ORIGINAL ARTICLE

Etiology and Treatment of Childhood Peptic Ulcer Disease in Taiwan: A Single Center 9-Year Experience

*Shu-Ching Huang,[1,6] Bor-Shyang Sheu,[2] Shui-Cheng Lee,[3] Hsiao-Bai Yang,[4,5] Yao-Jong Yang[1]**

Background/Purpose: Peptic ulcer disease (PUD) in children is relatively rare as compared with adults. This study aimed to assess the etiology, clinical and histological characteristics, and treatment of PUD in children.
Methods: All children aged < 18 years with an endoscopic diagnosis of PUD were enrolled in a tertiary referral center. The demographic data, clinical, endoscopic, and histological findings were compared between patients with different causes of PUD.
Results: From 1234 endoscopic examinations, 67 (5.4%) children (median age, 11.4 years) with gastric ulcer (GU; $n = 27$) or duodenal ulcer (DU; $n = 40$) were included. Thirty-two (47.7%) of them had *Helicobacter pylori* infection and 11 (16.5%) had previous use of non-steroidal anti-inflammatory drugs (NSAIDs). Non-*H. pylori*, non-NSAID PUD was found in 24 (35.8%) patients. Children with *H. pylori*-related PUD had a significantly higher mean age, antral chronic inflammatory score, rate of familial PUD, and presence of DU and nodular gastritis than those with NSAID-related and non-*H. pylori*, non-NSAID PUD ($p < 0.01$). In contrast, children with NSAID-related PUD had a higher rate of upper gastrointestinal bleeding, associated with acute febrile disease, than those with *H. pylori*-related and non-*H. pylori*, non-NSAID PUD ($p < 0.05$). All but two patients with non-*H. pylori*, non-NSAID PUD were disease free after *H. pylori* eradication and proton pump inhibitor treatment for 1–2 months.
Conclusion: In children, *H. pylori*-related PUD is associated with familial peptic ulcer and the presence of DU. However, short-term NSAID use is correlated highly with GU. The outcome of childhood PUD is good.
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Key Words: child, *Helicobacter pylori*, non-steroidal anti-inflammatory drugs, peptic ulcer

Peptic ulcer disease (PUD) is considered relatively uncommon but is potentially life-threatening in cases of childhood gastrointestinal disease.[1] PUD is a heterogeneous disease, which is determined by various etiological factors. *Helicobacter pylori* infection causes chronic gastritis and PUD in children.[2,3] In addition, it is a major cause of PUD in adult patients, and the eradication of *H. pylori* from adults with duodenal ulcer (DU) can prevent ulcer recurrence.[4,5] However, the rates of *H. pylori*-related DU and gastric ulcer (GU) are lower in children than that in adults.[6–8] Therefore, besides assessing the real impact of *H. pylori* infection on PUD in children, other possible etiological factors should be clarified, to assist in choosing the appropriate treatment.

Chronic use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) predisposes adult

Departments of [1]Pediatrics, [2]Internal Medicine, and [4]Pathology, National Cheng Kung University and Hospital, and [6]Department of Pediatrics, Kuo General Hospital, Tainan, [3]Institute of Nuclear Energy Research, Atomic Energy Committee, Taipei, and [5]Department of Pathology, Ton-Yen General Hospital, Hsinchu, Taiwan.

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***Correspondence to:** Dr Yao-Jong Yang, Department of Pediatrics, National Cheng Kung University and Hospital, 138 Sheng Li Road, Tainan 704, Taiwan.
E-mail: yaojong@mail.ncku.edu.tw

cardiologic and rheumatologic patients to a high prevalence of PUD development.[9–11] The relationship between chronic use of these drugs and childhood PUD is still controversial.[12–14] Some studies have reported that, in childhood, aspirin and NSAID use is associated with a high prevalence of ulceration of the stomach and duodenum. However, Keenan et al reported a low incidence (0.7%) of gastropathy in 702 children with juvenile rheumatoid arthritis who were treated with NSAIDs.[14] In practice, NSAIDs are used widely in healthy children and adults for acute febrile diseases or pain control.[15] Acute gastrointestinal bleeding associated with the short-term use of NSAIDs is a common adverse reaction, with a high rate of hospitalization and mortality in developed countries.[16–18] It is less clear about the adverse role of short-term NSAID use among children and its correlation with PUD.

