

# Management and response to treatment of *Helicobacter pylori* gastritis

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## Abstract

**Gastritis associated with *Helicobacter pylori* was present in gastric biopsies from 24/95 (25%) children and adolescents undergoing endoscopy for recurrent abdominal pain and upper gastrointestinal symptoms. *H pylori* associated gastritis occurred mainly in older children (8-16 years) and was significantly associated with low socioeconomic class and a family history of peptic ulcer disease. Antral nodularity was a common endoscopic finding in *H pylori* positive children. Eighteen children, all over 5 years of age, were treated with tripotassium dicitratobismuthate (De-Nol) for two months and ampicillin for two weeks. In 12 children follow up gastric biopsies were obtained six weeks after completion of treatment. In 9/12 (75%) children *H pylori* was eradicated, and gastritis improved.**

Colonisation of the stomach with *Helicobacter* (formerly *Campylobacter*) *pylori* is now firmly established as an important cause of chronic gastritis and peptic ulcer disease in adults.<sup>1 2</sup> Several studies have also established a role for this organism in children with abdominal pain and upper gastrointestinal symptoms.<sup>3-5</sup> We prospectively evaluated the prevalence of *H pylori* gastritis in children undergoing endoscopy for abdominal pain and upper gastrointestinal symptoms, and report here the clinical, socioeconomic, endoscopic and histopathological features, and the response to treatment. The systemic immune response to *H pylori* was also studied in these children and has been reported separately.<sup>6</sup>

## Methods

A prospective study was performed between July 1987 and July 1991 on consecutive children presenting with recurrent abdominal pain, protracted vomiting, haematemesis, and melaena. Patients with recurrent abdominal pain and protracted vomiting had symptoms of at least three months' duration. Ninety five children (51 females), age range 6 months to 16 years, median 10 years, were investigated by upper gastrointestinal endoscopy and mucosal biopsy. Endoscopy was performed using Olympus GIF P3, Olympus XP20, and Fujinon UGI PE paediatric endoscopes by two paediatric endoscopists (MJM, JML). Intravenous sedation using diazepam 0.5-1 mg/kg, maximum 25 mg, was used in 93 children; two children had endoscopy under general anaesthesia. At least two antral biopsies were taken from each child,

and in 55 an additional antral biopsy specimen was taken for gastric urease (CLO test, Delta West).

Biopsy specimens were fixed in neutral buffered formalin and stained with haematoxylin and eosin for grading of gastritis and Giemsa for detection of *H pylori*.<sup>7</sup> All specimens were examined by one histopathologist (JIW). Gastritis was graded using the Sydney classification: briefly, this grades the degree of mononuclear cell infiltration, neutrophil infiltration, atrophy, and intestinal metaplasia in gastric biopsy specimens, each on a scale of 0-3. In addition the intensity of *H pylori* colonisation is assessed also on a scale of 0-3.<sup>8</sup>

Treatment with tripotassium dicitratobismuthate (De-Nol, Brocades) and ampicillin was given to children over 5 years of age with *H pylori* associated gastritis. Children with 'lymphocytic gastritis' were excluded. Eighteen children with *H pylori* associated gastritis, aged 5-15, median 12.5 years, were treated with tripotassium dicitratobismuthate for two months, and ampicillin for the first two weeks of treatment. Tripotassium dicitratobismuthate dosage was 240 mg twice daily in those over 10 years, and 120 mg twice daily in those under 10 years. The ampicillin dose was 500 mg four times a day in those over 10, and 250 mg four times a day in those under 10 years. Follow up antral biopsies were obtained six weeks after completion of treatment in 12/18 children and were assessed for eradication of *H pylori* and severity of gastritis. For the purpose of comparing biopsy specimens taken before and after treatment the grades of mononuclear cell infiltration (0-3) and neutrophil infiltration (0-3) were added to devise a gastritis score (range 0-6).

Bismuth concentrations were measured in whole blood at completion of tripotassium dicitratobismuthate treatment by hydride generation atomic absorption spectroscopy (Rooney Laboratories).<sup>9</sup>

Informed consent was obtained from the children's parents, and the study was approved by the hospital ethics committee of Leeds East Health Authority.

Statistical analysis was performed using Fisher's exact probability test, and Wilcoxon's signed pair test.

