ORIGINAL ARTICLE OPEN ACCESS

Factors Associated With Decision to Treat or Not to Treat *Helicobacter pylori* Infection in Children: Data From the EuroPedHp Registry

Thu Giang Le Thi[1] | Katharina Werkstetter[1] | Kallirroi Kotilea[2] | Patrick Bontems[2] | José Cabral[3] | Maria Luz Cilleruelo[4] | Michal Kori[5,6] | Josefa Barrio[7] | Matjaž Homan[8] | Nicolas Kalach[9] | Rosa Lima[10] | Marta Tavares[10] | Pedro Urruzuno[11] | Zrinjka Misak[12] | Vaidotas Urbonas[13] | Sibylle Koletzko[1,14] | for the *Helicobacter pylori* Special Interest Group of ESPGHAN

[1]Department of Pediatrics, Dr. von Hauner Children's Hospital, LMU University Hospital Munich, München, Germany | [2]Université Libre de Bruxelles, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium | [3]Child and Adolescent Centre, CUF Tejo Hospital, Lisbon, Portugal | [4]Pediatrics Department, Gastroenterology Unit, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain | [5]Pediatric Gastroenterology, Kaplan Medical Centre, Rehovot, Israel | [6]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel | [7]Pediatrics Department, Gastroenterology Unit, University Hospital de Fuenlabrada, Fuenlabrada, Madrid, Spain | [8]Department of Gastroenterology, Hepatology, and Nutrition, University Children's Hospital, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia | [9]Saint Antoine Pediatric Clinic, Saint Vincent de Paul Hospital, Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), Catholic University, Lille, France | [10]Division of Pediatrics, Pediatric Gastroenterology Department, Centro Materno Infantil do Norte, ICBAS–Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal | [11]Pediatric Gastroenterology Unit, Hospital 12 de Octubre, Madrid, Spain | [12]Referral Centre for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia | [13]Clinic of Children's Diseases of Vilnius University Faculty of Medicine, Vilnius, Lithuania | [14]Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland

Correspondence: Sibylle Koletzko (sibylle.koletzko@med.uni-muenchen.de)

ABSTRACT

Background: European and North-American guidelines on management of *H. pylori* infection in children provide the option not to treat even if the infection is endoscopically confirmed. We used data from the EuroPed*Hp* Registry to identify factors associated with therapy decisions.

Methods: We included treatment-naïve patients reported between 2017 and 2020 from 30 centers in 17 European countries. Multivariable logistic regression identified factors including comorbidities within and outside the gastrointestinal (GI) tract influencing the decision for or against therapy.

Results: Of 1165 patients (52% females, median age 12.8), 28% (321/1165) reported any alarm symptom, 26% (307/1165) comorbidities, and 16% (192/1165) did not receive eradication treatment. Therapy was initiated less often in children having any GI comorbidity (57%, $n = 181$), particularly in those with eosinophilic esophagitis (60%, $n = 35$), inflammatory bowel disease (54%, $n = 28$), and celiac disease (43%, $n = 58$), compared to those with non-GI (86%, $n = 126$) or no comorbidity (89%, $n = 858$), despite similar frequencies of alarm and non-alarm symptoms, ulcers, erosions, and nodular gastritis. Patients with GI and without comorbidities remained more likely untreated in high versus low *H. pylori* prevalence countries ($p < 0.0001$). In children without comorbidities, factors favoring therapy included older age, being overweight, having symptoms, erosions, antral nodularity, and available antibiotic susceptibility results.

Conclusion: In this cohort, *H. pylori*-infected children with GI comorbidities compared to no comorbidity showed 75% reduced chance of receiving eradication therapy. We found no evidence supporting different management strategies in infected patients with GI comorbidities compared to all pediatric patients with endoscopically proven *H. pylori* infection.

1 | Introduction

Helicobacter pylori (*H. pylori*) infection is a bacterial infection of the stomach that causes chronic gastritis and affects half of the world population [1, 2]. It is predominantly acquired in early childhood and can present with or without symptoms [3, 4]. A recent meta-analysis including 75 studies with available histopathology of gastric biopsies from 5999 *H. pylori*-infected versus 17,782 non-infected children and adolescents showed that the infection was associated with significantly higher chronic and active inflammation, lymphoid follicles and gastric mucosal atrophy in the antrum and corpus, and a higher risk for intestinal metaplasia in the antrum [5]. Spontaneous eradication unlikely occurs without treatment, and reinfection is rare in Western countries [6, 7]. Infection with *H. pylori* increases the risk of gastric and duodenal peptic ulcer disease (PUD) [8], and at a later age for gastric adenocarcinoma [9] and marginal zone B-cell lymphoma (MALT lymphoma) [2, 10, 11]. *H. pylori* infection was classified as a class I carcinogen by the World Health Organization and as an infectious disease by the Kyoto consensus [12]. However, the vast majority of patients with *H. pylori* infection do not experience significant complications [10].

In adults, eradication of H. pylori infection has been proven to improve dyspeptic symptoms, gastric inflammation, heal gastritis, cure PUD, and reduce the risk of gastric cancer [10, 13]. Current guidelines for adults recommend to treat all infected patients with dyspepsia, even in the absence of peptic or premalignant lesions [14]. The most recent guidelines from Germany, a low prevalence country, state that "a positive test result for *H. pylori* Infection in adults implies an indication for treatment." [15] In contrast, pediatric management guidelines by ESPGHAN/NASPGHAN provide the option not to treat the infection in the absence of gastroduodenal ulcers or erosions or in pediatric patients in which the infection is an incidental finding at endoscopy [16, 17]. In these cases, the pros and cons of therapy should be carefully discussed with patients and parents. The rationale is that there is no evidence that infected children without ulcers or erosions benefit from eradication therapy in resolving their abdominal complaints [16]. Abdominal pain is not more frequent in infected children compared to non-infected children of the same age and region [18]. Compared to adults, the complication rate of *H. pylori* infection in children is much lower. In children undergoing endoscopy because of symptoms, PUD was reported in only 5% to 7.5% [19–21]. Gastric adenocarcinoma in pediatric patients is extremely rare, and cases were not related to *H. pylori* infection [17, 22]. Additional arguments not to treat the infection in young children but to defer eradication therapy to adulthood come from epidemiological studies and animal models [23, 24]. They suggest that *H. pylori* infection early in life may be beneficial by decreasing the risk of developing immune-mediated disorders [25]. Meta-analyses showed an inverse relation between childhood onset asthma and allergy [26], inflammatory bowel disease (IBD) [27], eosinophilic esophagitis (EoE) [28], and celiac disease (CeD) [29, 30]. On the contrary, gastrointestinal (GI) diseases like IBD, eosinophilic GI disorders (EGID), and CeD have an increased risk for gastric or duodenal lesions ranging from superficial erosions to deep ulcerations with a risk of perforation [31–34]. Comorbidities harboring an increased risk of peptic lesions or later complications due to the disease itself or due therapy with certain drugs may be one supporting factor to favor anti-*H. pylori* therapy in affected patients, even with *H. pylori* infection being an incidental finding during diagnostic endoscopy.

We retrieved data from the EuroPed*Hp* Registry from 2017 to 2020 to identify treatment-naïve *H. pylori*-infected children with and without comorbidities, including gastrointestinal (GI) and non-GI comorbidities, to identify factors associated with decisions to treat *H. pylori* infection or not, and to evaluate eradication success once therapy was prescribed.