In contrast, there has been an increase in non-*H. pylori*, non-NSAID PUD in adult and childhood patients in developed countries.[19–21] This could have resulted from improved sanitation and a drop in *H. pylori* seroprevalence in such countries.[22] In Taiwan, the prevalence of *H. pylori* infection in children has not decreased in the past decade.[23] Therefore, it was of interest to assess whether the prevalence of *H. pylori* infection in children with PUD was still high. We attempted to determine whether different characteristics of PUD exist in children, and to highlight the role of *H. pylori* infection and NSAID use in childhood PUD in Taiwan.

Patients and Methods

Enrolled patients

From February 1999 to April 2008, children aged < 18 years who underwent upper gastrointestinal endoscopy for various symptoms were analyzed retrospectively. The medical records of children who were diagnosed with DU or GU by endoscopy were analyzed. Patients who had a predisposing factor such as acute stress caused by a severe underlying disease, iatrogenic trauma, and previous treatment of *H. pylori* infection were excluded.

Endoscopic examination and diagnosis of H. pylori infection

During endoscopic examination, gastric specimens were obtained from the antrum and corpus. The two antral biopsies were sent for *H. pylori* culture and rapid urea test. The other two specimens from the antrum and corpus were embedded in formalin for histological examination. *H. pylori* infection was defined by positive culture or positive results for the rapid urea test and histology.

Histology of gastric biopsies

The same pathologist, unaware of the endoscopic and culture results, analyzed the gastric histology. The *H. pylori* density for each specimen used a previously published scale: 0, no bacteria; 1, one or two small clusters with < 10 bacteria; 2, less than half the superficial crypt area with < 10 bacteria in each crypt; 3, less than half the area but with > 10 bacteria, or more than half the area with < 10 bacteria in each crypt; 4, > 10 bacteria in foveola with some free areas; and 5, > 10 bacteria without a free area.[8] The acute inflammatory score (range, 0–3), chronic inflammation score (range, 0–3), atrophic change (range, 0–3), and intestinal metaplasia (range, 0–3) were graded using the updated Sydney system.[24]

Antimicrobial susceptibility test

Minimum inhibitory concentrations of amoxicillin, clarithromycin and metronidazole were determined by the Etest® (AB Biodisk, Solna, Sweden). The Etest® was performed on Mueller–Hinton sheep blood agar plates. Plates were incubated for 72 hours at 35°C under microaerophilic conditions. A strain was considered resistant if the MIC was > 2 μg/mL of amoxicillin, > 1 μg/mL of clarithromycin, and < 8 μg/mL of metronidazole, respectively.[25]

Treatment and follow-up

Once the *H. pylori*-related peptic ulcers were diagnosed, proton pump inhibitor (PPI)-based triple

therapy was prescribed for each patient according to the susceptibility test for *H. pylori*, and clarithromycin-based triple therapy was used in culture-negative *H. pylori*-infected patients. Successful eradication was defined by follow-up endoscopy, or when ^{13}C-urea breath test was negative for *H. pylori* 6 weeks after the completion of drug therapy. Patients with *H. pylori*-negative PUD were treated with lansoprazole (1 mg/kg/day, maximum dose, 30 mg/day) for 1–2 months. Healing of peptic ulcers was assessed by follow-up endoscopy performed 6 weeks after therapy, or by the resolution of dyspepsia, with a normal hematocrit and negative result for fecal occult blood after 2 and 6 months of follow-up.

Statistical analysis

The differences between patients with DU and GU were assessed by the χ^2 or independent *t* test for nominal or continuous variables, respectively. One-way analysis of variance with least significant difference correction was used to analyze parametric differences between patient groups. The Mann–Whitney and Kruskal–Wallis tests were used to analyze the statistical significance of non-parametric data of inflammatory scores between groups. A value of $p < 0.05$ was considered as significant.

Results

Prevalence and characteristics of PUD in children

During a 10-year period, PUD was diagnosed by endoscopy in 67 (5.4%) out of 1234 children with upper gastrointestinal symptoms. The median age was 11.4 years (range, 1.5–18.0 years) and the male to female ratio was 2.5 (48 boys and 19 girls). Endoscopy revealed 40 cases (59.7%) of DUs and 27 cases (40.3%) of GUs. Eleven (16.5%) children had a history of taking ulcerogenic drugs (1 involving aspirin, and 10 involving NSAIDs) 1 week before the onset of gastrointestinal symptoms. Thirty-two (47.7%) of the 67 peptic ulcers were diagnosed as primary *H. pylori* infection. The others (35.8%) were non-*H. pylori*, non-NSAID PUD. A positive family history of PUD was found in 11 (16.4%) children. The most common presentation of the patients was acute or chronic abdominal pain (80.6%), followed by upper gastrointestinal bleeding (64.2%), anemia defined as hemoglobin level < 11 g/dL (43.3%), and vomiting (41.8%).