## Results

Gastritis was present in antral biopsies from 25/95 children (26%). In 24 children (25%), age range 9 months to 15 years, median 12.5 years, chronic gastritis was associated with *H pylori*

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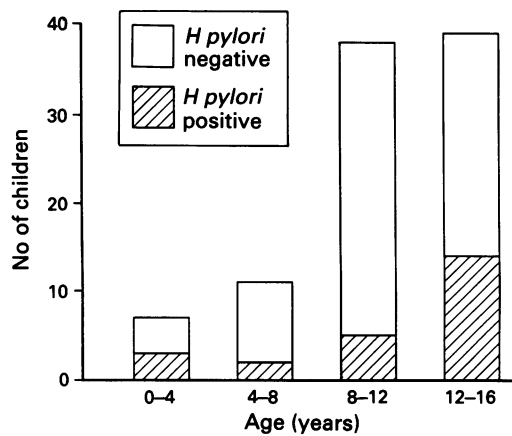


Figure 1 Age distribution of the study population.

colonisation (23 histology positive; one CLO positive, histology negative). Gastric histology was normal in the other 70 children and *H. pylori* was not detected on Giemsa staining or CLO test.

The CLO test was performed on 55 antral biopsies and was positive in 13. All 13 biopsies had gastritis on histology and 12/13 were positive for *H. pylori* on Giemsa staining. The other 42 biopsies showed normal gastric histology and all were negative for *H. pylori* on histology.

CLINICAL FEATURES

The age range of the children studied and those with *H. pylori* associated gastritis is shown in figure 1. *H. pylori* gastritis was present mainly in older children and adolescents aged 8-16 years, but was present in five young children aged 9 months, 15 months, 2 years, and two aged 5 years. The sex distribution of *H. pylori* gastritis was 10 boys and 14 girls. A family history of peptic ulcer disease in first degree relatives was present in 6/24 (25%) *H. pylori* positive children with gastritis compared with 2/70 (3%) of those who were *H. pylori* negative, with normal gastric histology ( $p < 0.003$ ).

Although several children had multiple symptoms, the major symptom leading to endoscopy was recurrent abdominal pain. This was further subdivided into epigastric pain and

central periumbilical pain. Epigastric pain was commoner in children with *H. pylori* gastritis, occurring in 13/24 (54%), compared with 28/70 (40%) of those with normal histology, although this difference was not statistically significant ( $p = 0.086$ ). Central periumbilical abdominal pain was more common in *H. pylori* negative children with normal gastric histology, 27/70 (39%), compared with 5/24 (20%) of those with *H. pylori* positive gastritis, but this difference did not reach statistical significance ( $p = 0.069$ ). Recurrent vomiting was the second most frequent symptom but was poorly discriminatory between the two groups, being present in 4/24 (17%) and 12/70 (17%) patients with and without *H. pylori* gastritis respectively. Other presenting symptoms in *H. pylori* positive children were haematemesis (one child), and melaena (one child). One child with *H. pylori* gastritis had refractory iron deficiency anaemia.

SOCIAL CLASS

The social class of the children studied was assigned according to the occupation of the head of the household using the registrar general's classification, and is shown in the table. For purposes of comparison, non-manual classes 1, 2, and 3NM were grouped together and compared with manual classes 3M, 4, and 5. The social class distribution of the study population was broadly similar to that of the population of West Yorkshire,<sup>10</sup> but there was a marked social class difference between *H. pylori* positive and negative children. Children of parents with manual occupations were overrepresented in the *H. pylori* positive gastritis group 21/24 (87.5%) compared with 44/71 (62%) in the *H. pylori* negative group ( $p < 0.02$ ), and no *H. pylori* positive child came from social class 1 or 2.

ENDOSCOPY

Endoscopic abnormalities were present in 20/24 children with *H. pylori* gastritis. The commonest abnormality was antral nodularity (fig 2) found in 13/24; five children had antral erythema and gastric erosions were present in two. Duodenal ulcers were diagnosed in two children (aged 15 and 13 years): one was associated with gastric erosions and coexistent *H. pylori* gastritis on antral histology, the other was an isolated finding and was not associated with *H. pylori* gastritis. The principal endoscopic finding in the *H. pylori* negative, normal gastric histology group was macroscopic oesophagitis, present in 14/70, and microscopic oesophagitis was found in a further eight on oesophageal biopsy.

HISTOLOGY

Of the 25 children with chronic gastritis, 22 had typical helicobacter associated chronic gastritis on histology. Three children showed the pattern of 'lymphocytic gastritis'.<sup>11</sup> one of these had helicobacter on histological staining, and one was positive on CLO test, while all three had positive *H. pylori* serology.<sup>6</sup> Thus 3/25 (12%) of children with chronic gastritis showed this special type of gastritis, a frequency higher than

Social class distribution of *H. pylori* positive and *H. pylori* negative children

	Non-manual classes			Manual classes		
	1	2	3NM	3M	4	5
<i>H. pylori</i> positive	0	0	3	6	7	8
	3 (12.5%)			21 (87.5%)*		
<i>H. pylori</i> negative	3	18	6	26	8	10
	27 (38%)			44 (62%)		
Study population	3 (3.1%)	18 (19%)	9 (9.5%)	32 (33.7%)	15 (15.8%)	18 (18.9%)
	30 (31.6%)			65 (68.4%)		
West Yorkshire (1981 census)	5%	23%	12%	36%	18%	6%
	40%			60%		

\*Significant difference between positive and negative groups ( $p < 0.02$ ).