2 | Methods

The EuroPed*Hp* Registry was initiated by the Working group of *Helicobacter pylori* infection of ESPGHAN to study antibiotic susceptibility results and the effectiveness of different treatment strategies in pediatric patients infected with *H. pylori* [21]. For this analysis, we included all patients with endoscopically confirmed *H. pylori* infection reported in the Registry between 2017 and 2020, who were treatment-naïve, defined as confirmation of having never been treated for *H. pylori* infection, diagnosed comorbidities, endoscopic findings, *H. pylori*-related symptoms, and treatment decisions.

Clinicians submitted anonymized data on patients' characteristics including age, gender, body weight, height, country of living, gastrointestinal symptoms, current co-medications, and primary indication for endoscopy. Alarm signs and symptoms were defined as anemia, GI-bleeding, weight loss, chronic diarrhea, dysphagia, recurrent vomiting indicating endoscopy, and a family history of CeD [35]. Non-alarm symptoms included abdominal pains, dyspeptic symptoms, nausea, bloating, and constipation.

Macroscopic findings were separately reported in the esophagus, stomach, and duodenum, either as normal or abnormal, specifying the abnormalities found. We categorized macroscopic findings as (i) any abnormal findings, including suspected EoE, ulcers, erosions, bleeding, and/or duodenal nodularity, except gastric nodularity; (ii) only gastric nodularity; and (iii) normal. Based on the reported alarm symptoms and macroscopic findings, we considered two scenarios to decide for/against anti-*H. pylori* infection therapy: (i) Any alarm symptom and/or any macroscopic abnormal findings, except gastric nodularity; (ii)

No alarm symptom, normal macroscopic findings, or only gastric nodularity.

Data on comorbidities were provided by answering the question about the confirmed diagnosis of any underlying disease (yes, no, unknown) and submitting details of confirmed comorbidities by choosing different options given in the questionnaire, including GI disease(s) (EoE, IBD, CeD, and others) and disorders of other organ systems. We categorized patients into three subgroups according to their diagnosed comorbidities:

a. GI comorbidities including IBD, EoE, CeD, and/or other GI disease(s).

b. Non-GI comorbidities encompassing diseases of the liver, heart, lung, kidney, and immune system including autoimmune diseases, malignancy except GI, allergy, genetic, hematologic, metabolic, neurological, psychological disorders, and remaining others.

c. No comorbidity.

Patients with other confirmed comorbidities mentioned in free text were additionally reviewed and categorized. In the group without comorbidities, patients were classified into three subcategories based on their BMI Z-score: (i) underweight/wasting, (ii) normal weight, and (iii) overweight/obese.

Treatment decisions were determined by reviewing the prescribed therapy. Clinicians were asked to give the reasons why patients were not treated, that is, no symptoms, no PUD, patients/care givers refusal, language barrier, or other reasons.

Based on residency and birthplace, we categorized country of living and country of birth into European regions (Northern, Western, Southern, Eastern) and included Israel, Turkey, the Middle East, Asia, Africa, and America (Data S1). Acknowledging variations in *H. pylori* prevalence in the participating countries [36], we stratified our sub-cohorts into high prevalence countries, including Israel, Turkey, and Southern European countries, and low prevalence countries, including countries in Northern, Western, and Eastern Europe. Based on this, we reported the perception of treatment decisions for *H. pylori*-infected children with and without comorbidities.

Eradication rate (ER) was calculated as a percentage (%) of the proportion of all successfully treated patients with a confirmed negative test result after completing treatment (*n*) relative to all patients treated (*N*). To investigate eradication success in patients with and without diagnosed comorbidities, we included only those who received the most common treatments, including PAM (proton-pump inhibitor, amoxicillin, metronidazole), PAC (proton-pump inhibitor, amoxicillin, clarithromycin), or sequential therapy (SEQ), since other therapies for treatment-naïve patients were only a few [21]. According to the most recent guidelines [16], we assessed the eradication success of patients receiving tailored triple therapy with either PAM or PAC with available antibiotic susceptibility, and

patients treated with SEQ if they were infected with fully susceptible strains.

Data of irreversibly anonymized patients were collected in the registry. The protocol of the survey and the questionnaires were approved by the data protection officer and the Ethical Committee of the LMU University Hospital Munich, Germany (project number: 105–13) with a waiver for informed consent of the anonymized patients and their caregiver. Participating centers achieved approval from their local ethical committee. The registry was financially supported by the ESPGHAN and by research funds of Prof. Dr med. Sibylle Koletzko, LMU University Hospital Munich, Germany.

2.1 | Statistical Analysis

Descriptive statistics were used to summarize the patient characteristics. Continuous variables are reported as median (interquartile range from 25th to 75th quartile, IQR), while categorical variables are presented with frequency (*n*) and proportion in percentage (%). To determine statistically significant differences between groups, we performed Mann–Whitney *U*-test for continuous variables, while Pearson's chi-square test, or Fisher's exact test for categorical variables, where appropriate. In case of multiple comparisons, we applied Sidak's correction. All tests were assessed with two-sided significance levels of 5%.

We conducted a multivariable logistic regression analysis to investigate factors associated with treatment decisions against *H. pylori* infection in the entire study population and the three comorbidity subgroups. Based on the characteristics of all patients who were treated or not treated for *H. pylori* infection, all factors associated with a high likelihood of treatment ($p \leq 0.25$) were included in the multivariable logistic regression. Applying backward elimination adjusted for gender, age (years), and country of living, the final logistic regression was presented with no missing in co-variates to determine the factors associated with treatment decision. Estimated odds ratio (OR) and 95% confidence interval (CI) with their respective *p* values obtained from Wald chi-square test are reported.

First, we applied this approach concerning all symptoms reported in the registry independently if they were alarm signs/symptoms or not, as well as peptic gastric or duodenal ulcers and erosions. In the second step, we performed the same approach but included aggregated parameters, such as any alarm signs/symptoms reported and any macroscopic abnormality detected in the esophagus, stomach, or duodenum, excluding the presence of *H. pylori* positive nodular gastritis. This in-depth analysis allows us to observe the likelihood of receiving anti-*H. pylori* therapy in patients who had neither any alarm sign/symptom, nor abnormal endoscopic findings except only gastric nodularity.

Statistical analyses were performed using SAS 9.4 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA) and Prism 10.1.1 (GraphPad Software, Boston, USA).

3 | Results

3.1 | Study Population

From all patients reported to the EuroPed*Hp* registry during the years 2017 until 2020, 1165 *H. pylori*-infected and treatment-naive children and adolescents met the criteria for inclusion (Data S2).

3.2 | Characteristics of *H. pylori*-Infected Patients With and Without Comorbidities

Table 1 presents the characteristics of all included patients and the three subgroups, providing *p* values for comparison. Among 1165 treatment-naive patients, 307 (26%) were diagnosed with comorbidities, including 126 (11%) with non-GI disorders and 181 (15%) with GI comorbidities. Of those with GI comorbidities, 28 patients were diagnosed with IBD, 35 with EoE, 58 with CeD, and 60 with other GI diseases (e.g., gastroesophageal reflux disease, swallowing disorders, different polyposis syndromes and GI malformations, food allergy, selerosing cholangitis, and other biliary diseases), thereof 16 had additional non-GI disorders. There were significant differences between the subgroups regarding gender and age, with more boys and older age in patients with non-GI comorbidities. Children with comorbidities were found to be more likely wasted/underweight compared to those without. A significantly higher proportion of *H. pylori*-infected children with GI comorbidities was reported in Israel, Turkey, Southern Europe and with non-GI comorbidities in Northern and Western Europe (Table 1).