Endoscopic features of children with DUs and GUs

Among 40 children with DUs, 29 had *H. pylori* infection. A characteristic endoscopic feature of antral nodularity was found more frequently in *H. pylori*-infected DU patients than in non-infected ones (87.5% *vs.* 2.6%, $p < 0.001$). In addition, three children with GU and *H. pylori* infection had coexisting antral nodularity. Among 11 children with GU and prior ulcerogenic drug use, nine (81.8%) of them presented with single ($n = 3$) or multiple ($n = 6$) circumferentially ulcerative mucosal lesions over the pre-pyloric region (Figures A and B). In contrast, in three children with GU and *H. pylori* infection, one had a single ulceration of the antrum, and the other two had single ulceration of the corpus.

Different characteristics between H. pylori, NSAID, and non-H. pylori non-NSAID PUD

The Table shows the demographic, clinical and endoscopic features, and histology of children with *H. pylori*-, NSAID-, or non-*H. pylori*, non-NSAID-related PUD. Children with *H. pylori*-related PUD had a significantly higher mean age ($p < 0.001$) and antral chronic inflammation score ($p < 0.001$), higher rate of familial PUD ($p = 0.007$), and greater presence of endoscopic DU ($p < 0.001$) and nodular appearance ($p < 0.001$) than those with NSAID-related and non-*H. pylori*, non-NSAID PUD. In contrast, children with NSAID-related PUD had a higher rate of upper gastrointestinal bleeding ($p = 0.02$), associated with acute febrile disease ($p < 0.001$) and GU ($p < 0.001$), than those with *H. pylori*-related and non-*H. pylori*, non-NSAID PUD. None of the patients had mucosal atrophy in the corpus and intestinal metaplasia in the antrum and corpus.

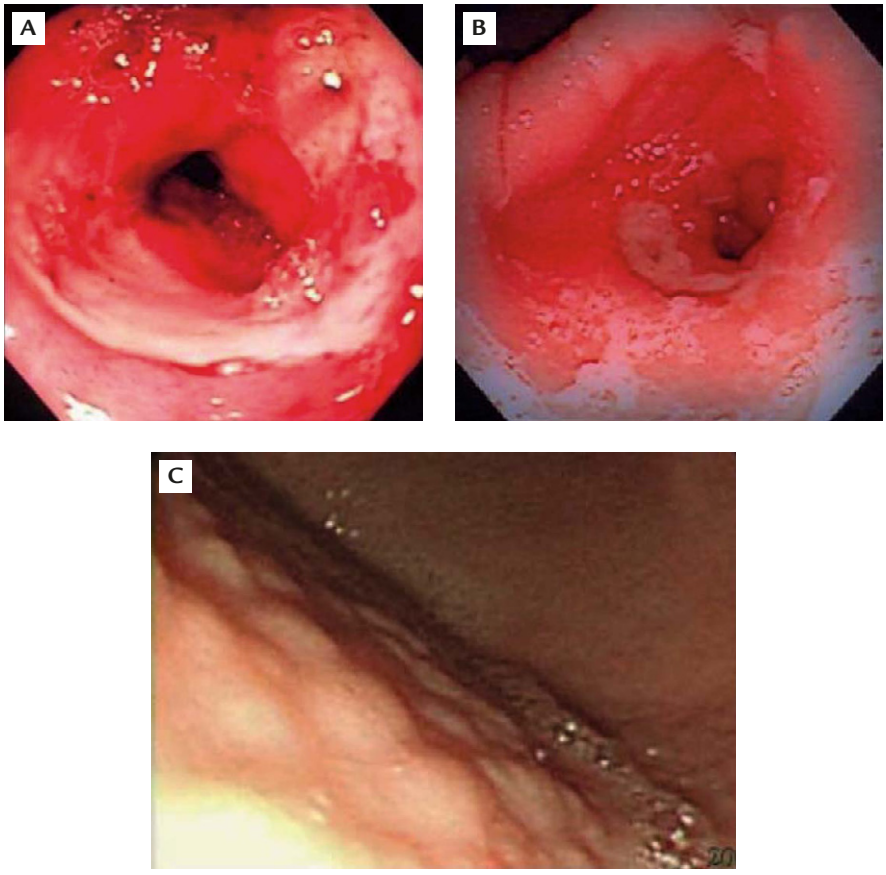

Figure. Children with gastric ulcer and previous ulcerogenic drug use usually presented with (A) large single or (B) multiple circumferentially ulcerative mucosal lesions over the pre-pyloric region. (C) In contrast, children with *Helicobacter pylori*-related duodenal ulcer usually had a characteristic feature of nodular gastritis.

