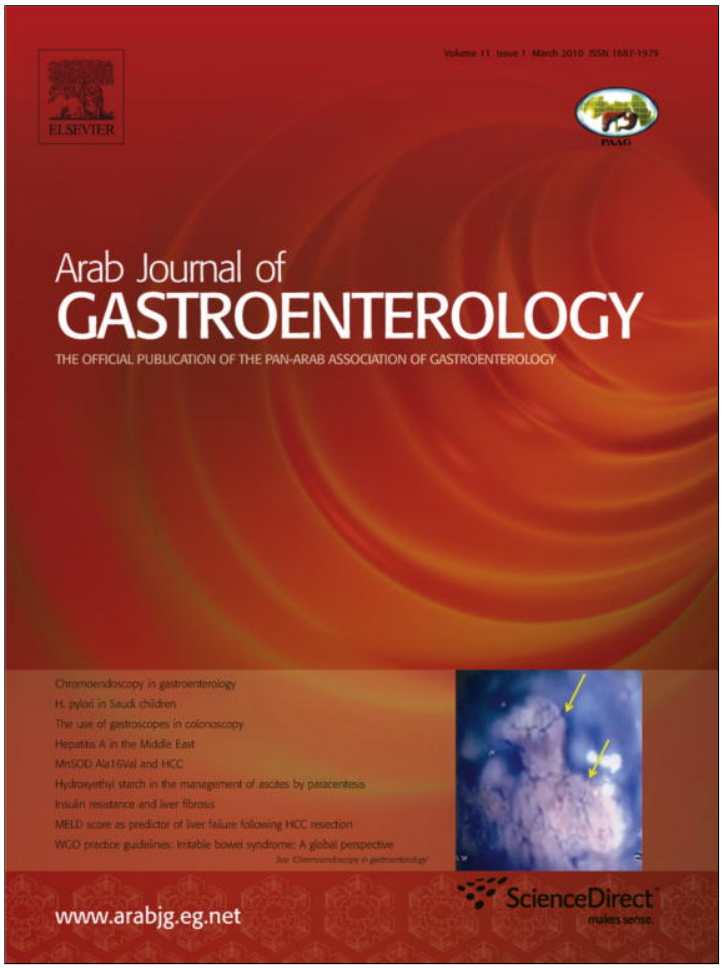

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Original Article

Helicobacter pylori infection in Saudi children; clinical, endoscopic and pathological findings

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ABSTRACT

Background and study aims: *Helicobacter pylori* (*H. pylori*) infection is common in the Saudi paediatric population. The aim of this study was to describe the clinical presentation, endoscopic abnormalities and associated histopathological changes in a group of Saudi children with *H. pylori* infection.

Patients and methods: This is a chart review of all Saudi children diagnosed at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia, between September 2001 and July 2005 with *H. pylori* infection.

Results: A total of 230 children were identified. One hundred and thiry six (55%) were females. The mean age was 11 ± 3.9 years (range, 2–17). Thirty-two (14%) were underweight and 12 (5%) were stunted. The main symptom was epigastric pain in 128 (56%). Nodular gastritis was the most frequent endoscopic finding in 94 patients (40%). The histopathological findings in the antrum showed moderate chronic inflammatory activity in 65%, mild glandular atrophy in 14% and intestinal metaplasia in 2%. In the corpus, moderate chronic inflammatory activity was found in more than 50%, glandular atrophy in 7%, and no cases with intestinal metaplasia. The density of *H. pylori* in the antrum was mild in 67% and moderate in 26% of cases. In the corpus, it was mild in 49% and moderate in 21% of patients.The mean gastritis score was 4.2 ± 1.3 in the antrum and 3.4 ± 1.3 in the corpus. Nodular gastritis was associated with the highest mean gastritis score of 4.9 ± 1.2 in the antrum (ANOVA < 0.001). The severity of gastritis in the antrum and the corpus was associated with higher density of *H. pylori* (ANOVA < 0.001).

