

# Gastric metaplasia and duodenal ulcer disease in children infected by *Helicobacter pylori*

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## Abstract

**Background**—*Helicobacter pylori* infection of the gastric mucosa is vital in the pathogenesis of duodenal ulcer disease. *H pylori* will only colonise gastric epithelium and its association with duodenal disease is therefore not easily explained. **Aims**—To determine if gastric metaplasia in the duodenum increases the risk of duodenal ulcer disease in children infected with *H pylori*.

**Patients**—All children undergoing upper endoscopy over a 20 month period in a children's hospital in Ireland.

**Methods**—Two biopsy specimens were obtained from the antral mucosa and two from the first part of the duodenum. One antral biopsy specimen was used in a rapid urease test (Clo Test). Biopsy sections were stained with haematoxylin and eosin and also with cresyl violet for identification of *H pylori*. Periodic acid Schiff (PAS) stain was performed to identify areas of gastric metaplasia.

**Results**—Gastric and duodenal biopsy specimens were obtained from 148 patients (M:F 1.2:1). Twenty five children (17%) had *H pylori* positive gastritis. Thirty four children (23%) had gastric metaplasia in the duodenum. Nine per cent of children under the age of 8 years had gastric metaplasia compared with 38% in those 12 years of age or over ( $p < 0.005$ ). Seven children had duodenal ulcer disease. Gastric metaplasia was present in six of seven (86%) children with duodenal ulcer disease compared with 28 of 141 (20%) without ulceration ( $p < 0.001$ ). While both *H pylori* and gastric metaplasia were each significant risk factors for duodenal ulcer disease, the combined presence of both factors was associated with a pronounced increase in duodenal ulcer disease. Duodenal ulcer disease occurred in over 50% of children with both *H pylori* infection and gastric metaplasia. In contrast duodenal disease did not occur in children (0 of 100) when both were absent.

**Conclusion**—The presence of gastric metaplasia in the duodenum is the major risk factor for duodenal ulcer disease in patients colonised by *H pylori*.

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**Keywords:** *Helicobacter pylori*, gastric metaplasia, gastritis, duodenal ulcer disease.

organism that colonises the gastric mucosa of humans. *H pylori* is the major cause of gastritis in children and adults.<sup>1-6</sup> There is a strong association between *H pylori* gastritis and duodenal ulcer disease.<sup>7,8</sup> Duodenal ulceration does not recur if *H pylori* is cured.<sup>7-9</sup> It is not known why *H pylori*, which will only colonise gastric tissue, has such a profound effect on the natural history of duodenal ulcer disease. There is speculation that *H pylori* colonises the gastric mucosa and subsequently colonises areas of gastric metaplasia in the duodenum leading to erosions and ulceration.<sup>10</sup> To date, no prospective study has shown an association between *H pylori* gastritis, gastric metaplasia of the duodenum, and duodenal ulcer disease. The hypothesis is difficult to prove in an adult population because there is a significant prevalence of chronic gastritis, gastric metaplasia in the duodenum, and duodenal ulcer disease among this age group. In contrast *H pylori* gastritis and duodenal ulceration are uncommon among children in developed countries. Children therefore represent an excellent population in which to study the relation between *H pylori* infection, gastritis, gastric metaplasia in the duodenum, and duodenal disease.

This study was carried out prospectively to discover if an association existed between *H pylori* colonisation of the gastric mucosa, the occurrence of gastric metaplasia in the duodenum, and duodenal ulcer disease.

## Methods

### Patients

One hundred and ninety three children underwent upper endoscopic examination over a 20 month period. Table I outlines the indications for endoscopy. During each examination, two biopsy specimens were obtained from the first part of the duodenum. A further two samples were taken from the antral mucosa, one of which was used for a rapid urease test (Clo, Delta West).

Forty five children were excluded from further study either because the biopsy specimens were unsuitable ( $n=11$ ) or because a full complement of specimens were not obtained ( $n=34$ ). The ages of those children excluded ranged from 0.25 to 15.5 years (mean (SD) age 5.8 (5.1)). The remaining 148 patients ranging in age from 0.3 to 17.7 (mean (SD) age 8.8 (4.6)) were entered in the study. The male to female ratio was 1.2:1. One patient had a history of alcohol consumption whereas no patient admitted to smoking. None of the children were taking non-steroidal anti-inflammatory drugs.