Antimicrobial susceptibility testing and eradication rate of H. pylori

Among 32 children with peptic ulcers and *H. pylori* infection, 21 (65.6%) of them had a positive culture for *H. pylori*. The antimicrobial susceptibility rates of *H. pylori* isolates were 100%, 76.2% and 85.7% for amoxicillin, clarithromycin and metronidazole, by the Etest®, respectively. There was only one strain (4.8%) that showed resistance to clarithromycin and metronidazole. Thirty patients had received eradication therapy and complete follow-up. The per-protocol eradication rate of *H. pylori* in children with peptic ulcer was 86.7%.

Follow-up and outcomes of childhood PUD

During a median of 2.8 years (range, 0.4–9.5 years) of follow-up, all patients showed disease resolution. For *H. pylori*-related PUD, three patients with DU and one with GU failed initial eradication therapy but were disease free after the second course of anti-*H. pylori* treatment. All patients with ulcerogenic drug-related GU were disease free. Two of 13 non-*H. pylori*, non-NSAID-related PUD patients had unhealed ulceration after 8 weeks of PPI treatment, but the ulceration resolved with a subsequent course of PPI.

Discussion

Over the past decade, there have been only a few reports in the literature concerning PUD in children. In our study, PUD was diagnosed in 5.4% of children who underwent upper gastrointestinal endoscopy for various symptoms. The low

Table. Demographic data, clinical manifestations, endoscopic findings, and histology of children with *Helicobacter pylori*-related, NSAID-related, and non-*H. pylori*, non-NSAID peptic ulcer disease (PUD)*

	H. pylori-related PUD ($n=32$)	NSAID-related PUD ($n=11$)	Non-*H. pylori* non-NSAID PUD ($n=24$)	*p*
Demographic data				
Mean age (yr)	13.5	4.5†	8.5†‡	<0.001
Sex, male	22 (68.8)	9 (81.8)	17 (70.8)	0.710
Family history of peptic ulcers	10 (31.3)	0 (0)†	1 (4.2)†	0.007
Clinical manifestations				
Abdominal pain	26 (81.3)	7 (63.6)	21 (87.5)	0.250
Duration of pain < 2 wk	10 (31.3)	4 (36.4)	9 (37.5)	0.780
Upper gastrointestinal bleeding	20 (62.5)‡	11 (100)	12 (50.0)‡	0.020
Anemia (hemoglobin < 10 g/dL)	15/28 (53.6)	4 (36.4)	10/21 (47.6)	0.620
Febrile disease within 1 wk	1 (3.1)‡	8 (72.7)	4 (16.7) †‡	<0.001
Endoscopy and histology				
Duodenal ulcer	29 (90.6)	1 (9.1)†	10 (40.0)†	<0.001
Gastric ulcer	3 (9.4)‡	10 (90.9)	14 (60.0)‡	<0.001
Antral nodularity	28 (87.5)	0 (0)†	1 (4.2)†	<0.001
Antral CIS	2.7	1.4†	1.3†	<0.001
Antral AIS	1.5	0.8	0.2†	0.005

**Data presented as mean or n (%); †p < 0.05 vs. H. pylori-related PUD; ‡p < 0.05 vs. NSAID-related PUD. NSAID = non-steroidal anti-inflammatory drugs; CIS = chronic inflammation score; AIS = acute inflammation score.*

prevalence of PUD was consistent with other reports, which suggests that, even in the era of endoscopy, PUD remains a rare cause of upper gastrointestinal complaint in children.[6,7] However, in our study, a high proportion (64.2%) of children presented with serious upper gastrointestinal hemorrhage. This highlights that childhood PUD is a potential life-threatening disorder, although it rarely occurs.