Conclusion: Saudi children with *H. pylori* infection were commonly found to have abnormal endoscopic findings which were associated with significant gastric mucosal inflammation.

Introduction

Helicobacter pylori (*H. pylori*) infection is common in the paediatric population. Its acquisition is related to poor socioeconomic conditions. In the developing countries infection is more frequent and acquired at an earlier age than industrialized nations [1]. Once acquired, infection persists and may or may not produce peptic ulcer disease. The prevalence of *H. pylori* infection in asymptomatic population in Saudi Arabia is about 40% in children younger than 10 years and 70% in children and adolescents between 10 and 20 years of age [2]. This is more than what have been reported from developed countries [3].

However, the prevalence of *H. pylori* in Saudi patients with peptic ulcer disease, gastritis, and duodenitis may not significantly differ from internationally reported prevalence [4,5]. The development of peptic ulcer disease depends on the virulence of the organism. The virulence factors Cag A and Vac A have been associated with the gastroduodenal disease caused by *H. pylori* organisms [6]. The prevalence of the virulent factors Cag A and Vac A antibodies reported for Saudi children with *H. pylori* infection was 67% and 60%, respectively [7].

The reported studies from Saudi Arabia regarding *H. pylori* infection in children were mainly describing the epidemiology and seroprevalence. There were no published clinical studies in Saudi children with *H. pylori* infection that include a large number of patients. Therefore, in this study, we aim to describe the clinical picture of *H. pylori* infected children at presentation, endoscopic findings and various histopathological changes associated with *H. pylori* infection in a group of children at King Abdul-Aziz University in the Western region of Saudi Arabia and to compare them with similar studies from other parts of the world.

Patients and methods

This is a retrospective chart review of all Saudi children and adolescents admitted to the endoscopy unit at King Abdul-Aziz

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University Hospital, Jeddah, Saudi Arabia, in the period between September 2001 and July 2005 with the clinical diagnosis of *H. pylori* infection. The diagnosis was based on a positive rapid urease test (CLO test) performed in the biopsy specimen taken during upper gastrointestinal endoscopy. Data were collected including demographic data, upper gastrointestinal symptoms at presentation, growth parameters, endoscopic findings, histopathological report, haemoglobin level and details of treatment given. The histopathology was also reviewed and reported according to the revised Sydney system [8].

The weight and height were recorded at the time of endoscopy. The z-scores for weight for age (WAZ), height for age (HAZ) and body mass index (BMI) were calculated using an anthropometric software program (EpiInfo, Centers for Disease Control and Prevention, Atlanta, GA, USA).

Table 1
Anthropometric measurements in 230 children with *H. pylori* infection.

Weight for age z-score (WAZ)	
No. of children (%) with WAZ < −2.5	32 (14%)
Mean ± SD	−0.59 ± 1.59
Range	−3.1 to 4.89
Height for age z-score (HAZ)	
No. of children (%) with HAZ < −2.5	12 (5%)
Mean ± SD	−1.04 ± 1.28
Range	−4.3 to 1.02
Body mass index (BMI)	
No. of children (%) with BMI <18.5	115 (50%)
No. of children (%) with BMI 18.5–24.9	103 (45%)
No. of children (%) with BMI 25–29.9	12 (5%)
Mean ± SD	17.4 ± 3.9
Range	13.8–27.6

Table 2
The presenting symptoms in 230 children with *H. pylori* infection.

Symptoms	Number	Percentage
Epigastric pain	128	56
Recurrent vomiting	44	19
Nausea	20	8
Haematemesis	10	4

Table 3
Endoscopic findings in 230 children with *H. pylori* infection.

Endoscopic findings	Number	Percentage
Normal	30	13
Antral nodular gastritis	94	40
Superficial gastritis	60	26
Peptic ulcer disease	30	13

Upper gastrointestinal endoscopy was performed by the author at the endoscopy unit at King Abdul-Aziz University Hospital using an Olympus Gastroscope. Children were given conscious sedation using midazolam intravenous injection. For all children a total of three biopsy specimens were taken from the antral mucosa. In addition, 180 children had also biopsy specimens taken from the corpus. A rapid urease test (CLO test) was performed on the first antral biopsy, and the remaining specimens were sent for histopathological evaluation. The possible endoscopic diagnosis included normal, superficial gastritis, nodular gastritis, and peptic ulcer disease.