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*Helicobacter pylori* is a Gram negative spiral

TABLE I Major indication for endoscopy

Small bowel biopsy	42
Abdominal pain	92
Vomiting/haematemesis	53
Crohn's disease	6
Total	193

The study was approved by the ethics committee at Our Lady's Hospital for Sick Children, Dublin. Full informed parental consent was obtained.

#### Endoscopy

Oesophagogastroduodenoscopy was performed under general anaesthetic in all children. An Olympus GIF X P10 or Q 200 endoscope (Keymed, Ireland) was used depending on the size of the child.

#### Histological examination of biopsy specimens

Gastric and duodenal biopsy specimens were fixed in 10% neutral formalin, embedded in paraffin wax, and cut at 5 microns. The sections were stained with haematoxylin and eosin for light microscopy.

#### Gastric specimens

Gastritis was defined according to established histological criteria using the Sydney classification.<sup>11</sup> Three patterns of gastritis were looked for: chronic, acute, and special forms (for example, granulomas, eosinophilic infiltration). In chronic gastritis the predominant cell infiltrate consists of lymphocytes and plasma cells. These infiltrates were graded mild, moderate or severe. The morphology of chronic gastritis was further described using the following graded variables: (a) activity: the presence of neutrophil granulocytes in either or both the lamina propria and intraepithelial sites; (b) atrophy: the loss of gastric glands; (c) the presence of *H pylori*; (d) the presence of intestinal metaplasia.

Acute gastritis was defined as a predominantly neutrophil infiltrate in either or both the lamina propria and intraepithelial sites.

Formalin fixed specimens were stained with cresyl violet to identify *H pylori*. The organisms were easily identified because of their spiral or curved shape and their unique location beneath and within the mucous layer on the surface of the gastric mucosa. *H pylori* colonisation was graded according to the numbers of organisms seen as mild, when occasional micro-organisms were present, moderate when there was a patchy distribution of bacteria, and severe if a layer of bacteria was present on the surface of the section.<sup>11</sup>

#### Duodenal specimens

Chronic non-specific duodenitis was defined according to Hasan *et al.*<sup>12</sup> Duodenitis was characterised by the presence of neutrophils in the lamina propria, crypts or surface epithelium in addition to an increase in the number of mononuclear cells. Duodenitis was graded from mild to severe depending on the number of neutrophils present.

All duodenal biopsy specimens were stained with periodic acid Schiff reagent (PAS) stain to assist the identification of areas of gastric metaplasia. Gastric epithelium was defined as the presence of adjacent surface epithelial cells con-

taining PAS positive neutral mucin. The extent of gastric metaplasia was graded on a scale from 1 to 3. When eight or less consecutive cells of gastric metaplasia were present in the duodenal epithelium, this was considered to be grade 1. Grade 2 gastric metaplasia was present if islands of gastric metaplasia were scattered between areas of duodenal epithelium. In grade 3, all the biopsy tissue showed changes of gastric metaplasia.

Cresyl violet staining was then used for *H pylori* identification as with gastric biopsy sections.

All of the specimens were examined by a pathologist who was unaware of the clinical history, endoscopic findings or the urease test result.

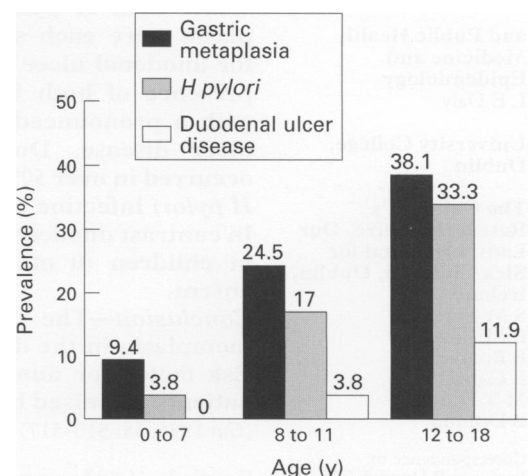
#### Statistics

Results were expressed as mean (SD) or as relative risks. Differences between groups were compared using the  $\chi^2$  test. Where there were small numbers in some categories, the two tailed Fisher's exact test was used. Confidence intervals for relative risk were based on a Taylor series expansion.<sup>13</sup>

