

PEPTİK ÜLSERLİ ÇOCUK HASTALARIN DEĞERLENDİRİLMESİ: TEK MERKEZ DENEYİMİ

EVALUATION OF CHILD PATIENTS WITH PEPTIC ULCER: A SINGLE CENTER EXPERIENCE

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ÖZET

AMAÇ: Çocukluk çağında peptik ülser sıklığı ve Helicobacter pylori (Hp) dışındaki risk faktörleri ile ilgili veriler yetersizdir. Bu çalışmanın amacı çocuklarda gastroduodenal ülser sıklığını, klinik bulgularını, risk faktörlerini ve komplikasyonları belirlemektir.

GEREÇ VE YÖNTEM: Merkezimizde Mayıs 2011 - Aralık 2018 tarihleri arasında özofagogastroduodenoskopi yapılan çocukların endoskopi raporları ve dosya bilgileri geriye dönük olarak incelendi.

BULGULAR: İncelenen 5892 pediyatrik hastanın 448'inde (%7,6) peptik ülser vardı. Değerlendirilen ülselerin %69'u duodenal, %27,4'ü gastrik ve %3,6'sı hem gastrik hem de duodenal ülser idi. En sık (%52,2) semptom dispepsi idi. Peptik ülselerde en sık risk faktörü Hp (%66,5) idi. Nonsteroid antiinflamatuar ilaçlar ikinci en yaygın (%5,8) risk faktörü olarak bulundu. Vakaların %14,95'inde herhangi bir risk faktörü gösterilememiştir. Hastaların 70'inde (%15,7) peptik ülser hastalığına sekonder komplikasyonlar saptandı. Komplikasyon 50 (%12,7) hastada kanama, 11 (%2,4) hastada gastrik çıkış obstrüksiyonu ve 2 (%0,4) hastada perforasyon idi.

SONUÇ: Helicobacter pylori enfeksiyonu çocuklarda peptik ülser için en önemli risk faktörüdür. Ancak Hp'nin gösterilemediği durumlarda diğer risk faktörleri araştırılmalıdır.

ANAHTAR KELİMELELER: Peptik ülser hastalığı, Helicobacter pylori, epidemiyoloji, Risk faktörleri, Komplikasyon

ABSTRACT

OBJECTIVE: Data on the incidence of peptic ulcer in childhood and risk factors other than Helicobacter pylori (Hp) are insufficient. The aim of this study is to determine the frequency, clinical findings, risk factors and complications of gastroduodenal ulcer in children.

MATERIAL AND METHODS: The endoscopy reports and file information of the children who underwent esophagogastroduodenoscopy in our center between May 2011 and December 2018 were reviewed retrospectively.

RESULTS: Of the 5892 pediatric patients examined, 448 (7.6%) had peptic ulcers. Of the ulcers evaluated, 69% were duodenal, 27.4% were gastric, and 3.6% were both gastric and duodenal ulcers. The most common (52.2%) symptom was dyspepsia. The most common risk factor in peptic ulcers was Hp (66.5%). Nonsteroidal anti-inflammatory drugs were found to be the second most common (5.8%) risk factor. No risk factor could be demonstrated in 14.95% of the cases. Complications secondary to peptic ulcer disease were detected in 70 (15.7%) of the patients. The complications were; bleeding in 50 (12.7%) patients, gastric outlet obstruction in 11 (2.4%) patients, and perforation in 2 (0.4%) patients.

CONCLUSIONS: Helicobacter pylori infection is the most important risk factor for peptic ulcer in children. However, in cases where Hp cannot be demonstrated, other risk factors should be investigated.

KEYWORDS: Peptic ulcer disease, Helicobacter pylori, Epidemiology, Risk factors, Complication

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INTRODUCTION

Peptic ulcer disease (PUD) is less common in children than in adults. However, peptic ulcer (PU) can cause life-threatening complications such as bleeding, gastric outlet obstruction (GOO) and perforation (1 - 4). The causal relationship between PU and *Helicobacter pylori* (Hp) was first revealed by Warren and Marshall (5). It has been the most common risk factor for PUD in both adults and children (1). In recent years, the frequency of Hp infection has been decreasing in both adults and children, related to the improvement of sanitation conditions and the increase in diagnosis and treatment possibilities. Therefore, a relative increase in the frequency of Hp-negative PUD is observed. Non-Hp risk factors for PUD are also gaining importance (6 - 9). In this study, the frequency, risk factors and complications of PUD in children and adolescents who underwent diagnostic upper gastrointestinal endoscopy (UGE) were evaluated.