The rapid urease test kit (CLO test, Ballard Medical Products, UTAH, USA) was routinely used. The gastric biopsy specimens were immediately embedded into the gel in the kit. The kit was placed in the room temperature for 24 h. The test is considered positive if the colour change into red or magenta.

Immediately after collection, gastric biopsy specimens were fixed in 10% buffered formaldehyde and embedded in paraffin for sectioning. Tissue was examined for the presence of inflammation, atrophy, and intestinal metaplasia. Biopsy samples were also stained with Giemsa stains to detect *H. pylori* in the tissue. The grade and activity of gastritis was assessed using the updated Sydney system [8]. The degree of inflammation was divided into (1) monocyte infiltration, (2) neutrophil infiltration, (3) glandular atrophy, and (4) intestinal metaplasia, and scored as normal (0), mild (1), moderate (2), or marked (3) using the visual analogue scale applied to microscopic examination results. The sum of the scores obtained from each patient was used as the gastritis score [9].

The density of *H. pylori* organisms was quantified as no bacteria (0), only few bacteria (1), more bacteria in several areas (2), and abundance of bacteria in most glands (3).

Statistical analysis was performed using the Stata Statistical Software (Release 6.0, College Station, TX). Data were expressed as mean ± standard deviation (SD) for normal distributions and as median and interquartile range for skewed distributions, or as proportions of the total group. The *t*-test and ANOVA on ranks were used when appropriate. A p-value <0.05 was considered significant.

Results

Two hundred thirty children were identified from the endoscopy unit records with the diagnosis of *H. pylori* infection based on rapid urease test. One hundred thirty six (55%) were females. The mean age at diagnosis was 11 ± 3.9 years (range, 2–17). All patients were Saudi nationals. One hundred seventy nine patients (78%) were living in Jeddah, while 51 (22%) came from nearby cities and towns. The socioeconomic status was assessed based on the recorded patient's social history. Forty six (20%) patients were in the low category, 133 (58%) were in the middle, and 51 (22%) were in the high category.

The analysis of the anthropometric measures taken at presentation is shown in Table 1. Thirty two (14%) patients were under-

Table 4
Histopathological characteristics of children with *H. pylori* gastritis according to the updated Sydney classification.

	Antrum $n = 230$ Number of patients (%)				Corpus $n = 180$ Number of patients (%)			
	Normal	Mild	Moderate	Marked	Normal	Mild	Moderate	Marked
Neutrophil infiltration	2 (1)	83 (36)	137 (60)	8 (3)	16 (9)	60 (33)	100 (56)	4 (2)
Monocyte infiltration	0 (0)	83 (36)	140 (61)	7 (3)	16 (9)	65 (36)	9 (53)	4 (2)
Glandular atrophy	198 (86)	32 (14)	0 (0)	0 (0)	168 (93)	12 (7)	0 (0)	0 (0)
Intestinal metaplasia	226 (98)	4 (2)	0 (0)	0 (0)	180 (100)	0 (0)	0 (0)	0 (0)
H. pylori density	2 (1)	154 (67)	60 (26)	14 (6)	40 (22)	88 (49)	38 (21)	14 (8)

weight with weight for age *z*-score less than −2.5, 12 (5%) were stunted with height for age *z*-score less than −2.5, and 115 (50%) were found with low body mass index (BMI).

All patients were referred for upper gastrointestinal endoscopy because of upper gastrointestinal symptoms. The main reason for performing endoscopy was epigastric pain in 128 patients (56%) followed by vomiting, nausea, and haematemesis (Table 2).