## Results

### GASTRITIS

*H pylori* colonisation of the gastric mucosa was confirmed by both the rapid urease test (Clo test) and cresyl violet stain in 25 children. All had histological evidence of chronic gastritis. Twenty four per cent had mild chronic gastritis, 36% moderate chronic gastritis, and 40% active chronic gastritis. Gastric atrophy and intestinal metaplasia were not identified in specimens from these children. *H pylori* infection was graded mild to severe. Fifty six per cent (n=14) of children had mild *H pylori* infection with 40% (n=10) having moderate and 4% (n=1) severe *H pylori* infection respectively. The urease test and cresyl violet stain were both negative on specimens from each of the other 123 patients.



Relation between patients' ages, *H pylori*, gastric metaplasia, and duodenal disease. The prevalence of *H pylori* ( $\chi^2=14.58$ ,  $df=2$ ,  $p<0.01$ ), gastric metaplasia ( $\chi^2=10.99$ ,  $df=2$ ,  $p<0.005$ ), and duodenal ulcer disease ( $\chi^2=7.54$ ,  $df=2$ ,  $p<0.05$ ), all increase with age.

TABLE II Patients with duodenal ulcer disease

Sex	Age	Endoscopy findings	Histology	H pylori on gastric mucosa	Gastric metaplasia
M	13.1	Duodenal ulcer	Normal	Moderate	Grade 2
M	14.2	Duodenal ulcer	Severe duodenitis	Moderate	Grade 3
M	14	Duodenal ulcer	Severe duodenitis	Mild	Absent
M	13.1	Duodenal ulcer	Acute duodenitis	Mild	Grade 3
F	11.6	Duodenal ulcer	Acute duodenitis	Moderate	Grade 2
F	11.7	Duodenal ulcer	Severe duodenitis	Mild	Grade 2
F	12	Duodenal ulcer	Normal	Moderate	Grade 2

The M:F ratio of children with *H pylori* gastritis was 1.8:1. Ages ranged from 3.8 to 16 years (mean (SD) 11.7 (2.87)). The prevalence of *H pylori* infection increased with age (Figure). Four per cent (two of 53) of children between 0 and 7 years of age had *H pylori*. This contrasted with prevalence of 17% (nine of 53) and 33% (14 of 42) in the 8–11 year old and 12–18 year old age groups respectively ( $\chi^2=14.58$ ,  $df=2$ ,  $p<0.001$ ).

#### GASTRIC METAPLASIA

Gastric metaplasia in the duodenum was present in 34 of 148 (23%) patients. Children with gastric metaplasia ranged from 1 to 17 years of age (mean (SD) age 11.1 (3.39)). Twenty nine of these 34 children (85%) had grade 2 gastric metaplasia. In contrast only two children (6%) had grade 1 gastric metaplasia and three (9%) had grade 3 gastric metaplasia.

The prevalence of gastric metaplasia increased with age (Figure). Nine per cent (five of 53) of children under 8 years had evidence of gastric metaplasia. In contrast, 25% (13 of 53) of patients between 8 and 11 years and 38% (16 of 42) of patients who were 12 years or more, were found to have metaplasia ( $\chi^2=10.99$ ,  $df=2$ ,  $p<0.005$ ). Gastric metaplasia occurred equally in both sexes (M:F ratio 1.2:1).

#### Gastric metaplasia and gastritis

Gastric metaplasia was associated with *H pylori* colonisation of the gastric mucosa. Eleven of 34 (32%) patients with gastric metaplasia had *H pylori* present on the gastric mucosa. Fifty five per cent had mild *H pylori* colonisation and 45% moderate. In contrast, 14 of 114 (12%) patients who did not have gastric metaplasia were colonised with *H pylori* ( $\chi^2=7.52$   $df=1$ ,  $p<0.01$ ).