MATERIALS AND METHODS

Children and adolescents with gastrointestinal (GI) symptoms or non-gastrointestinal symptoms who underwent diagnostic UGE at our center between May 2011 and December 2018 were included in our study. 5892 patients under the age of 18 who underwent UGE were evaluated retrospectively. File records and endoscopy findings of the patients were reviewed. 448 patients with PU were included in the study. Age, gender, indication for endoscopy, presence of acute critical illness and chronic disease, history of gastrototoxic drug use, presence of systemic disease, family history of PUD, and cases with endoscopic findings and recurrence were recorded.

Cases diagnosed with Hp infection by histopathological examination of upper gastrointestinal endoscopic biopsy materials were included in the Hp positive group.

Ethical Committee

Ethics committee approval and official permission were obtained from Health Sciences University Keçiören Training and Research Hospital Clinical Research Ethics Committee (2012-

KAEK-15/1993) and Health Sciences University Dr. Sami Ulus Obstetrics, Gynecology and Child Health and Diseases Training and Research Hospital the Medical Specialization Education Board, respectively.

Statistical Analysis

The analysis of the data obtained from the study group was performed using the Statistical Package for the Social Sciences (SPSS) statistical package program (Version 16.0; SPSS, Inc., Chicago, IL, USA). The data obtained with the measurement were expressed as mean \pm standard deviation, median (interquartile range, and grouped data as number (percentage). The conformity of the data to the normal distribution was determined by the Kolmogorov Smirnov test. Student t-test was used to compare the normal distribution of quantitative data between two groups. The Mann-Whitney U test was used for the comparisons between two groups of the variables that did not show normal distribution.

RESULTS

The mean age of 448 patients included in the study was 11.72 ± 4.6 years. Number of male and female patients were 221 (49.3%) and 227 (50.7%), respectively.

The reasons for performing an endoscopic examination in our 448 patients with PU were dyspeptic complaints (epigastric pain, burning, discomfort, GI fullness, early satiety, bloating, belching, nausea and vomiting) in 234 (52.2%) patients, abdominal pain in 65 (14.5%) patients, hematemesis/melena in 55 (12.3%) patients and vomiting in 49 (10.9%) patients. The other causes of endoscopic examination in 45 patients with PU but without GI symptoms included failure to thrive in 17 patients (3.8%), suspected celiac disease (CD) in 7 patients (1.7%), ingestion of corrosive substances in 6 patients (1.3%), suspected inflammatory bowel disease (IBD) in 6 patients (1.3%), investigation of anemia etiology in 5 patients (1.1%), and screening for varicose veins and gastropathy caused by portal hypertension (PHT) in 4 patients (0.9%).

A family history of ulcers was positive in 17 (3.8%) of the patients in their first-degree relatives. Ulcers were duodenal in 309 patients

(69.0%), gastric in 123 patients (27.5%), and both gastric and duodenal in 16 patients (3.6%). Demographic characteristics of PU patients are presented in **Table 1**.

Table 1: Demographic characteristics of peptic ulcer patients

Variations	n: 448 (%)
Gender	
Male	221 (49.3%)
Female	227 (50.7%)
Age distribution (years)	
0-4 years	39 (8.7%)
5-8 years	54 (12.1%)
9-12 years	121 (27%)
13-17 years	234 (52.2%)
Indication for UGE	
Dyspepsia	234 (52.2%)
Abdominal pain	65 (14.5%)
Hematemesis/melena	55 (12.3%)
Vomiting	49 (10.9%)
Failure to thrive	17 (3.8%)
Suspected celiac disease	7 (1.7%)
Ingestion of corrosive substance	6 (1.3%)
Suspected inflammatory bowel disease	6 (1.3%)
Investigation of anemia etiology	5 (1.1%)
Screening of varicose veins and gastropathy in patients with portal hypertension	4 (0.9%)
Ulcer localization	
Duodenal	309 (69%)
Gastric	123 (27.4%)
Gastric+Duodenal	16 (3.6%)
Hp status	
Hp (+)	298 (66.5%)
Hp (-)	150 (33.5%)
Family history of PU	
Positive	17 (3.8%)
Negative	431 (96.2%)
PU Recurrence	
Positive	6 (1.3%)
Negative	442 (98.7%)
Complication	
Positive	70 (15.6%)
Negative	378 (84.4%)