Abnormal endoscopy examination was found in 200 patients (70%) (Table 3). Nodular gastritis was the most frequent finding occurring in 94 patients (40%). The mean age ± SD of patients with nodular gastritis was 11 ± 3.2 years. Superficial gastritis was the next most common endoscopic finding that was found in 60 children (26%) with a mean age ± SD of 12 ± 4.6 years. Peptic ulcer disease was also found in 30 patients (13%). The mean age ± SD of patients with peptic ulcer disease was 14 ± 3 years. Twelve had gastric ulcers mainly prepyloric, and 18 had duodenal ulcer.

Based on the updated Sydney system, each of the inflammatory components including neutrophil infiltration, monocyte infiltration, glandular atrophy and intestinal metaplasia were graded as normal, mild, moderate or marked in the biopsy taken from both antrum and corpus (Table 4). In the gastric antrum, most patients had moderate chronic inflammatory activity. Mild glandular atrophy was found in only 14% and intestinal metaplasia in 2% of cases. In the corpus, moderate chronic inflammatory activity occurred in more than 50% of the patients and glandular atrophy was found in 7% of patients, but no intestinal metaplasia. In the antrum, the density of *H. pylori* organisms was graded into mild and moderate scale in 67% and 26% of patients, respectively. In the corpus, 49% of cases were graded as mild and 21% graded as moderate.

The mean ± SD gastritis score which is the sum of the four components of the Sydney system was 4.2 ± 1.3 in the antrum and 3.4 ± 1.3 in the corpus. Nodular gastritis was associated with the highest mean antral gastritis score of 4.9 ± 1.2. The difference between the mean gastritis score in the antrum in patients with nodular gastritis and patients with other endoscopic abnormalities was statistically significant (ANOVA < 0.001) (Fig. 1).

The severity of gastritis as indicated by gastritis score in the antrum was associated with higher density of *H. pylori* organisms. This was found to be statistically significant (ANOVA < 0.001) (Fig. 2). The same association was also seen in the corpus in 180 patients studied (Fig. 3).

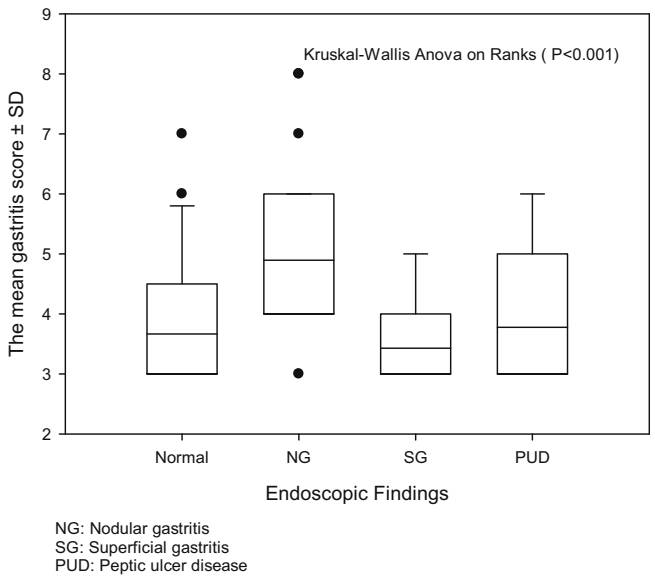

Fig. 1. The mean gastritis score in the antrum in various endoscopic findings.