TABLE III The association between gastric metaplasia, gastritis, H pylori infection, and duodenal ulcer disease

	Number	Duodenal ulcer disease		p Value
		Prevalence (%)	Relative risk (95% CI)	
<i>H pylori</i>				
Present	25	7 (28)		
Absent	123	1 (0)	*	<0.0001
Gastric metaplasia				
Present	34	6 (17.6)	20.1 (2.5 to 161.4)	
Absent	114	1 (0.9)	1.0	<0.001
<i>H pylori</i> present				
Gastric metaplasia present	11	6 (54.5)	7.6 (1.1 to 54.4)	
Gastric metaplasia absent	14	1 (7.1)	1.0	<0.01
<i>H pylori</i> absent				
Gastric metaplasia present	23	0 (0)		
Gastric metaplasia absent	100	0 (0)		

\*Undefined because of zero cases.

#### DUODENAL ULCER DISEASE

Duodenal disease was present in only nine patients. Seven of these children had duodenal ulceration, five of whom had acute or severe chronic duodenitis (Table II). Two children who had a normal endoscopic appearance of the duodenum, were found to have moderate duodenitis on histological examination. Patients with duodenal ulcer disease ranged in age from 11.6 to 14.2 years (mean (SD) age 12.8 (1.07)). The prevalence of ulcer disease increased with age (Figure). Duodenal ulcer disease did not occur in children under 8 years of age. Four per cent (two of 53) of children between 8 and 11 years had duodenal ulceration compared with 12% (five of 42) of children who were 12 years or more ( $\chi^2=7.54$ ,  $df=2$ ,  $p<0.05$ ). Duodenal biopsy specimens obtained from the remaining 139 children showed no evidence of inflammation.

#### H pylori gastric metaplasia, and duodenal ulcer disease

*H pylori* colonisation of the gastric mucosa and gastric metaplasia in the duodenum were major risk factors for duodenal ulcer disease. Seven of 25 children with *H pylori* colonisation of the gastric mucosa had duodenal ulcer disease. In contrast none of the 123 children who were not colonised with *H pylori* had duodenal ulceration ( $p<0.001$ ) (Table III). The risk of duodenal ulcer disease in children colonised by *H pylori* was greatly decreased if gastric metaplasia was absent. Duodenal ulcer disease occurred in only one of 14 (7.1%) children colonised by *H pylori* when gastric metaplasia was not identified (Table III).

Thirty four children had gastric metaplasia and of these six had duodenal ulcer disease compared with only one of 114 children who did not have gastric metaplasia ( $p<0.001$ ). The relative risk of duodenal ulcer disease among children with gastric metaplasia was 20.1 compared with those without gastric metaplasia (Table III). However, duodenal ulcer disease did not occur in children with gastric metaplasia if *H pylori* was not present on the gastric mucosa.

If both *H pylori* colonisation of the antral mucosa and gastric metaplasia in the duodenum were present in a child, the prevalence of duodenal ulcer disease was over 50% (Table III). In contrast when both *H pylori* and gastric metaplasia were absent ( $n=100$ ) duodenal ulcer disease never occurred.

#### Discussion

This is, to our knowledge, the first prospectively carried out study among adults or children examining the relation between *H pylori* gastritis, gastric metaplasia in the duodenum, and duodenal ulcer disease. *H pylori* colonisation of the gastric mucosa plays a critical part in the pathogenesis of duodenal ulcer disease. Eradication of *H pylori* results in longterm healing of duodenal ulcers.<sup>7-9 14 15</sup> Duodenal ulceration recurs if there is persistent or recurrent infection of the gastric mucosa by



*H pylori*.<sup>7-9 14 15</sup> It is not known why a bacterial infection of the antral mucosa is critical in the pathogenesis of ulcers that occur in the duodenum. It has been hypothesised that *H pylori* colonises areas of gastric metaplasia in the duodenum with the subsequent development of duodenal inflammation and possibly ulceration.<sup>10</sup> It is difficult for studies of adult patients to establish a relation between *H pylori* infection, gastric metaplasia, and duodenal ulcer disease because of the comparatively high prevalence of *H pylori* colonisation and duodenal ulcer disease among adults. In contrast children present an ideal group in whom to examine this association. In developed countries both *H pylori* colonisation of the gastric mucosa and duodenal ulcer disease are uncommon in children.<sup>5 6 16-20</sup>