Hp: Helicobacter pylori; PU: Peptic Ulcer; UGE: Upper gastrointestinal endoscopy

Helicobacter pylori was positive in 298 (66.5%) cases and negative in 150 (33.5%) cases. While the age group with the highest Hp positivity (56.4%) was the 13-17 years old period, Hp positivity was the lowest (6.0%) in the 0-4 age group ($p=0.001$). The male/female ratio for Hp positivity was 70.6% / 62.6% ($p=0.044$).

When the relationship between ulcer location and Hp infection was evaluated, Hp positivity in duodenal ulcer (DU), gastric ulcer (GU) and both gastric and duodenal was 72.8%, 23.8%, 3.4%, respectively ($p=0.043$).

The incidence of PU risk factors in patients was Hp infection ($n=298$, 66.5%), non-steroidal anti-inflammatory drugs (NSAID) ($n=26$, 5.8%), percutaneous endoscopic gastrostomy (PEG) ($n=15$, 3.3%), CD ($n=9$, 2%), acute critical illness ($n=9$, 2%), IBD ($n=6$, 1.3%), corrosive substances ($n=5$, 1.1%), portal hypertensive gastropathy ($n=4$, 0.9%), corticosteroids ($n=3$, 0.6%), eosinophilic gastroenteritis ($n=2$, 0.4%), acute cytomegalovirus (CMV) infection ($n=1$, 0.2%), trichobezoar ($n=1$, 0.2%) and Henoch Schönlein Purpura (HSP) ($n=1$, 0.2%), respectively.

Fifteen patients with ulcers had a history of both Hp infection and NSAID use. Cases with a history of NSAID use were using NSAID for acute febrile disease. None of them had a history of chronic NSAID use. There was no significant difference in the presence of GI bleeding between patients with a history of NSAID use ($n=26$), co-infection with Hp ($n=15$) and patients with Hp negative ($n=9$) ($p=0.4$).

In 68 of the cases (15.2%), a risk factor for PUD could not be demonstrated. Twenty-eight of the patients had a history of using antibiotics for different indications in the last month. Thirty-two patients had a history of proton pump inhibitor (PPI) use. Nineteen (65%) of the patients using antibiotics and 24 (75%) of those using PPI were in the group with no risk factors. Ulcer recurrence was detected in six (1.3%) of the patients during the follow-up. Of the patients with ulcer recurrence, 4 (66.7%) of them were located in the duodenal region and 2 of them (33.3%) were located in the gastric region. There was no significant relationship between ulcer localization and recurrence ($p=0.861$). Hp was positive in 5 (83.3%) of the relapsed cases and negative in one (16.7%). There was no significant relationship between Hp infection and ulcer recurrence ($p=0.659$).

Complications related to PUD were detected in 70 (15.7%) of the patients. Complications were bleeding in 50 (12.7%), GOO in 11 (2.4%) and perforation in 2 (0.4%) patients. When the distribution of complications according to age was examined, it was determined that 46.2% of them were under the age of five ($p=0.00$). In the presence of complications according to localization, more complications were observed in GU ($p=0.001$).

Complications were more common in Hp-negative cases than in Hp-positive cases, and in boys than in girls. One of the two cases who developed perforation was Hp positive and the other Hp negative, and they were diagnosed with CD and both were adolescents. Five of the patients with GOO were Hp positive, two were patients with PEG, and one was diagnosed with eosinophilic gastroenteritis. Corrosive ingestion was present in one patient. The characteristics of patients according to the Hp status are given in **Table 2**.