Patients with GI comorbidities compared to those without any comorbidity reported lower rates of GI symptoms such as abdominal pain (62% vs. 73%, *p* = 0.008), nausea/dyspepsia (5% vs. 16%, *p* < 0.0001), and vomiting (5% vs. 16%, *p* < 0.0001), but had a higher rate of chronic diarrhea (9% vs. 4%, *p* = 0.010, respectively) (Table 1). Gastric nodularity indicating nodular gastritis, a common but not pathognomonic finding in children with *H. pylori* infection, was less common in patients with comorbidities compared to those without (75–77% vs. 83%, respectively, *p* = 0.04). There was no significant difference in the proportion of gastric or duodenal ulcers and erosions between patients with and without comorbidities (Table 1).

Patients with GI comorbidities showed a significantly higher rate of primary metronidazole resistance compared to those without or with non-GI comorbidities (34% vs. 20% vs. 20%, *p* = 0.002, respectively). This pattern was reflected in the MET-R/CLA-S group (27% vs. 15% vs. 14%, *p* = 0.004, respectively) when stratified by resistance to metronidazole and clarithromycin (Table 1).

3.3 | Factors Associated With Treatment Decision

Among *H. pylori*-infected patients, 16% (192/1165) were not prescribed eradication therapy (Table 2). Reasons for no-treatment included age younger than 6 years (*n* = 14), patient or parent refusal (*n* = 8), language barrier (*n* = 3), no symptoms (*n* = 55), absence of PUD (*n* = 6), and a large variety of other reasons (*n* = 105), and one missing answer.

Of 80 patients with gastric or duodenal ulcers, 74 (93%) received anti-*H. pylori* treatment as recommended by the previous and current guideline [16, 17] (Table 2). Provided reasons for no initiation of therapy in the remaining six patients included very young age, parents' refusal, or parents wished to postpone treatment. Five of the six patients had no comorbidity, and one child had been diagnosed with a non-GI comorbidity.

Prescribing treatment was significantly more likely with increasing age, in overweight/ obese children, those having symptoms such as abdominal pain, nausea, or vomiting, and macroscopic findings including nodular gastritis or erosions (Table 2). Available results of antibiotic susceptibility testing also influenced the decision to initiate treatment; particularly, children harboring strains resistant to both clarithromycin and metronidazole were less likely to be treated (Table 2). The number of children not treated was notably significant across living regions (*p* < 0.001) with the lowest proportion in Eastern Europe (6%) and the highest in Israel and Turkey (37%).

Receiving therapy against *H. pylori* infection was inversely associated with the presence of comorbidities (*p* < 0.01). Children with GI comorbidities (*n* = 181) were less likely treated compared to those without comorbidities (*n* = 858) (43% vs. 11%, respectively, *p* < 0.001). Over half (57%) of children with CeD (*n* = 58), 46% of IBD (*n* = 28), 40% of EoE patients (*n* = 35), 27% of those with other GI diseases (*n* = 44), and 31% of those with multi-disorders including GI (*n* = 16) did not receive *H. pylori* eradication treatment, in contrast to only 14% of children with non-GI comorbidities (*n* = 126) and 11% of those without comorbidities (*n* = 858) (*p* < 0.001) (Table 2). Drug therapy in IBD and EoE appeared to have minimal impact on the decision to treat or not to treat (Data S3). Of the 28 IBD patients, 9 were on long-term therapy with azathioprine, thereof 6 (67%) received anti-*H. pylori* therapy. Of 25 children with EoE, 15 were on PPI therapy, thereof 9 (60%) patients received eradication therapy. In addition, the presence of abdominal pain, erosions, or nodular gastritis did not lead to higher rates of eradication therapy in subgroups with different GI comorbidities (Table 3).

Of 858 infected children without comorbidities, about half of them (47%, *n* = 401) had neither any alarm symptom nor an abnormal macroscopic finding except gastric nodularity. In this subgroup, the treatment rate was highest in overweight or obese children (94%), compared to those being underweight (87%) or having a normal BMI z-score (85%) (Table 3). The treatment rates were similarly high in children without comorbidities but having either alarm signs or abnormal macroscopic findings in addition to gastric nodularity, again with the highest rate in overweight/obese subgroup (93%).

Data S4A,B depicts the percentage of children who were treated against *H. pylori* infection by different GI, non-GI and without comorbidities, stratified by living in a high or low prevalence country. Treatment was less often prescribed to children with GI comorbidities in high versus low prevalence countries (47% vs. 78%, *p* < 0.001), for example, EoE (54% vs. 86%, ns), IBD (42% vs. 63%, ns), and CeD (35% vs. 89%, *p* = 0.004, respectively), other GI disorders (61% vs. 86%), while in patients with non-GI disorders or without comorbidities the decision for anti-*H. pylori* therapy was not influenced by region of living (85%–92%) (Data S4).

TABLE 1 | Characteristics of treatment-naïve pediatric patients with *H. pylori* infection by known comorbidities, $N = 1165$.

Factors n (%, column percent)	All $N = 1165$	GI comorbidity $n = 181$ (15%)	Non-GI comorbidity $n = 126$ (11%)	No comorbidity $n = 858$ (74%)	*p* value[a]
Demographics					
Female	609 (52%)	90 (50%)	49 (39%)	470 (55%)	**0.003**
Age (years), median (IQR)	12.8 (9.8, 15.2)	11.9 (8.8, 14.5)	13.3 (10.5, 16.3)	12.9 (10.1, 15.2)	**0.003**
BMI-*z*-score categories[b]					
Wasting	47 (4%)	9 (5%)	10 (8%)	28 (3%)	**0.02**
Underweight	139 (12%)	27 (15%)	12 (10%)	100 (12%)	
Normal	660 (57%)	103 (57%)	65 (52%)	492 (57%)	
Overweight	206 (18%)	32 (18%)	19 (15%)	155 (18%)	
Obesity	113 (10%)	10 (6%)	20 (16%)	83 (10%)	
Country of living[c]					
Northern/Western Europe	322 (28%)	42 (23%)	55 (44%)	225 (26%)	**<0.0001**
Southern Europe	485 (42%)	81 (45%)	38 (30%)	366 (43%)	
Eastern Europe	234 (20%)	18 (10%)	26 (21%)	190 (22%)	
Israel and Turkey	124 (11%)	40 (22%)	7 (6%)	77 (9%)	
Symptoms					
Non-alarm GI symptoms					
Abdominal pain	820 (70%)	112 (62%)	80 (63%)	628 (73%)	**0.002**
Nausea, dyspepsia	171 (15%)	9 (5%)	21 (17%)	141 (16%)	**0.0003**
Bloating	62 (5%)	11 (6%)	3 (2%)	48 (6%)	0.29
Constipation	43 (4%)	6 (3%)	5 (4%)	32 (4%)	0.95
Report of any non-alarm GI symptom	865 (74%)	116 (64%)	86 (68%)	663 (77%)	**<0.001**
Alarm symptoms and signs[d]					
Anemia	53 (5%)	4 (2%)	11 (9%)	38 (4%)	**0.03**
Chronic diarrhea	53 (5%)	17 (9%)	3 (2%)	33 (4%)	**0.002**
Dysphagia	20 (2%)	5 (3%)	1 (1%)	14 (2%)	0.40
Family history of Celiac disease (CeD)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0.84
GI-bleeding	45 (4%)	9 (5%)	6 (5%)	30 (3%)	0.55
Recurrent vomiting	174 (15%)	9 (5%)	23 (18%)	142 (17%)	**<0.001**
Weight loss	4 (0%)	0 (0%)	1 (1%)	3 (0%)	0.50
Presence of any alarm symptom	321 (28%)	40 (22%)	41 (33%)	240 (28%)	0.11
Presence of ≥ 2 alarm symptoms	35 (3%)	4 (2%)	4 (3%)	27 (3%)	0.79
Macroscopic findings					
Suspected eosinophilic esophagitis (EoE)	69 (6%)	33 (18%)	4 (3%)	32 (4%)	**<0.001**
Gastric nodularity with or without additional macroscopic abnormalities	948 (81%)	140 (77%)	95 (75%)	713 (83%)	**0.04**

