms[113]; males were affected more often than females, by about 4:1. The underlying aetiology is thought to be vaso-occlusive with abnormal healing of the resulting ulcer[114], rather than being caused by acid hypersecretion, which has not been demonstrated in sickle cell disease.

Other granulomatous gastritides

These disorders are rare, the differential diagnosis including foreign body reaction, idiopathic granulomatous gastritis, sarcoidosis, Langerhans cell histiocytosis (histiocytosis X) and tuberculosis.[115–120]

Phlegmonous gastritis and emphysematous gastritis

Phlegmonous gastritis is a rare, life-threatening condition in which a rapidly progressive bacterial inflammation of the gastric wall results in necrosis and gangrene.[121]

Acute emphysematous gastritis is an often-fatal complication of phlegmonous gastritis in which gastric wall infection is caused by gas-forming bacteria.[122–125] Predisposing factors include the ingestion of caustic agents and abdominal surgery; it has also been reported in a leukaemic child[124], a child with a phytobezoar[122] and a patient who ingested large volumes of a carbonated beverage.[125] Emphysematous gastritis must be distinguished from two other entities that cause gas to be present in the gastric wall: gastric emphysema and cystic pneumatosis. These usually follow instrumentation or gastric outlet obstruction and are, of themselves, not clinically significant.

Other infections

Other infections causing gastritis, erosion and ulcers include *Helicobacter heilmanii* (previously *Gastrospirillum hominis*)[126–129], *Herpes simplex* in immunosuppressed patients[130,131], *Herpes zoster*[132,133], Influenza A[134], *Mycobacterium tuberculosis* (usually associated with tuberculosis elsewhere or with immune deficiency)[119,120], and syphilis.[135] Fungal infections of the stomach, such as *Candida albicans* infection, histoplasmosis and mucormycosis, may occur, especially in sick neonates, malnourished children and those with burns or immune deficiencies.[136–144] Acute gastric anisakiasis occurs not infrequently in Japan and in areas of high consumption of raw fish. Early endoscopy allows for diagnosis and the relief of symptoms by removal of the worm.[145,146]

Radiation gastropathy

This is rare but has been associated with massive abdominal irradiation given to patients with malignancy, causing erosions or ulcers particularly in the gastric antrum and pre-pyloric regions.[147]

DIAGNOSIS

General approaches

As in adults, the differential diagnosis of peptic ulcer disease includes oesophagitis, gastritis or gastropathy, functional dyspepsia, gallbladder or liver disease, pneumonia, pancreatitis and giardiasis. In children, while abdominal pain is relatively common, pain that is truly localized to the epigastrium is relatively uncommon and always requires investigation. However, pain may not always be easily localized by children, especially those below the age of 10 years or so. Upper gastrointestinal bleeding, whether or not accompanied by pain, also always requires investigation in children.

The accuracy of upper gastrointestinal contrast studies for the diagnosis of ulcer disease in children is poor, with poor sensitivity and a high rate of false positivity. Reports of 'duodenal spasm' or 'irritability', 'duodenitis', 'poor filling of the duodenal cap' and 'possible ulcer disease' are common in children and are not reliable predictors of the presence of ulcer disease. Even when X-rays do show ulcer(s) more definitively, their aetiology cannot be accurately determined, nor can it be determined whether or not an ulcer is present. Although antral nodularity associated with *H. pylori* disease may occasionally be seen on contrast study, such nodularity persists months or years even when *H. pylori* infection has been eradicated or is no longer present.

As in adults, the definitive diagnosis of ulcer disease is made with upper gastrointestinal endoscopy, which can confirm or exclude the presence of ulcers and effect haemostasis in cases of active bleeding. However, the performance of endoscopy in children is a highly specialized undertaking, the least problematic aspects of which are the actual passage of an appropriately sized endoscope, and the taking of biopsies or performance of endoscopic haemostasis. Many other cognitive and practical paediatric skills are important to ensure the appropriate, safe and humane performance of endoscopy in children.[148] The diagnosis of the aetiology of peptic ulcer(s) obviously has important implications for treatment, as illustrated by the different treatment approaches to *H. pylori*-associated and *Helicobacter*-negative ulcer disease. When a *Helicobacter*-negative ulcer is diagnosed, multiple biopsies of the stomach, duodenum

and oesophagus must be carefully examined for the possibility of Crohn's disease. In addition, a fasting plasma gastrin level should be obtained to exclude one of the rare G-cell disorders or Zollinger–Ellison syndrome.