Table 2: Characteristics of *Helicobacter pylori* positive and negative peptic ulcer patients

	Hp (+)	Hp (-)	p-values
Age range (years)			
0-4 years	18(6.0%)	21(14%)	p=0.001
5-7 years	27(9.1%)	27(18%)	p=0.001
9-12 years	85(28.5%)	36(24%)	p=0.001
13-17 years	168(56.4%)	66(44%)	p=0.001
Gender			
Female	142(47.7%)	85(56.7%)	p= 0.044
Male	156(52.3%)	65(43.3%)	p= 0.044
Ulcer localization			p=0.043
Duodenal	217(72.8%)	92(61.3%)	
Gastric	71(23.8%)	52(34.7%)	
Gastric + duodenal	10(3.4%)	6(4.0%)	
Complication			p=0.006
Positive	36(12.1%)	34(22.7%)	
Negative	262(87.9%)	116(77.3%)	
Relapse			p=0.669
Positive	5(1.7%)	1(0.7%)	
Negative	293(98.3%)	149(99.3%)	
Family history			p=0.196
Positive	14(4.7%)	3(2%)	
Negative	284(95.3%)	147(98%)	

Hp: *Helicobacter pylori*

Risk factors and ulcer localization in Hp negative cases are shown in **Table 3**, and characteristics of patients according to the presence of complications are shown in **Table 4**. Control endoscopic examination was performed in 398 patients.

Table 3: Risk factors and ulcer localization in *Helicobacter pylori* negative cases

Risk factors	Gastric ulcer (n)	Duodenal ulcer (n)	Gastric+Duodenal ulcer (n)
NSAID	14	6	6
Gastrostomy	12	3	0
Acute critical disease	6	2	1
Celiac disease	1	6	2
Crohn disease	0	1	5
Corrosive substance	4	0	1
Portal hypertensive gastropathy	3	0	1
Corticosteroid usage	3	0	0
Eosinophilic gastroenteritis	1	0	1
Acute CMV infection	1	0	0
HSP	0	0	1
Trichobezoar	1	0	0
TOTAL	46	18	18

NSAID: Nonsteroidal anti-inflammatory drugs, CMV: Cytomegalovirus, HSP: Henoch Shoenlein purpura

Table 4: Characteristics of peptic ulcer patients by presence of complications

	Complication negative n (%)	Complication positive n (%)	Total n	p-values
Gender				
Male	173 (78.3%)	48 (21.7%)	221	p=0.001
Female	205 (90.3%)	22 (9.7%)	227	
Age range (year)				p=0.000
0-4 year	21 (53.8%)	18 (46.2%)	39	
5-7 year	41 (75.9%)	13 (24.1%)	54	
9-12 year	109 (90.1%)	12 (9.9%)	121	
13-17 year	207 (88.5%)	27 (11.5%)	234	
Ulcer localization				p=0.001
Duodenal	274 (88.7%)	35 (11.3%)	309	
Gastric	92 (74.8%)	31 (25.2%)	123	
Gastric + duodenal	12 (75.0%)	4 (25.0%)	16	

DISCUSSION

This study is one of the largest series of PUD reported in children and adolescents in a single center. In studies reported from different geographical regions of the world, the frequency of PUD in children is 1.8-33.1% (10-14). In studies conducted in our country, the frequency of PUD was reported between 0.98-13.2% (15-20). In our study, the frequency of PUD was found 7.6% in children, and it is similar to the literature. It was thought that geographical differences, ethnic elements, environmental factors, diversity in the age groups of cases and endoscopy indications were effective in finding quite different results regarding the frequency of peptic ulcers in childhood. We think that another important reason is that the prevalence of Hp infection, which is still the most common risk factor in PUD, varies according to region and living conditions. One of the most striking examples of this situation (10) is the multicenter study in which European countries participated. In this study, the prevalence of peptic disease was reported in a wide range of 0-22%. In our study, apart from patients with GI symptoms, patients who were diagnosed with PUD after a diagnostic UGE for different systemic diseases were also evaluated. In this way, the importance of non-Hp risk factors in the etiopathogenesis of PUD has been evaluated.

In our study, 79.2% of the PUD detected were aged eight years and over. Other studies have reported that the incidence of PUD in children increases with age (10, 12 - 14, 16, 18 - 20). This was thought to be related to higher rates of Hp infection, which is the risk factor for PUD, most common in older children and adolescents (21).

In our study, the incidence of PUD was not different for both genders. There are different results in the literature on this subject. Although there are studies that detect the incidence of PUD in males (12 - 14, 16, 20) more, there are also studies reporting that there is no difference (1, 11, 15). When the localizations were evaluated in our study, it was seen that most of the ulcers (69.0%) were located in the duodenum. In the

literature, studies in which the frequency of DU is higher than GU in children are the majority (9, 13, 15, 18, 20). It was thought that this situation was the result of the duodenal localization of the majority of ulcers with Hp positivity. However, although the major risk factor was Hp in the studies of Egbaria et al. (11) and Ecevit et al. (16), the majority of ulcers were located in the stomach.