(Continues)

TABLE 1 | (Continued)

Factors *n* (%, column percent)	All $N = 1165$	GI comorbidity $n = 181$ (15%)	Non-GI comorbidity $n = 126$ (11%)	No comorbidity $n = 858$ (74%)	*p* value[a]
Peptic ulcers	80 (7%)	8 (4%)	11 (9%)	61 (7%)	0.29
Erosions	174 (15%)	22 (12%)	20 (16%)	132 (15%)	0.52
Macroscopic lesions in esophagus					
Suspected EoE, ulcers, and/or erosions	150 (13%)	39 (22%)	16 (13%)	95 (11%)	**0.005**
Varices and/or stenosis	23 (2%)	4 (2%)	2 (2%)	17 (2%)	
Normal findings	992 (85%)	138 (76%)	108 (85%)	746 (87%)	
Macroscopic lesions in stomach					
Ulcer and/or erosions and/or bleeding	143 (12%)	16 (9%)	21 (17%)	106 (12%)	0.09
Only gastric nodularity	863 (74%)	134 (74%)	84 (66%)	645 (75%)	
Normal findings	159 (14%)	31 (17%)	21 (17%)	107 (13%)	
Macroscopic lesions in duodenum					
Ulcer and/or erosions and/or bleeding	120 (10%)	13 (7%)	11 (9%)	96 (11%)	**<0.001**
Only duodenal nodularity	113 (10%)	46 (25%)	8 (6%)	59 (7%)	
Normal findings	931 (80%)	122 (68%)	106 (85%)	703 (82%)	
Macroscopic lesions in esophagus, stomach and/or duodenum					
Any abnormal finding incl. suspected EoE, ulcers, erosions, bleeding, and/or duodenal nodularity, except gastric nodularity	453 (39%)	103 (57%)	46 (37%)	304 (36%)	**<0.001**
Only gastric nodularity	599 (51%)	62 (34%)	63 (50%)	474 (55%)	
Normal findings	113 (10%)	16 (9%)	17 (13%)	80 (9%)	
Scenarios supporting therapy against anti *H. pylori* infection					
Any alarm symptom and/or any macroscopic abnormal finding, except gastric nodularity	648 (56%)	122 (67%)	69 (55%)	457 (53%)	**0.002**
No alarm symptom, normal macroscopic findings, or only gastric nodularity	517 (44%)	59 (33%)	57 (45%)	401 (47%)	
Positive rapid urease test (RUT), $n = 449$	402 (90%)	47 (85%)	41 (91%)	314 (90%)	0.56
Histology confirmed[e], $n = 712$	644 (90%)	89 (83%)	68 (93%)	487 (92%)	0.07
Antibiotic susceptibility testing					
Susceptibility testing					
Culture positive and/or PCR available	996 (85%)	146 (81%)	103 (82%)	747 (87%)	0.12
Culture negative and no PCR	62 (5%)	11 (6%)	9 (7%)	42 (5%)	
Not applicable or unknown	107 (9%)	24 (13%)	14 (11%)	69 (8%)	
Antibiotic resistance profile					
Metronidazole resistance, $n = 901$	197 (22%)	44 (34%)	19 (20%)	134 (20%)	**0.002**
Clarithromycin resistance[f], $n = 974$	240 (25%)	33 (23%)	20 (20%)	187 (26%)	0.35

(Continues)

TABLE 1 | (Continued)

Factors n (%, column percent)	All $N=1165$	GI comorbidity $n=181$ (15%)	Non-GI comorbidity $n=126$ (11%)	No comorbidity $n=858$ (74%)	p value[a]
Amoxicillin resistance, $n=797$	7 (1%)	1 (1%)	1 (1%)	5 (1%)	0.93
Tetracycline resistance, $n=703$	5 (1%)	0 (0%)	2 (3%)	3 (1%)	0.11
Levofloxacin resistance, $n=850$	44 (5%)	5 (4%)	8 (9%)	31 (5%)	0.16
Rifampicin resistance, $n=196$	21 (11%)	4 (13%)	3 (19%)	14 (9%)	0.45
Susceptibility groups[g], $n=900$					
MET-S/CLA-S	536 (60%)	66 (50%)	64 (67%)	406 (60%)	**0.004**
MET-S/CLA-R	167 (19%)	21 (16%)	12 (13%)	134 (20%)	
MET-R/CLA-S	142 (16%)	36 (27%)	14 (15%)	92 (14%)	
MET-R/CLA-R	55 (6%)	8 (6%)	5 (5%)	42 (6%)	
Therapy, $n=973$					
Therapy prescribed	973 (84%)	104 (57%)	108 (86%)	761 (89%)	**<0.0001**
Common treatments used, $n=956$					
PPI + antibiotic	4 (0%)	1 (1%)	0 (0%)	3 (0%)	0.78
PPI + AMO + CLA	439 (46%)	49 (48%)	47 (45%)	343 (46%)	
PPI + AMO + MET	375 (39%)	36 (35%)	44 (42%)	295 (39%)	
PPI + CLA + MET	9 (1%)	2 (2%)	2 (2%)	5 (1%)	
PPI + AMO + antibiotic	20 (2%)	4 (4%)	2 (2%)	14 (2%)	
PPI + AMO + CLA + MET sequential	95 (10%)	9 (9%)	9 (9%)	77 (10%)	
PPI + AMO + CLA + MET	7 (1%)	1 (1%)	0 (0%)	6 (1%)	
PPI + antibiotic + Bismuth	7 (1%)	0 (0%)	0 (0%)	7 (1%)	
Therapy duration, $n=964$					
10 days	135 (14%)	13 (13%)	12 (11%)	110 (15%)	0.61
14 days	829 (86%)	90 (87%)	94 (89%)	645 (85%)	
Daily intake frequency, $n=891$					
Twice a day	720 (81%)	78 (87%)	79 (80%)	563 (80%)	0.33
Three times a day	171 (19%)	12 (13%)	20 (20%)	139 (20%)	
Use of probiotics, $n=969$	157 (16%)	11 (11%)	8 (7%)	138 (18%)	**0.002**

Note: Results were presented in median and interquartile range (IQR) from 25% quartile to 75% quartile for continuous variables and in frequency (n) and column percentage (%) for categorical variables. Bold p values indicate significant differences in the proportion of respective factors between comorbidity groups with a p value ≤0.05.

Abbreviations: AMO, amoxicillin; BMI, Body Mass Index; CeD, celiac disease; CLA, clarithromycin; EoE, eosinophilic esophagitis; GI, gastrointestinal; *H. pylori*, Helicobacter pylori; IBD, inflammatory bowel disease; MET, metronidazole; MET-R/CLA-R: Strains resistant to both metronidazole and clarithromycin; MET-R/CLA-S: Strains resistant to metronidazole but susceptible to clarithromycin; MET-S/CLA-R: Strains susceptible to metronidazole but resistant to clarithromycin; MET-S/CLA-S: Strains susceptible to both metronidazole and clarithromycin; PCR, polymerase chain reaction; PPI, proton-pump inhibitor; RUT, rapid urease test.

[a]p values obtained by Mann–Whitney U-test for continuous variables, while Pearson's chi-square test or Fisher's exact test for categorical variables as appropriate.

[b]BMI Z-score was calculated according to CDC-WHO BMI-for-age Z-scores for children <20 years, available from https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm and https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age, last access on April 20, 2024. We used BMI Z-score cut-points of < −2.0 SD, < −1.0 SD, > +1.0 SD, > +2.0 SD to define wasting, underweight, overweight, and obesity, respectively, as recommended by WHO.