Approach to suspected *Helicobacter pylori* disease

In the approach to children, a central guiding premise is that the goal most useful to pursue is that of determining the cause of presenting symptoms rather than the mere presence of the infection.

The prevalence of gastric infection with *H. pylori* is variable between countries and socio-economic groups, but even where it is common, children are considerably less susceptible to peptic ulcers and other pathological sequelae than are adults. As a result, the risk-to-benefit ratio of diagnostic studies and therapeutic regimes for *H. pylori* are likely to be different in adult and paediatric populations. Therefore, guidelines for the diagnostic approach to suspected *H. pylori* disease, and the management of paediatric *H. pylori* infection, have been developed by paediatric consensus groups.[21,149]

Given the low prevalence of this infection in North America and Western Europe, it is important to recognize that indiscriminate testing and treatment programmes in children are not currently recommended and may indeed threaten the optimal care of children. Diagnostic tests should be employed judiciously and be reserved for those children who are most likely to derive measurable benefit, for example those likely to have peptic ulcer disease. At this time, a test-and-treat strategy in children is not considered prudent, evidence-based or cost-effective. It is appropriate to limit diagnostic testing to those individuals in whom *H. pylori* is a probable cause of presenting symptoms.

The specific recommendations are as follows.

1. The goal of diagnostic intervention should be to determine the cause of presenting symptoms rather than the presence of the infection

Tests for *H. pylori* infection should be undertaken only if there is a high probability that the symptoms are the result of peptic ulcer disease. If during investigation a peptic ulcer is identified, it is reasonable at that time to test for *H. pylori*.

2. Testing for Helicobacter pylori *is appropriate only when treatment is planned if the test result is positive*

Even though health benefits from eradication cannot be assured in any given individual, it is recommended that an infection known to be currently present be treated. The controversial nature of this issue should be discussed, and treatment be offered with parental informed consent.

3. Antibody tests utilizing whole blood, serum or saliva are not recommended

Because of the low prevalence of *H. pylori*-related diseases in children, the low specificity and sensitivity of antibody tests for whole blood, serum and saliva reduce their value for establishing the presence of current *H. pylori* infection. In addition, antibody levels may remain elevated for years after the eradication or resolution of infection. Therefore, a positive test does not necessarily mean that infection is present at the time of testing.

4. Upper gastrointestinal endoscopy with multiple biopsies is the optimal approach to the investigation of the patient with chronic upper abdominal symptoms or suspected peptic ulcer disease

The differential diagnosis of abdominal pain in a child may include oesophagitis due to reflux or other causes, gastritis or gastropathy from a variety of causes, and peptic ulcer disease, either *H. pylori* associated or not.[2] Endoscopy with biopsies provides the most accurate approach for the definitive diagnosis of upper gastrointestinal mucosal diseases. Endoscopy is the only acceptable diagnostic test in children with upper gastrointestinal bleeding, recurrent vomiting or persistent undiagnosed abdominal pain.

5. ^{13}C (or ^{14}C) urea breath tests are not an approriate alternative to upper gastrointestinal tract endoscopy for the primary diagnosis of Helicobacter pylori *infection in children. Use of the urea breath test often is more appropriate than repeat endoscopy to confirm the successful eradication of* Helicobacter pylori

The sensitivity and specificity of labelled urea breath tests, which are non-invasive, are close to those of endoscopic biopsies for the presence of *H. pylori*. Breath testing is also less expensive than endoscopy. However, in most clinical scenarios in paediatrics, the diagnosis of the cause of the patient's symptoms is a more useful goal than simply determining whether *H. pylori* is present. For example, a positive breath test does not confirm or exclude the presence of an ulcer, other gastritides, gastropathies or oesophageal disease. Similarly, this indirect testing cannot determine gastroduodenal pathology and rule out alternative diagnoses in the event of a negative result.