This study shows that the presence of gastric metaplasia in the duodenum is the major risk factor for the development of duodenal ulcer disease in children colonised by *H pylori*. *H pylori* infection of the antral mucosa and gastric metaplasia in the duodenum were each risk factors for duodenal ulceration and inflammation. The presence of *H pylori* on the antral mucosa in the absence of gastric metaplasia in the duodenum, however, was associated with duodenal disease in only one child. In contrast the presence of both *H pylori* and gastric metaplasia together resulted in a remarkable increase in the risk of duodenal disease.

When duodenal ulceration occurs in children the clinical course is identical to that seen in adult patients. Children have chronic symptoms and ulcers usually recur after stopping treatment with histamine receptor blocking agents.<sup>19-22</sup> The prevalence of duodenal ulcer disease increases progressively with age. It is extremely unusual for primary duodenal ulceration to occur under 10 years of age.<sup>19 20</sup> In this study we found that the prevalence of *H pylori* colonisation and gastric metaplasia each increased progressively with age. The previously unexplained absence of primary ulceration in very young children is probably because of the very low prevalence of gastric metaplasia and *H pylori* in this age group.

There is a high prevalence of *H pylori* infection among children in underdeveloped countries.<sup>23-25</sup> Unfortunately the prevalence of duodenal ulcer disease among these children is unknown. In Canada, Hassall and Dimmick have shown that both *H pylori* infection and duodenal ulcer disease are much more common among North American Indian children than among white children.<sup>26</sup> Furthermore duodenal ulcers generally occurred in native Indian children when they were over 9 years old. The incidence of duodenal ulceration among adolescents might therefore approach adult levels if *H pylori* infection was more prevalent in young children as gastric metaplasia seems to be comparatively common in teenagers.

Gastric metaplasia has not previously been examined prospectively in children. Two specimens were obtained from the first part of the duodenum in an effort to identify most children with gastric metaplasia. Wyatt *et al* have

shown that a single duodenal biopsy specimen identifies metaplasia in only 63% of patients in whom gastric metaplasia is identified if multiple specimens are taken, while two duodenal specimens are successful in identifying metaplasia in 94% of such patients.<sup>27</sup> We found gastric metaplasia in a high proportion of teenagers. A previous retrospective study of biopsy specimens obtained from Canadian children found gastric metaplasia in 42% of *H pylori* colonised children.<sup>28</sup> The low incidence of metaplasia in the under 10 year old age group suggests that gastric metaplasia is not congenital in origin. One of the factors promoting the development of metaplasia with increasing age seems to be the presence of gastritis. Wyatt *et al* found a similar association between gastritis and the prevalence of gastric metaplasia in adults.<sup>27 29</sup> Other factors, however, must be important in promoting the development of gastric metaplasia as gastric metaplasia in the duodenum did occur in the absence of *H pylori* colonisation.

In this study gastric metaplasia was identified in 89% of children with duodenal inflammation. A possible association between duodenitis and gastric metaplasia has previously been suggested in adults.<sup>30</sup> More recently Wyatt *et al* have confirmed an association between *H pylori* infection, gastric metaplasia in the duodenum, and the presence of duodenitis.<sup>27 29</sup> In their study, active duodenitis was rarely seen in the absence of gastric metaplasia. Carrick *et al* reviewed their experience of gastric metaplasia and found that 90% of patients with active duodenal ulceration or a previous history of duodenal ulcer disease had gastric metaplasia.<sup>31</sup> In contrast only 30% of the population who do not have a history of duodenal ulceration have metaplasia. It seems therefore that gastric metaplasia is an important factor in the development of active duodenitis even in the absence of frank ulceration.

In summary our findings show that the coexistence of gastric metaplasia in the duodenum and *H pylori* colonisation of the antral mucosa is critical for the development of duodenal ulcer disease in children. Further studies are required to determine the significance of *H pylori* colonisation in promoting the development of gastric metaplasia.

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