Inflammation caused by Hp in PUD is currently the most important and frequently encountered risk factor in the world (22, 23). In studies reported from different geographical and ethnic groups, the prevalence of Hp infection in children varies according to age and living conditions of the communities in which they live. In a meta-analysis, the data of forty-five different studies were evaluated; 95% Hp positivity was reported in DU and 25% in GU (23). In the following years, Hp positivity was shown with a frequency of 20-77.4% in pediatric PUD in studies conducted from different geographical and socio-cultural regions of the world (7 - 14). In our study group, Hp positivity was found in total cases, DU and GU cases were %66.5, 70.2% and 57.7%, respectively. In studies reported in our country, 20%-85.2%, of Hp positivity was reported in children (15, 16, 18, 19). The common feature of the reported studies is that Hp positivity is lower in developed countries than in developing countries, except for Japan. At the same time, although there has been a decrease in Hp positivity in PUD in children over the years, the results of our study have been found to be similar to those in developing countries and our country. Our hospital is generally a center that cares for people of low socioeconomic status in the Central Anatolia region. The higher Hp positivity in the patients included in our study suggested that it was related to the poorer living conditions of the patients.

In societies where socioeconomic conditions are insufficient, inadequate sanitation conditions and crowded family environments facilitate Hp transmission in children at an early age and positivity continues unless treated (24, 25). In our study, when the distribution of Hp infection by age groups is examined, it is seen that Hp positivity increases significantly with age

($p=0.001$). In a study conducted in our country, Hp positivity was low under 2 years of age, while a significant increase with age was reported in others (26). While the prevalence of Hp infection has decreased in children as in adults, NSAID and other gastrototoxic pharmacological agents, systemic diseases and idiopathic cases have attracted attention (7, 9, 10, 11 - 13, 27, 28). Helicobacter pylori infection still maintains its importance as a risk factor in PUD performed in our country (16, 18, 19) However, in Yaman et al's (8) study, a decrease in the prevalence of Hp in children in our country was reported in the last two decades. In our study, NSAID (15.2%) was the highest risk factor in the Hp infection-negative group. Egbaria et al. (11), Shu-Huang et al. (12), Kalach et al. (10) reported that 17.5%, 16.5%, and 14.3% of Hp negative PUD cases had history of NSAID use, respectively. Elitsur (9) did not find significance in a history of NSAID usage among the risk factors in PUD cases in children. NSAID, is frequently used in children and adults for its antipyretic, analgesic and less frequently anti-inflammatory effects. (27, 29). Although GI tract side effects +related to the use of NSAID are generally associated with the dose and duration of use, short-term use of antipyretics may also pose a risk (2). In our study, the use of NSAID was antipyretic, with a short-term purpose. These results are remarkable for the careful use of NSAIDs to prevent childhood PUD and its complications.

Today, the frequency of PUD, associated with non-Hp and non-NSAID risk factors, is increasing (1, 7). In our study, the frequency of PUD associated with non-Hp and non-NSAID risk factors was found to be 12.5%. Systemic diseases (CD;IBD;HSP), PHT; Infections, drugs, corrosive substances, acute critical illness, and PEG-related mucosal trauma were other risk factors identified for PUD. This situation demonstrates the importance of close monitoring of symptoms and not delaying endoscopic examinations in children in the risk group for PUD for early diagnosis and prevention of complications. In our study, there was no detectable risk factor in 15.2% of PUD. Studies describing Hp-negative PUD in children are limited. However, an increasing number of studies that draw attention to Hp-negative and idiopathic PUD are repor-

ted (7, 9, 11, 12). For the definition of idiopathic PUD, possible risk factors for PUD should be excluded, drug use history should be questioned, and Hp should be excluded with at least two different diagnostic tests (30). In our study, endoscopic biopsy samples were examined to show the presence of Hp, but at least one of the diagnostic tests such as urease and Hp antigen in the stool could not be studied in all patients. Another remarkable point is that a significant portion of our patients had a history of PPI use before they applied to our hospital, which is a tertiary center. For these reasons, we think that the presence of Hp could not be definitively excluded in cases where no risk factors were found in our study. This is an important shortcoming of this study.