6. Helicobacter pylori *cultures are not routinely required for diagnosis but may be warranted after failure of the initial treatment or as part of a surveillance programme for antibiotic resistance*

7. Children previously suspected on barium study to have a peptic ulcer should be examined by endoscopy if their symptoms recur

Barium studies are not reliable for evaluating suspected lesions of the upper gastrointestinal tract in the paediatric population. In children whose peptic ulcer was previously diagnosed by an upper gastrointestinal series, endoscopy with biopsies should be performed to confirm the presence of an ulcer and to diagnose *H. pylori* infection. An alternative would be to consider doing a ^{13}C-urea breath test if the barium study is considered truly diagnostic; this, however, would be very unusual.

8. Screening for Helicobacter pylori *infection in asymptomatic individuals is not warranted*

Screening for *H. pylori* infection is costly and currently has no established public health benefits in asymptomatic children.

9. Family members of previously infected patients who have benefited from Helicobacter pylori *eradication can be considered for testing and treatment*

It is rational, although totally unproven, that testing and treating family members for *H. pylori* infection may be justified by a possible reduced risk of reinfection in a child who has benefited from eradication. However, the projected benefits should be weighed against the risks and costs of this strategy in individual families.

TREATMENT

General

The treatment of specific disorders in children is similar to that in adults. The differences reflect the issues specific to children, such as the management of fluid and electrolyte balance in resuscitation, the dosage, palatability and appropriate forms (tablets, capsules or liquid) of medication, and the potential adverse effects of medication. Acid-reducing operations such as vagotomy and antrectomy have a high morbidity and failure rate in children.[23] With the highly effective acid-suppressive medications available in recent years, such operations have become virtually obsolete in children. Current indications for surgery in peptic disease are perforation of the stomach or duodenum, active bleeding that cannot be controlled by medical management or endoscopic haemostasis, gastric outlet or duodenal obstruction caused by scarring, or a failure of medical treatment in hypersecretory syndromes.

Helicobacter pylori

The major issue of debate currently pertains to the treatment of *H. pylori*-related diseases – whom to treat, and how to treat. The following are guidelines produced by paediatric consensus.[21,149]

Whom to treat

The empirical treatment of gastrointestinal symptoms, with eradication of *H. pylori*, is not recommended in either children or adults. Instead, treatment should be provided only after *H. pylori* infection has been diagnosed by an appropriate test for an appropriate indication. The indications for treatment are peptic ulcer disease proven to be current and associated with *H. pylori*, and MALT lymphoma. The latter has been reported in fewer than five children. Abdominal pain not caused by peptic ulcer disease is not an indication for treatment. However, if the presence of *H. pylori* is established to be current, whatever the indication for the test, treatment should be offered to the child after discussion of the pros and cons with the family.

What to use

For true non-*H. pylori* duodenal ulcer disease, acid suppression alone is the preferred effective treatment. More recently, it has been our practice to use a proton pump inhibitor and follow the response of symptoms, also following the ulcer to endoscopic healing.

With regard to *H. pylori*-associated peptic ulcer disease, the multidrug regimens that are effective in eradicating *H. pylori* in at least 80% of adults have not yet been tested with the same rigor in children. Most paediatric treatment trials have instead been conducted in single centres with a limited sample size and have been uncontrolled. Although these provide a preliminary basis for predicting that regimens effective in adults will provide similar efficacy in children, there are important unanswered questions about the relative risk of adverse events and how, or whether, doses should be modified by chronological age, body weight or surface area. Because of a relative absence of data, it is difficult to make specific recommendations for the treatment of *H. pylori* in children that are rigorously evidence-based. Data from some studies in children and some in adults are extrapolated with the understanding that modification

may be necessary once appropriate trials are conducted in the paediatric age group. It is important to recognize that the relative efficacy and relative risk of adverse events may well be different in children from in adults.

The currently recommended regimens generally include a proton pump inhibitor in combination with antibiotics. In adults, there do not currently appear to be major differences between the efficacy of omeprazole, lansoprazole and pantoprazole for the healing of peptic ulcers. However, at present, there is little published paediatric experience with lansoprazole, and even less with pantoprazole, but dosing regimens, efficacy and safety have been established for omeprazole use in children with erosive oesophagitis.[150] Although the regimens have not been well tested in children, one currently in favour includes omeprazole 1–2 mg/kg per day in day divided doses, plus clarithromycin with either metronidazole or amoxycillin in therapeutic doses, for 2 weeks.[5,151] Although 1-week therapy has been used[152], its efficacy in children requires further validation.

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