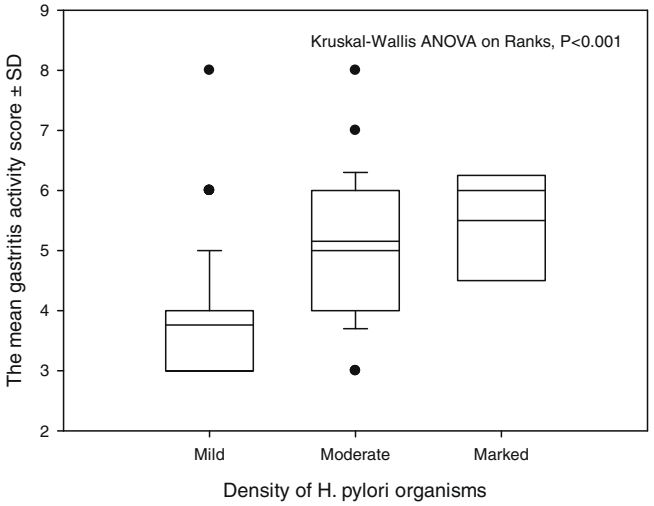

Fig. 2. The mean gastritis score in the antrum in relation to the density of *H. pylori* organisms.

In patients with various endoscopic abnormalities, the density of the *H. pylori* organisms in the antrum was assessed. There was no statistically significant difference in the density of the *H. pylori* organisms in patients with nodular gastritis and patients with other endoscopic findings (Fig. 4).

Haemoglobin was tested in 116 patients. Fifty eight (50%) were anaemic with a mean haemoglobin level of 11.3 ± 0.45 (range, 8.5–12). There was a statistically significant difference between children with and without anaemia in both the antrum (mean gastritis score: 4.3 ± 1.2 vs. 3.7 ± 0.8, $p < 0.05$) and corpus (mean gastritis score: 3.5 ± 1.2 vs. 2.6 ± 0.8, $p < 0.05$). The difference in the density score of *H. pylori* organism between children with or without anaemia was only significant in the corpus (the mean density score: 3.5 ± 1.2 vs. 2.6 ± 0.8, $p < 0.05$) but not in the antrum.

All patients were treated for 2 weeks with the triple therapy using amoxicillin in a dose of 50 mg/kg/day (up to 1 g bid), clarithromycin in a dose of 15 mg/kg/day (up to 500 mg bid) in addition to a proton pump inhibitor in a dose of 1 mg/kg/day (up to 20 mg bid). The proton pump inhibitor used was omeprazole in 112 (49%) patients, pantaoprazole in 107 (46%) patients and esomeprazole in 11(5%) patients.

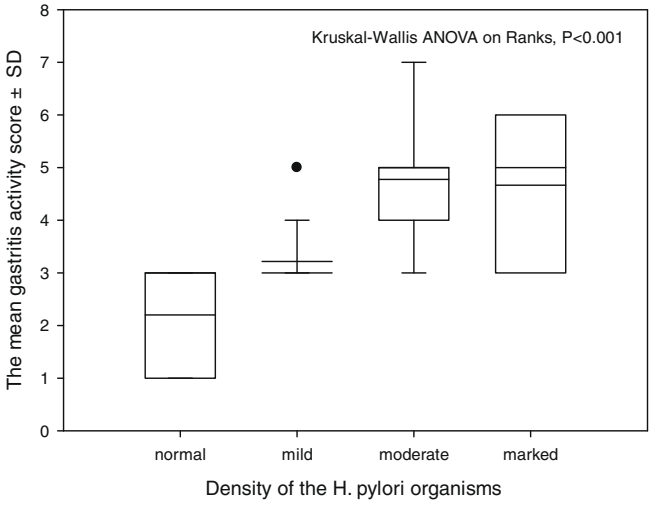

Fig. 3. The mean gastritis score in the corpus in relation to the density of *H. pylori* organisms.