It has been reported that recurrence is more common in idiopathic PUD in adult studies (31-33). Similarly, in the study of Tam et al. (13), it was reported that recurrence was higher in Hp-negative idiopathic PUD in children than in Hp-positive PUD. In our study, there was no difference in the frequency of ulcer recurrence between Hp positive, Hp negative and idiopathic patients. This situation was associated with the presence of treatable systemic diseases and gastrotoxic drug use in the majority of Hp negative group cases.

Although complications of PUD in childhood are not as common as in adults, serious life-threatening complications can be encountered (2-4, 34). In our study, bleeding, GOO and perforation were the complications found. In our study, the risk of complications increased inversely with the age of the patient. The group under the age of five had the highest risk of complications ($p < 0.000$). The incidence of complications was found to be higher in Hp-negative cases than in Hp-positive cases ($p = 0.006$). This situation can be related to the higher rate of Hp negativity in younger ages, as well as the presence of severe systemic diseases, NSAID use, stress-related and idiopathic ulcers in the Hp-negative group. Another factor that increased the risk of complications was the location of the ulcer. Complication risk was increased in patients with gastric localization and both gastric and duodenal localizations ($p = 0.001$).

When the frequency of complications encountered in our study was evaluated, bleeding was the most encountered complication with a frequency of 12.7%. Gastric outlet obstruction (2.2%) and perforation (0.7%) were the complications we encountered less frequently. Although peptic ulcer bleeding is not a common finding in children, it is among the common causes of upper GI bleeding (35, 36). In other studies, the frequency of bleeding in childhood PUD has been reported in a wide range from 2.4% to 64.2% (2, 11, 14).

There was no significant difference in the presence of GI bleeding between those who used NSAID and Hp infection together (3.3%) and those who only used NSAID (2.25%) ($p = 0.42$). In the study of Huang et al. (12) the group using NSAID and groups with Hp positive and non-Hp, Non-NSAID were compared, and more bleeding was observed in the group using NSAID, and there was no case in which both risk factors were found together. The importance of Hp eradication in NSAID-induced hemorrhages has been emphasized (37). In our cases, the fact that Hp positivity and NSAID use were not found to be significant for the increased risk of bleeding together raises the question of whether acute febrile disease or short-term use of NSAID does not constitute a risk factor. To answer this question, we think that more cases should be investigated.

Another complication we have identified is GOO. One of the most common benign causes of GOO, which has many causes, is PUD (38). Gastric outlet obstruction is found in less than 5% of peptic ulcers (39). The number of studies reporting the frequency of GOO in childhood PUD is low (7, 14). In our study, the frequency of GOO was found to be 2.2%, while Joo et al. (7) reported a frequency of 1.6% and Ankouane et al. (14) 13%. In our cases, most of them had duodenal stenosis that resolved with medical treatment, and one case had GOO that improved after surgical dilation, and it was thought that it did not adversely affect the prognosis. Although perforated peptic ulcer is a serious complication with high mortality, it is rarely seen in children (3, 40). Perforated peptic ulcer in 52 cases in a 20-year period from a single-center was

reported in Taiwan (3). In our study, perforation was reported with a frequency of 0.4%, and it provided treatment without sequelae and mortality with surgical treatment. Endoscopy is contraindicated in patients with suspected perforation. In our study, patients with perforation were referred to our department after surgical treatment, and ulcers and ulcer scars were detected in the endoscopic examination performed during their follow-up.

Our study had some limitations. The most important limitations of the study are its retrospective nature and the fact that most of the patients received PPI or antibiotic treatment before. This may have caused the Hp negative PU group to be detected higher than it actually is.

Helicobacter pylori infection is still the most common risk factor in childhood PU in our country. However, PUD may develop secondary to many systemic diseases in childhood. For this reason, other risk factors should be investigated in the cases with PUD and no Hp in the etiology. Typical GI symptoms are not always present in PUD in childhood, especially at younger ages, and the risk of complications is high. Therefore, it is important to be careful when determining the indications and timing of diagnostic UGE. Complications of PU are more common in younger ages and Hp-negative cases pose a higher risk for the presence of complications.

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