H. pylori infection is a well-recognized cause of chronic gastritis and plays an important role in the pathogenesis of PUD in adults and children.[2–7] As in the present study, the prevalence of *H. pylori*-related PUD in children has been shown to be lower than in adults.[2,6,7,26–28] The rate of *H. pylori* infection among childhood PUD has been shown to be 33–92% in patients with DU and 20–75% in those with GU.[2,3,6,7,29] However, there was still a strong causal relationship between *H. pylori* and childhood PUD, as compared with a low prevalence (12.3%) of *H. pylori* infection in children aged 13–15 years in Taiwan.[30] In contrast to the chronic NSAID user, we demonstrated that 16.5% of 67 children with PUD had a short course of ulcerogenic drug use for their febrile disease. Non-*H. pylori*, non-NSAID-related childhood PUD was found frequently (35.8%) in our patients, as by other investigators.[19–21] These results imply that factors other than *H. pylori* infection and NSAID use play an important role in childhood PUD.

The endoscopic findings differed between children with PUD of different etiologies. Nodular gastritis of the antrum was found in 90.7% of the 32 patients with *H. pylori*-related PUD (26 DUs and 3 GUs). The characteristic antral nodularity has been reported more frequently in children than in adults with *H. pylori* infection.[31–33] We found a high prevalence (82%) of pre-pylorus circumferential ulceration in ulcerogenic drug users. This suggests that it is a hallmark of acute adverse effects of ulcerogenic drugs (especially NSAIDs) in children.

In contrast to the close relationship between *H. pylori* infection and PUD in adults, *H. pylori*-related

PUD, especially in GUs, was found less frequently in children. Thus, we tried to find other characteristic factors in DU-dominant, *H. pylori*-related PUD and GU-dominant, NSAID-related PUD. As shown in the Table, in addition to the presence of DU ($p<0.001$), older age ($p<0.001$) and a family history of peptic ulcers ($p=0.007$) were significantly more frequent in the children with *H. pylori*-related than NSAID-related PUD.[2,3] Furthermore, previous short-term use of ulcerogenic drugs was related closely to the development of GU. These findings might have been responsible for the higher rate of *H. pylori* infection in DU than in GU patients, and imply that the mechanisms of ulcerogenesis in children taking NSAIDS are indeed different from those in adults with chronic NSAID use.[34]

The purpose of taking NSAIDs in childhood is usually the antipyretic effect rather than the anti-inflammatory effect in adults.[15] This is why childhood GU is correlated highly with the occurrence of febrile disease. However, whether the pathogens of febrile disease have a synergistic effect with NSAIDs to induce ulcer formation is still unknown.

The incidence of non-*H. pylori*, non-NSAID PUD in children has increased around the world.[20,21] However, as in this study, which had a high proportion (50%) of patients with upper gastrointestinal bleeding, Chan et al suggested that biopsy urea test is insufficient to diagnose *H. pylori* infection in patients with bleeding.[35] Xia et al demonstrated that the presence of comorbid diseases and the absence of epigastric pain/discomfort are independent factors for adult non-*H. pylori*, non-NSAID DU.[22] We also showed that the clinical manifestations, and endoscopic and histological findings are really different between childhood non-*H. pylori*, non-NSAID PUD and *H. pylori*- and NSAID-related PUD. The etiology and specific characteristics of childhood non-*H. pylori*, non-NSAID PUD requires further investigation.

H. pylori isolates from children have a high clarithromycin resistant rate, which leads to treatment failure.[25,36,37] In our country, the rates of resistance to clarithromycin and metronidazole have increased compared with a decade ago.[25] This rapid evolution of antimicrobial resistance of *H. pylori* in children has led us to be more conscientious in the treatment of childhood *H. pylori* infection. In the present study, the overall eradication rate of *H. pylori* in children with PUD was 86.7%. This result was superior to that in European studies (79.7%) of PUD patients.[38] Moreover, we did not find that the eradication rate was superior in children with clarithromycin-based triple therapy according to the antibiotic susceptibility test for *H. pylori* isolates than in culture-negative patients with the same regimen ($p>0.05$). The cost–benefit of endoscopic antibiotic susceptibility testing for *H. pylori* eradication needs a larger-scale study.

In conclusion, we demonstrated that PUD is an uncommon disorder in children. The etiology, clinical characteristics, and histopathology were different between *H.pylori*-, NSAID-, and non-*H.pylori*, non-NSAID-related PUD in children. In addition to *H. pylori* infection and ulcerogenic drugs, unknown factors are also important in childhood PUD. Therefore, proper and efficient diagnosis and treatment protocols should be adopted for *H. pylori* eradication and long-term ulcer healing.

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