[c]Country distribution was given in Data S1.

[d]Symptoms were classified as alarm symptoms according to Thakka et al. [35] and assessed using data regarding symptoms associated with *H. pylori* infection, primary indication for endoscopy, and additional details provided in the questionnaire by physicians.

[e]Data of histology were collected from 2018 to 2020.

[f]Data were collected from thereof real-time polymerase chain reaction (RT-PCR) test.

[g]Data are based on all available susceptibility test results for metronidazole (MET) and clarithromycin (CLA).

In the multivariable logistic regression (adjusted for gender, age, region of residence, and the availability of antibiotic susceptibility results), the decision to initiate therapy was positively associated with symptoms such as abdominal pain (OR = 1.64, $p = 0.01$) or dyspepsia/nausea (OR = 3.3, $p = 0.005$), being overweight (OR = 2.12, $p = 0.009$), the presence of erosions (OR = 2.9, $p = 0.005$) or nodular gastritis (OR = 3.04, $p < 0.0001$), and having positive antibiotic susceptibility results from culture and/or PCR results (OR 3.98, $p < 0.0001$) (Figure 1A). Inverse significant associations between the decision to treat were confirmed for living in a high prevalence country and having a GI comorbidity. Patients diagnosed with GI comorbidities had a 70% to 75% reduced chance of receiving therapy against *H. pylori* infection compared to those with non-GI comorbidities and those without any comorbidity (OR = 0.31, $p = 0.0006$ and OR = 0.25, $p < 0.0001$, respectively) (Figure 1A).

When we exchanged in the model the single symptoms against the two categories (non-alarm symptoms or any alarm symptom) and erosions against any abnormal macroscopic finding except gastric nodularity, decision for therapy was significantly related to presence of non-alarm symptoms, but not to alarm symptoms, and was not influenced by the presence of abnormal macroscopic findings compared to only antral nodularity (Figure 1B).

In the post hoc analysis, we investigated further abdominal pain in different subgroups of comorbidities, since abdominal pain was the most common symptom reported in 70% of our cohort as well as representing 59% of the primary indication for endoscopy. There was no significant difference in reported abdominal pain between patients diagnosed with IBD, EoE, and CeD compared to children with no comorbidity (Figure 2A). In addition, there was no difference in reported abdominal pain in children detected with gastric or duodenal ulcers, erosions only or antral nodularity compared to children with normal endoscopic findings (Figure 2B). Comparing the presence of any alarm sign or symptom in the different subgroups revealed significantly lower percentages in children with CeD (9%) than in normal weight children without comorbidity (30%) (Data S5A). No surprisingly, children with EoE or CeD showed a higher rate of any abnormal macroscopic findings with or without gastric nodularity than infected children without comorbidities (Data S5B).

When we performed multivariable logistic regression (adjusted for gender, age, region of residence, and the availability of antibiotic susceptibility results) by the three clinical subgroups, age, region of living, abdominal pain, antral nodularity, and having a positive antibiotic susceptibility result remained significantly related to the decision to treat in patients with GI and in those without comorbidities while the presence of erosions (not ulcers) and overweight favored to treat the infection only in the 858 otherwise healthy children (Figure 3, Data S6).

3.4 | Eradication Success in Patients With and Without Comorbidities

Once therapy against *H. pylori* infection was prescribed, the regimen was chosen according to the available susceptibility testing results. The eradication success rates were not significantly related to the presence of comorbidities, both in children treated with PAC, PAM, or SEQ ($n = 612$) (Data S7A), and those receiving a regimen tailored to antibiotic susceptibility as recommended in the guidelines [16] ($n = 521$) (Data S7B). Tailored triple therapy with PAM tended to achieve higher eradication success rates compared to PAC in patients with GI comorbidities (95% vs. 85%, $p = 0.39$), non-GI comorbidities (96% vs. 87%, $p = 0.34$), or those without comorbidities (91% vs. 89%, $p = 0.61$) (Data S7B). Rates for compliance with therapy were high in patients with GI and non-GI comorbidities (94%–97%) and slightly lower 92% in patients without any comorbidities (n.s.).

Adverse events during guideline-conform therapy (PAM, PAC or SEQ) were reported in 4% of patients with GI comorbidities, 15% with non-GI, and 13% or children without any comorbidities, with the majority reporting abdominal pain. During the monitoring visit after therapy, only 5%–7% of children reported complaints within the last week, with no patient reporting diarrhea in those with comorbidities (Data S8).

4 | Discussion

The goal of this analysis was to identify factors associated with a decision to treat or not to treat *H. pylori* infection once it had been confirmed by biopsy-based tests. Of 1165 *H. pylori*-infected and treatment-naïve children reported in the EuroPedHp registry who met our inclusion criteria for this analysis, 192 (16%) had not received anti-*H. pylori* therapy. Multivariable logistic regression disclosed that the decision to receive therapy or not was significantly related to age, country of living, being overweight, having an underlying GI disease, non-alarm symptoms like abdominal pain or dyspepsia, endoscopic abnormalities, and a positive culture with antibiotic susceptibility results.

The in 2017 updated ESPGHAN/ NASPGHAN guidelines recommend to treat *H. pylori* infection in children if gastric or duodenal peptic lesions (ulcers, erosions) are present. In the absence of mucosal lesions, treatment should be carefully considered, taking into account the individual risk–benefit-ratio for the child, including age, risk of short- and medium-term complications from the infection versus treatment, regional prevalence of the infection, antibiotic resistance, available drugs, and treatment options [16]. Our finding that older children and those with peptic mucosal lesions are more likely to be treated is in accordance with these recommendations. However, there is no rationale that patients with antral nodularity were three time more likely to be treated compared to those without. Nodular gastritis is a common, but not pathognomonic finding in *H. pylori*-infected children [5], but not related to the bacterial load or symptoms [37]. Antral nodularity was identified in 81% of our cohort, which is similar to 80% reported in asymptomatic infected children identified during a screening study and followed for their natural history by endoscopy over 2 years [37].

Our analysis allowed us to identify 858 children and adolescents without underlying comorbidities, thereof 28% had been investigated because of any alarm sign or symptom. The remaining patients reported only unspecific symptoms (recurrent abdominal pain, dyspepsia, bloating, or constipation)

TABLE 2 | Characteristics of treatment-*naïve* pediatric patients with *H. pylori* infection by decision for anti-*H. pylori* treatment, N = 1165.

Factor n (%, row percent)	All N = 1165	Treated n = 973 (84%)	Not treated n = 192 (16%)	p value[a]
Demographics				
Female	609	517 (85%)	92 (15%)	0.19
Age (years), median (IQR)	12.8 (9.8, 15.2)	13.2 (10.3, 15.3)	10.5 (7.7, 14.1)	**<0.001**
BMI z-score in categories[b]				
Wasting	47	39 (83%)	8 (17%)	**0.03**
Underweight	139	110 (79%)	29 (21%)	
Normal	660	540 (82%)	120 (18%)	
Overweight	206	185 (90%)	21 (10%)	
Obesity	113	99 (88%)	14 (12%)	
Country of living[c]				
Northern/Western Europe	322	276 (86%)	46 (14%)	**<0.001**
Southern Europe	485	399 (82%)	86 (18%)	
Eastern Europe	234	220 (94%)	14 (6%)	
Israel and Turkey	124	78 (63%)	46 (37%)	
Comorbidity				
Diagnosis with any comorbidity				
Yes	307	212 (69%)	95 (31%)	**<0.001**
No	858	761 (89%)	97 (11%)	
Diagnosed with comorbidity				
GI comorbidity	181	104 (57%)	77 (43%)	**<0.001**
Eosinophilic esophagitis (EoE)	35	21 (60%)	14 (40%)	
Inflammatory bowel disease (IBD)	28	15 (54%)	13 (46%)	
Celiac disease (CeD)	58	25 (43%)	33 (57%)	
Other GI disorders	44	32 (73%)	12 (27%)	
GI disorders and other non-GI disorders	16	11 (69%)	5 (31%)	
Non-GI comorbidity	126	108 (86%)	18 (14%)	
No comorbidity	858	761 (89%)	97 (11%)	
Symptoms				
Non-alarm GI symptoms				
Abdominal pain	820	710 (87%)	110 (13%)	**<0.001**
Nausea, dyspepsia	171	164 (96%)	7 (4%)	**<0.001**
Bloating	62	51 (82%)	11 (18%)	0.78
Constipation	43	35 (81%)	8 (19%)	0.70
Report of any non-alarm GI symptom				
Yes	865	752 (87%)	113 (13%)	**<0.001**
No	300	221 (74%)	79 (26%)	