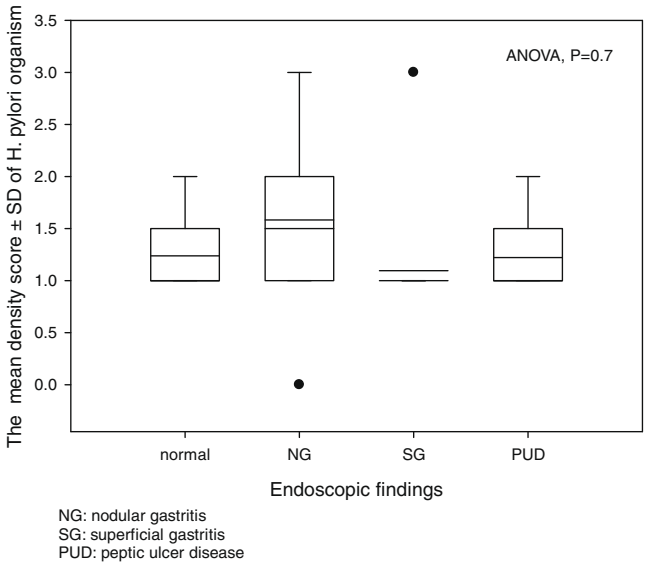

Fig. 4. The density score of *H. pylori* organisms in various endoscopic findings.

Only 196 patients were seen at follow up after 8 weeks. All but four reported improvement in their presenting symptoms during their follow up visits. The other four patients continued to have abdominal pain in spite of good compliance with the treatment and were subjected for further evaluation.

Discussion

H. pylori infection is almost always acquired in childhood and if untreated infection is usually life-long [10,11]. *H. pylori* infection in childhood is usually more prevalent in children with low socioeconomic conditions [12,13]. Special emphasis has been focused on the maternal educational level. In this study, most children were in the middle category. Children in the high category still can be infected with *H. pylori* organisms. In this study, 22% were in the high category. This was slightly higher than what have been reported by Parente et al. [14] with 16.4% of their patients being in the high socioeconomic group.

Children infected with *H. pylori* may be found to have retarded growth. In this study at the time of diagnosis, we found 14% being underweight and 5% of children with short stature. Low BMI was found in almost half of the patients. In the absence of control, it is hard to relate this growth failure to infection by *H. pylori*. Oderda et al. [15] found that *H. pylori* infection was not a risk factor for short stature, and growth failure was most likely related to the patient's socioeconomic and ethnic condition rather than an effect of *H. pylori* infection.

Although nonspecific for *H. pylori* gastritis, most of our patients with *H. pylori* infection had epigastric pain. Unlike, the classical recurrent abdominal pain syndrome that present with recurrent central abdominal pain in otherwise healthy children [16,17], the presence of epigastric pain especially if associated with dyspeptic symptoms is more associated with abnormal gastric pathology. Singh et al. [18] found that *H. pylori* infection was diagnosed in 53% of 240 Indian children presented with epigastric pain. Therefore, the yield from upper gastrointestinal endoscopy in children with epigastric pain is more revealing.

Nodular gastritis was the most frequent endoscopic finding in our cohort of children. It occurs in 94 patients (40%). Endoscopic findings of nodularity in *H. pylori* infection with cobblestone pattern predominantly observed in the gastric antrum can be seen in the stomach of children much more frequently than in adults [19,20]. Nodular gastritis was associated with more active inflammation as indicated by a high mean gastritis score of 4.9 ± 1.2 as estimated according to the updated Sydney system [8] in the antrum. The difference was significant when compared to patients without nodular gastritis. Bahu et al. [9] found nodular gastritis in 44% of 50 Brazilian children with *H. pylori* infection. In their study, they reported significant correlation of nodular gastritis with the degree of histological inflammation in agreement with our finding. They also found a correlation between nodular gastritis and increase density of *H. pylori* organism, a finding that we could not confirm in this study as we reported no association between the density of the *H. pylori* organisms and the presence of nodular gastritis.

Ten children in this study presented with haematemesis and were found to have peptic ulcer disease at endoscopy. Peptic ulcer disease was diagnosed in 30 patients (13%). It was considered rare in children with *H. pylori* as compared to adults [21]. Almost half of the symptomatic adult patients with *H. pylori* infection had peptic ulcer disease [22]. It is not clear why children with *H. pylori* infection have a low tendency to develop peptic ulcer disease. Bontems et al. [23] found that interferon gamma secretion in the stomach of *H. pylori* infected patients is lower in children than in adults. This immune phenotype seems to confer protection of children from severe gastroduodenal disease.