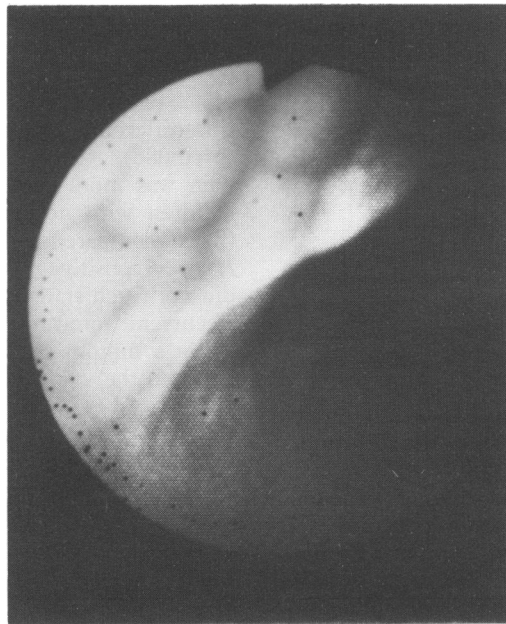


Figure 2 Antral nodularity seen at endoscopy in a child with *H pylori* gastritis.

that seen in adults, where it is present in 2% of patients with chronic gastritis.<sup>11</sup> None of the biopsy specimens showed reactive gastritis or any of the other special forms of gastritis recognised by the Sydney system.

The 22 children with helicobacter associated chronic gastritis (excluding cases of lymphocytic gastritis) were graded according to the Sydney system. All showed some increase in chronic inflammatory cells, and lymphoid follicles were present in biopsies from 12/22 (55%) children (fig 3). The presence of 'activity' of chronic gastritis is assessed by the degree of neutrophil infiltration of the epithelium. This was present in specimens from 10/22 (45%) children only, although it is characteristically present in adults with helicobacter gastritis.<sup>12</sup>

None of the biopsy specimens showed architectural irregularity to suggest there had been any atrophy of antral glands, and none of them showed intestinal metaplasia.

#### RESULTS OF TREATMENT

In the 12 children in whom antral biopsy specimens before and after treatment were studied, *H pylori* eradication was achieved in

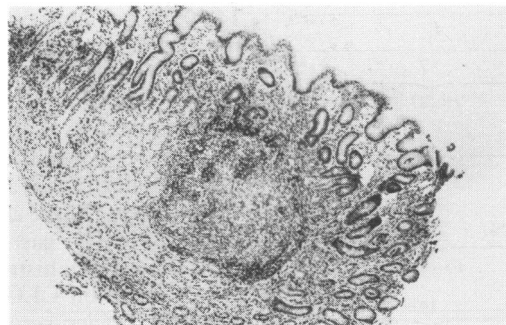


Figure 3 Lymphoid follicle in the antral mucosa of a child with *H pylori* gastritis.

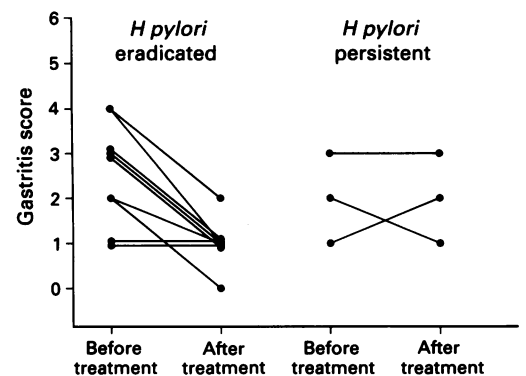


Figure 4 Severity of gastritis in antral biopsy specimens before and after treatment, showing significant reduction ( $p < 0.025$ ) in gastritis score where *H pylori* was eradicated.

9/12 (75%). Gastritis scores improved in the *H pylori* eradication group from mean (SD) of 2.55 (1.13) before treatment to 1 (0.5) after treatment ( $p < 0.025$ ) (fig 4). Symptoms resolved in seven children but were unchanged in two despite eradication of *H pylori* and improvement in gastritis score. In the three children in whom *H pylori* was not eradicated, gastritis score was not significantly altered, and all remained symptomatic. Six other children had identical treatment and all experienced an improvement in symptoms, but follow up endoscopy was declined by their parents. The 15 year old adolescent with duodenal ulcer and coexistent *H pylori* gastritis was treated with tripotassium dicitratobismuthate and ampicillin at doses mentioned above, and ranitidine 150 mg twice daily. Follow up endoscopy 11 months after presentation showed healing of the ulcer but mucosal biopsies were not obtained.