(Continues)

TABLE 2 | (Continued)

Factor n (%, row percent)	All $N = 1165$	Treated $n = 973$ (84%)	Not treated $n = 192$ (16%)	p value[a]
Alarm symptoms[d]				
Anemia	53	51 (96%)	2 (4%)	**0.01**
Diarrhea	53	40 (75%)	13 (25%)	0.11
Dysphagia	20	11 (55%)	9 (45%)	**<0.001**
Family history of CeD	1	0 (0%)	1 (100%)	n.a.
GI-bleeding	45	35 (78%)	10 (22%)	0.29
Vomiting	174	159 (91%)	15 (9%)	**0.002**
Weight loss	4	3 (75%)	1 (25%)	0.65
Any alarm symptom				
Present	321	274 (85%)	47 (15%)	0.30
Absent	844	699 (83%)	145 (17%)	
≥ 2 alarm symptoms				
Present	35	31 (89%)	4 (11%)	0.41
Absent	1130	942 (83%)	188 (17%)	
Macroscopic findings				
Suspected eosinophilic esophagitis (EoE)	69	47 (68%)	22 (32%)	**0.01**
Gastric nodularity with or without additional macroscopic abnormalities	948	819 (86%)	129 (14%)	**<0.001**
Peptic ulcers	80	74 (93%)	6 (7%)	**0.025**
Erosions	174	161 (93%)	13 (7%)	**<0.001**
Macroscopic lesions in esophagus				
Suspected EoE, ulcers, and/or erosions	150	115 (77%)	35 (23%)	**0.050**
Varices and/or stenosis	23	20 (87%)	3 (13%)	
Normal findings	992	838 (84%)	154 (16%)	
Macroscopic lesions in stomach				
Ulcer and/or erosions and/or bleeding	143	132 (92%)	11 (8%)	**<0.001**
Only gastric nodularity	863	729 (84%)	134 (16%)	
Normal findings	159	112 (70%)	47 (30%)	
Macroscopic lesions in duodenum				
Ulcer and/or erosions and/or bleeding and/or nodularity	120	112 (93%)	8 (7%)	**<0.001**
Only duodenal nodularity	113	75 (66%)	38 (34%)	
Normal findings	931	785 (84%)	146 (16%)	

(Continues)

TABLE 2 | (Continued)

Factor n (%, row percent)	All $N = 1165$	Treated $n = 973$ (84%)	Not treated $n = 192$ (16%)	p value[a]
Macroscopic lesions in esophagus, stomach and/or duodenum				
Any abnormal macroscopic finding incl. suspected EoE, ulcers, erosions, bleeding, and/or duodenal nodularity, except gastric nodularity	453	367 (81%)	86 (19%)	<0.001
Only gastric nodularity	599	525 (88%)	74 (12%)	
Normal findings	113	81 (72%)	32 (28%)	
Scenarios supporting therapy against anti *H. pylori* infection				
Any alarm symptom and/or any macroscopic abnormal finding, except gastric nodularity	648	530 (82%)	118 (18%)	0.08
No alarm symptom, normal macroscopic findings, or only gastric nodularity	517	443 (86%)	74 (14%)	
Antibiotic susceptibility testing				
Susceptibility testing				
Culture positive and/or PCR available	996	852 (86%)	144 (14%)	**<0.001**
Culture negative and no PCR	62	39 (63%)	23 (37%)	
Not applicable or unknown	107	82 (77%)	25 (23%)	
Metronidazole and clarithromycin resistance–Susceptibility subgroups[e], $n = 900$				
MET-S/CLA-S	536	474 (88%)	62 (12%)	**<0.001**
MET-S/CLA-R	167	144 (86%)	23 (14%)	
MET-R/CLA-S	142	113 (80%)	29 (20%)	
MET-R/CLA-R	55	38 (69%)	17 (31%)	

Note: Results were presented in median and interquartile range (IQR) from 25% quartile to 75% quartile for continuous variables and in frequency (n) and column percentage (%) for categorical variables. Bold p values indicate significant differences in the proportion of treated group (or not treated group) across different categories of a specific factor with a $p \leq 0.05$.

Abbreviations: BMI, Body Mass Index; CeD, celiac disease; EoE, eosinophilic esophagitis; GI, gastrointestinal; IBD, inflammatory bowel disease; MET-R/CLA-R, Strains resistant to both metronidazole and clarithromycin; MET-R/CLA-S, Strains resistant to metronidazole but susceptible to clarithromycin; MET-S/CLA-R, Strains susceptible to metronidazole but resistant to clarithromycin; MET-S/CLA-S, Strains susceptible to both metronidazole and clarithromycin; PCR, polymerase chain reaction.

[a]p values obtained by Mann–Whitney U-test for continuous variables, while Pearson's chi-square test or Fisher's exact test for categorical variables as appropriate.

[b]BMI Z-score was calculated according to CDC-WHO BMI-for-age Z-scores for children <20 years, available from https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm and https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age, last access on April 20, 2024. We used BMI Z-score cut-points of < −2.0 SD, < −1.0 SD, > +1.0 SD, > +2.0 SD to define wasting, underweight, overweight, and obesity, respectively, as recommended by WHO.

[c]Country distribution was given in Data S1.

[d]Symptoms were classified as alarm symptoms according to Thakka et al. [35] and assessed using data regarding symptoms associated with *H. pylori* infection, primary indication for endoscopy, and additional details provided in the questionnaire by physicians.

[e]Data are based on all available susceptibility test results for metronidazole (MET) and clarithromycin (CLA).

which are concordant with the Rome IV criteria for functional abdominal GI disorders in children [38]. Three quarters of infected, but otherwise healthy children showed as only endoscopic abnormality antral nodularity, while 13% had completely normal mucosa. These children most likely suffered from functional abdominal pain, and *H. pylori* gastritis was an incidental finding during endoscopy to exclude organic disease and not the cause of their complaints. Even in children without alarm sign or mucosal lesions, parents and doctors decided in 90% to treat the infection now and not to defer treatment to adulthood when better treatment options are available. There may be several reasons for parents and physicians to decide to treat these children in the absence evidence that the infection is causing the complaints: They hope that the child's symptoms will improve being aware that it may be due to a placebo effect. In addition, the knowledge that the child is infected with a bacterium which is considered to be a carcinogen and may cause ulcers or gastric cancer later in life induces anxiety in the parents or even the child and may reinforce functional pain disorders. These more psychological reasons to initiate therapy now and not to defer eradication therapy into adulthood may be differently weighted in younger children compared to adolescents. In contrast, there is no rationale for our finding that overweight children

TABLE 3 | Comorbidities and treatment decisions regarding non-alarm GI symptoms, alarm symptoms, and macroscopic findings in *H. pylori*-infected children, *N* = 1165.