The updated Sydney system [8] was introduced to improve the agreement between pathologists and to generate reproducible and clinically useful diagnoses. According to the updated Sydney system, each of the inflammatory components including, neutrophil infiltration, monocyte infiltration, glandular atrophy and intestinal metaplasia was graded as normal, mild, moderate or marked. We found moderate gastric chronic inflammatory activity in most patients, both in the antrum and the corpus. Kamada et al. [24] studied 112 Japanese patients under 29 years of age with *H. pylori* gastritis. They reported neutrophil infiltration as mild in 11.6%, moderate in 67.9%, and marked in 20.5% of patients. Regarding monocyte infiltration 5.4% were mild, 46.4% were moderate, and 48.2% of patients were marked. In another Japanese study by Kato et al [25] in 131 cases of *H. pylori* infected children, they found neutrophil infiltration in 84% of patients, most of which was mild, and monocyte infiltration in 59.5%, most of which was moderate. Another study from Korea by Koh et al. [26] showed neutrophil infiltration to be mild in 46.3%, moderate in 28% and marked in 0.3% of cases. They also found monocyte infiltration to be mild in 43.3%, and moderate in 20.1% of patients. In this study, we found neutrophil infiltration in 99% of children, most of which were moderate. This result was similar to that reported by Kamada et al. [24] and Koh et al. [26] and different from the study by Kato et al. [25] that showed most of the neutrophil infiltration to be mild. Monocyte infiltration was seen in all of our patients, most of which were moderate. That was similar to what have been reported by Kato et al. [25]. Kamada et al. [24] have found similar proportion between moderate and marked monocyte infiltration, while Koh et al. [26] found mostly mild monocyte infiltration.

Mild glandular atrophy was found in 14% of our patients in the antrum and 7% in the corpus. The proportion of our patients with glandular atrophy was much less than that reported by Kamada et al. [24], Kato et al. [25] and Koh et al. [26] of 25.9%, 51.9% and 55.2%, respectively. Several clinical reports confirmed that gastric atrophy is a pathology not only limited to adult patients [27–30]. Its prevalence varies between 0% and 72% according to different studies. The possible explanation for the overestimation is that the reported prevalence in children included all histological grades, whereas in the majority of adults' studies only medium and severe grades were considered. We also found mild focal intestinal metaplasia in 2% of cases in the antrum, but none in the corpus. This prevalence is similar to that reported in a group of Turkish children

with *H. pylori* infection of 2.8% [30] and less than what have been reported by Kamada et al. [24] and Kato et al. [25] of 5.4% and 4.6%, respectively.

In our study, we found that the degree of gastritis as estimated by the gastritis score which represents the sum of the four elements of Sydney system was proportional to the increased density of *H. pylori* organisms in the antrum and the corpus. Two different studies by Bahu et al. [9] and Rafeey et al. [31] have reported the relation between increased *H. pylori* density and the severity of gastritis. They also correlated this finding with the presence of nodular gastritis in endoscopy. We found a positive correlation between the activity of gastritis and nodular gastritis, but we could not confirm the correlation between increased *H. pylori* density and the presence of nodular gastritis.

Haemoglobin level was estimated in 116 patients. Fifty eight had low haemoglobin level. We found that patients with anaemia had more severe chronic inflammation than non anaemic patients. This may indicate that patients with more active inflammation have less utilization of iron. This was associated with a higher density of the *H. pylori* organisms in the corpus but not in the antrum. The tendency for iron deficiency anaemia in children is mostly related to inadequate intake of iron. It has been also suggested that *H. pylori* is a contributing factor to the development of iron deficiency anaemia [32]. Patients with *H. pylori* gastritis have reduced gastric ascorbic acid which is an important promoter of iron absorption together with gastric acidity [33]. Anaemia in those patients is usually refractory to iron therapy and may respond better to eradication of *H. pylori* infection even without iron supplement [34].

In conclusion, Saudi children with *H. pylori* infection were commonly found to have abnormal endoscopic findings which were associated with significant gastric mucosal inflammation.

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