No child developed side effects from treatment. Bismuth concentrations ranged from 3 to 29 ng/ml, mean 14.8 ng/ml. Bismuth toxicity is associated with concentrations above 50 ng/ml.<sup>13</sup>

#### Discussion

This study confirms the findings of other workers that *H pylori* gastritis is a significant cause of abdominal pain in the paediatric age group.<sup>3-5</sup> The clinical profile of paediatric *H pylori* gastritis that emerges from this study is of epigastric pain in the older child and adolescent (8-16 years) from a family of low socioeconomic status and a family history of peptic ulcer disease. However, we have found that *H pylori* gastritis can occur in young children, and 20% of our cases were in children aged 5 years or younger. The bias towards low socioeconomic groups in *H pylori* positive children suggests that social class is a factor in *H pylori* acquisition in childhood. Children from higher social class groups appear to be less susceptible to *H pylori* infection, and similar results have been found in adults in the United Kingdom.<sup>14</sup> Although the reservoir of infection and modes of spread of *H pylori* are not known, the social patterns are suggestive of faecal-oral transmission, and social class differences may reflect differences in sanitation and hygienic practices.<sup>15</sup>



Positive endoscopic findings are common in children with *H pylori* associated gastritis, especially antral nodularity. Lymphoid follicles were present in biopsies from 55% children; the presence of follicles was not correlated with the activity of the gastritis, nor the density of bacterial colonisation. As the antral mucosa in children is thinner than that in adults, it is likely that the presence of large lymphoid follicles accounted for the nodularity apparent on endoscopy.

Lymphocytic gastritis is an unusual pattern of inflammation in adults, but was seen rather more frequently in our paediatric biopsy specimens (3/25). As in adults, these children showed serological evidence of *H pylori* infection, although the bacteria were apparent on histology in only one of three children. The relationship between lymphocytic gastritis and *H pylori* infection is still uncertain.

The precise indications for treatment and the optimal treatment regimen for children with *H pylori* gastritis remain to be established.<sup>16</sup> We chose treatment with tripotassium dicitratobismuthate and ampicillin as this combination gave optimal results in a large adult study.<sup>17</sup> We achieved a *H pylori* eradication rate of 75% and this is similar to other paediatric studies using a combination of ampicillin and bismuth preparations.<sup>5 18</sup> In adult studies better eradication rates have been achieved with dual therapy using a bismuth preparation and metronidazole, but there are problems with metronidazole resistance.<sup>19</sup> Blood bismuth concentrations were measured because of concern about potential toxicity of bismuth preparations in children, and all were in the non-toxic range. Tripotassium dicitratobismuthate was well tolerated and no child developed side effects.

The discovery of *H pylori* in 1983, and the subsequent demonstration of its role in gastroduodenal pathology, has been one of the most exciting developments in gastroenterology in the past decade. Chronic abdominal pain in children has always been an important part of the paediatrician's workload.<sup>20</sup> This study and others suggest a role for *H pylori* in children with chronic abdominal pain and upper gastrointestinal symptoms.<sup>3-5</sup> Although relatively uncommon in children, a strong association exists between *H pylori* gastritis and duodenal ulceration. Furthermore, eradication of *H pylori* has been shown to improve ulcer healing and to reduce ulcer relapse rate in children.<sup>21</sup> The natural history of *H pylori* gastritis is still being delineated, but present evidence suggests a slow progression to atrophic gastritis and gastric atrophy over a period of 20-40 years. Atrophic gastritis and gastric atrophy are known to be precursor lesions for the development of gastric carcinoma,<sup>22</sup> and this potential carcinogenicity of *H pylori* makes it a significant pathogen in children.

Treatment with bismuth preparations and antibiotics can eradicate *H pylori* and improve

gastritis in about 75% of patients, but long term follow up and control studies are lacking. Recent reviews have sounded a note of caution about the indiscriminate treatment of *H pylori* especially the risk of antibiotic resistance, both in children<sup>16</sup> and in adults.<sup>19</sup> Serological detection of *H pylori* IgG antibodies is valuable in screening children with chronic abdominal pain for *H pylori* gastritis,<sup>6</sup> and perhaps endoscopy should be reserved for detection of associated duodenal ulcer disease. Treatment to eradicate *H pylori* would then be justified in view of the role of *H pylori* in duodenal ulcer healing and relapse.<sup>21</sup> Further research remains to be done before we fully understand the precise role of *H pylori* in children with chronic gastrointestinal symptoms, the indications for treatment, and the optimal agents.

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