Factors	GI comorbidity, *N* = 181					Non-GI comorbidities, *n* = 126	No comorbidity[a], *n* = 858		
	EoE comorbidity, *n* = 35	IBD comorbidity, *n* = 28	CeD comorbidity, *n* = 58	Other GI disorders, *n* = 44	GI and other disorders, *n* = 16		Wasting/ Underweight, *n* = 128	Normal weight, *n* = 492	Overweight/ Obesity, *n* = 238
Abdominal pain	20 (57%)	19 (68%)	36 (62%)	30 (68%)	7 (44%)	80 (64%)	92 (72%)	356 (72%)	180 (76%)
Treated	14 (70%)	12 (63%)	17 (47%)	25 (83%)	3 (43%)	71 (89%)	81 (88%)	316 (89%)	171 (95%)
Not treated	6 (30%)	7 (37%)	19 (53%)	5 (17%)	4 (57%)	9 (11%)	11 (12%)	40 (11%)	9 (5%)
Any non-alarm GI symptom[b]	20 (57%)	19 (68%)	37 (64%)	31 (70%)	9 (56%)	86 (68%)	97 (76%)	379 (77%)	187 (79%)
Treated	14 (70%)	12 (63%)	18 (49%)	26 (84%)	5 (56%)	77 (90%)	85 (88%)	337 (89%)	178 (95%)
Not treated	6 (30%)	7 (37%)	19 (51%)	5 (16%)	4 (44%)	9 (10%)	12 (12%)	42 (11%)	9 (5%)
Any alarm symptom[c]	4 (11%)	10 (36%)	5 (9%)	17 (39%)	4 (25%)	41 (33%)	34 (27%)	146 (30%)	60 (25%)
Treated	3 (75%)	5 (50%)	3 (60%)	8 (47%)	2 (50%)	36 (88%)	31 (91%)	130 (89%)	56 (93%)
Not treated	1 (25%)	5 (50%)	2 (40%)	9 (53%)	2 (50%)	5 (12%)	3 (9%)	16 (11%)	4 (7%)
Ulcers	1 (3%)	3 (11%)	1 (2%)	3 (7%)	0	11 (9%)	6 (5%)	32 (7%)	23 (10%)
Treated	1 (100%)	3 (100%)	1 (100%)	3 (100%)	0	10 (91%)	6 (100%)	28 (88%)	22 (96%)
Not treated	0	0	0	0	0	1 (9%)	0	4 (13%)	1 (4%)
Erosions	3 (9%)	8 (29%)	6 (10%)	5 (11%)	0	20 (16%)	18 (14%)	76 (15%)	38 (16%)
Treated	3 (100%)	5 (63%)	3 (50%)	5 (100%)	0	18 (90%)	17 (94%)	73 (96%)	37 (97%)
Not treated	0	3 (37%)	3 (50%)	0	0	2 (10%)	1 (6%)	3 (4%)	1 (3%)
Gastric nodularity[d]	26 (74%)	19 (68%)	51 (88%)	33 (75%)	11 (69%)	95 (75%)	104 (81%)	413 (84%)	196 (82%)
Treated	17 (65%)	9 (47%)	21 (41%)	28 (85%)	8 (73%)	86 (91%)	95 (91%)	370 (90%)	185 (94%)
Not treated	9 (35%)	10 (53%)	30 (59%)	3 (15%)	3 (27%)	9 (9%)	9 (9%)	43 (10%)	11 (6%)
Any abnormal macroscopic finding[e]	29 (83%)	14 (50%)	36 (62%)	19 (43%)	5 (31%)	46 (37%)	32 (25%)	177 (36%)	95 (40%)
Treated	17 (59%)	9 (64%)	11 (31%)	14 (74%)	2 (40%)	40 (87%)	29 (91%)	155 (88%)	90 (95%)
Not treated	12 (41%)	5 (36%)	25 (69%)	5 (26%)	3 (60%)	6 (13%)	3 (9%)	22 (12%)	5 (5%)
Only gastric nodularity[f]	5 (14%)	10 (36%)	20 (34%)	18 (41%)	9 (56%)	63 (50%)	80 (63%)	274 (56%)	120 (50%)

(Continues)

TABLE 3 | (Continued)

Factors	GI comorbidity, N = 181						No comorbidity[a], n = 858		
	EoE comorbidity, n = 35	IBD comorbidity, n = 28	CeD comorbidity, n = 58	Other GI disorders, n = 44	GI and other disorders, n = 16	Non-GI comorbidities, n = 126	Wasting/ Underweight, n = 128	Normal weight, n = 492	Overweight/ Obesity, n = 238
Treated	3 (60%)	3 (30%)	12 (60%)	16 (89%)	7 (78%)	58 (92%)	72 (90%)	243 (89%)	111 (93%)
Not treated	2 (40%)	7 (70%)	8 (40%)	2 (11%)	2 (22%)	5 (8%)	8 (10%)	31 (11%)	9 (8%)
Normal macroscopic findings	1 (3%)	4 (14%)	2 (3%)	7 (16%)	2 (13%)	17 (13%)	16 (13%)	41 (8%)	23 (10%)
Treated	1 (100%)	3 (75%)	2 (100%)	2 (29%)	2 (100%)	10 (59%)	13 (81%)	27 (66%)	21 (91%)
Not treated	0	1 (25%)	0	5 (71%)	0	7 (41%)	3 (19%)	14 (34%)	2 (9%)
Any alarm symptom and/or any macroscopic abnormal finding, except gastric nodularity[g]	29 (83%)	19 (68%)	39 (67%)	27 (61%)	8 (50%)	69 (55%)	57 (45%)	273 (55%)	127 (53%)
Treated	17 (59%)	10 (53%)	13 (33%)	17 (63%)	4 (50%)	60 (87%)	52 (91%)	239 (88%)	118 (93%)
Not treated	12 (41%)	9 (47%)	26 (67%)	10 (37%)	4 (50%)	9 (13%)	5 (9%)	34 (12%)	9 (7%)
No alarm symptom, normal macroscopic findings, or only gastric nodularity	6 (17%)	9 (32%)	19 (33%)	17 (39%)	8 (50%)	57 (45%)	71 (55%)	219 (45%)	111 (47%)
Treated	4 (67%)	5 (56%)	12 (63%)	15 (88%)	7 (88%)	48 (84%)	62 (87%)	186 (85%)	104 (94%)
Not treated	2 (33%)	4 (44%)	7 (37%)	2 (12%)	1 (13%)	9 (16%)	9 (13%)	33 (15%)	7 (6%)

Note: Results were presented in frequency (*n*) and proportion (%) of patients having a specific characteristic among their respective group (*n*). For this specific characteristic, frequency (*n*) and proportion (%) of patients who were treated or not treated were reported.

Abbreviations: BMI, Body Mass Index; CeD, celiac disease; EoE, eosinophilic esophagitis; GI, gastrointestinal; IBD, inflammatory bowel disease.

[a]No comorbidity group includes all patients who were not reported with any comorbidity. In addition, we stratified this group into three subgroups: (1) wasting/underweight: (2) normal weight: and (3) overweight/obesity based on their calculated BMI Z-score according to CDC-WHO BMI-for-age Z-scores for children <20 years, available from https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm and https://www.who.int/tools/growth-refer ence-data-for-5to19-years/indicators/bmi-for-age, last access on April 20, 2024. We used BMI Z-score cut-points of < −2.0 SD, < −1.0 SD, > +1.0 SD, > +2.0 SD to define wasting, underweight, overweight, and obesity, respectively, as recommended by WHO.

[b]Any non-alarm GI symptom encompasses patients reported abdominal pain, nausea, bloating, and/or constipation.

[c]Symptoms were classified as alarm symptoms according to Thakka et al. [35] and assessed using data regarding symptoms associated with *H. pylori* infection, primary indication for endoscopy, and additional details provided in the questionnaire by physicians.

[d]Gastric nodularity indicates group of patients detected with nodularity in the stomach with and without additional macroscopic abnormalities.

[e]Any abnormal macroscopic finding including suspected EoE, ulcers, erosions, bleeding, and/or duodenal nodularity, except gastric nodularity.

[f]Only gastric nodularity detected in the stomach without any other macroscopic finding.

[g]Any alarm GI symptom and/or any macroscopic abnormal finding in the esophagus, stomach, and/or duodenum, except gastric nodularity.
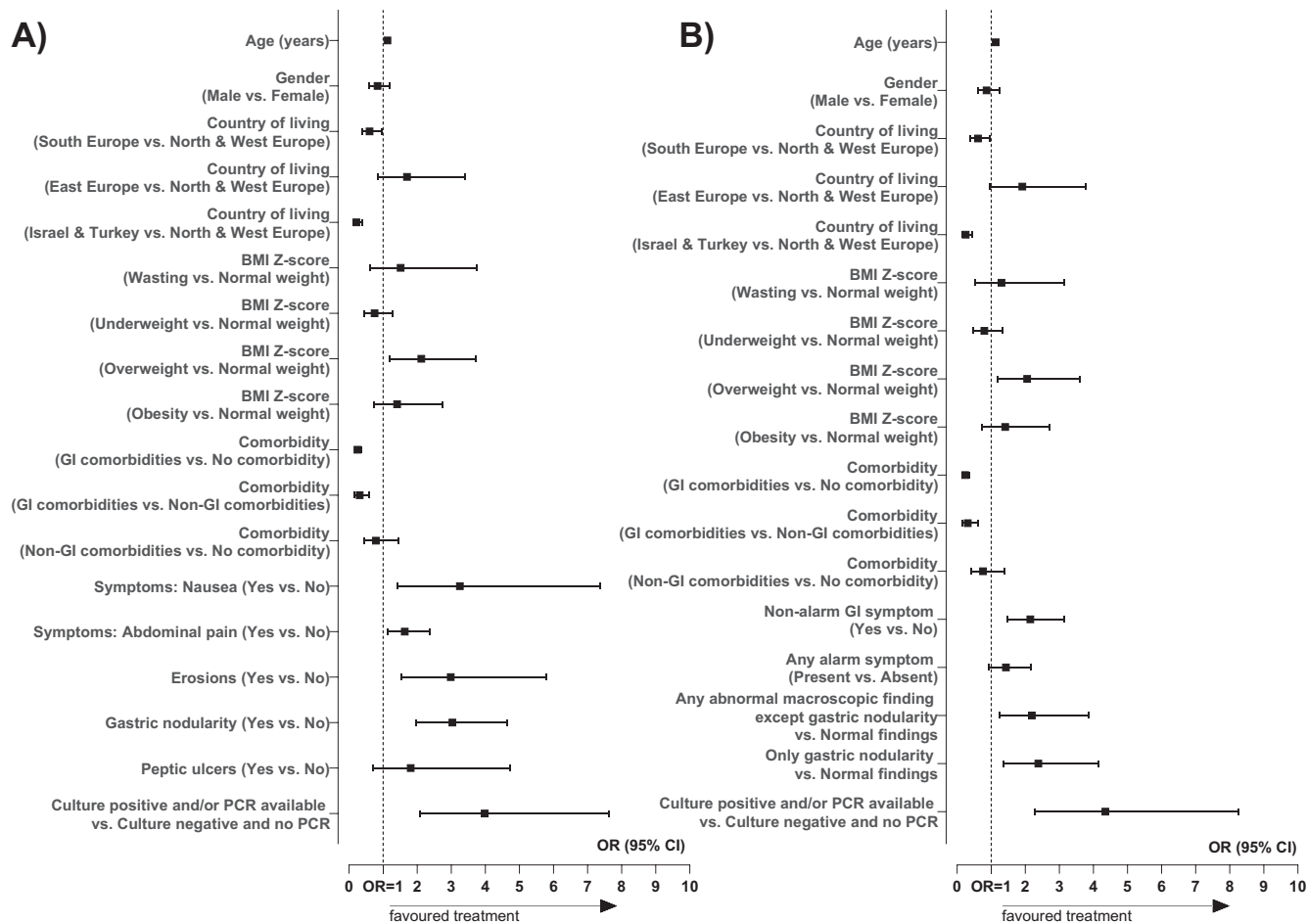
FIGURE 1 | Factors associated with the decision for therapy in treatment-naïve *H. pylori*-infected patients (*N* = 1165): (A) multivariable logistic regression concerning all symptoms reported and gastric nodularity, peptic ulcers, and erosions detected, (B) multivariable logistic regression concerning non-alarm GI symptom, any alarm symptom, and macroscopic findings in the esophagus, stomach, and duodenum. Odds ratios with 95% confidence intervals (95% CI) were obtained from the final multivariable logistic regression adjusted for gender, age, region of residence, and the availability of antibiotic susceptibility results. *p* values were determined using the Wald chi-square test to access the significance of the odds ratio (OR). BMI, Body Mass Index; GI, gastrointestinal; PCR, polymerase chain reaction; OR, odd ratio.

are more than twice as likely to be treated as children with normal BMI. Of particular interest, this association was only found in the subgroup of otherwise healthy children with no comorbidities (Figure 3). In contrast, the four times higher likelihood of being treated if antibiotic susceptibility results are available to guide the choice of antibiotics was equal in all clinical subgroups and is a strong argument to perform gastric biopsies for susceptibility testing unless the decision against treatment is made prior to endoscopy, in case histopathology proves *H. pylori* gastritis.

A comorbidity was reported by one out of four children of the cohort (307/1165), with 181 patients having a GI and 126 a non-GI disorder. In total, 18 of 28 patients with IBD and 15 of 35 patients with EoE had specifically been treated for their underlying disease prior to endoscopy, while all children with CeD underwent diagnostic endoscopy to confirm the suspected diagnosis prior to initiation of a gluten free diet. The main indication for endoscopy in the cohort with underlying GI disorders was abdominal pain or dyspepsia (70%), any alarm signs or symptoms such as anemia, GI-bleeding, weight loss or chronic diarrhea (17%) or monitoring of disease

activity after initiation of a specific therapy. However, children with GI comorbidities, particularly those with EoE, IBD, and CeD, were significantly less likely to be treated for the infection than patients with other comorbidities, despite a similar prevalence of reported abdominal pain and endoscopically visible mucosal lesions. Treatment decisions were influenced by the prevalence of *H. pylori* infections in the background population, suggesting that there are different perceptions of risks and benefits of *H. pylori* therapy among countries and regions. In countries where the prevalence of *H. pylori* infection is high and the infection is more likely to be detected incidentally during endoscopy, and in the absence of PUD, pediatricians more frequently decide against treatment [39, 40]. Surprisingly, in high prevalence countries the decision to treat the infection was particularly decreased in patients with GI comorbidities (47%) compared to those with non-GI comorbidities (87%) or patients with no comorbidities (86%). We did not find any evidence for selective opting out in children with IBD, CeD, or EGID compared to otherwise healthy *H. pylori*-infected children since the groups did not differ in the presence of abdominal pain, mucosal lesions, or antral nodularity. In newly diagnosed patients with Crohn's disease reported in
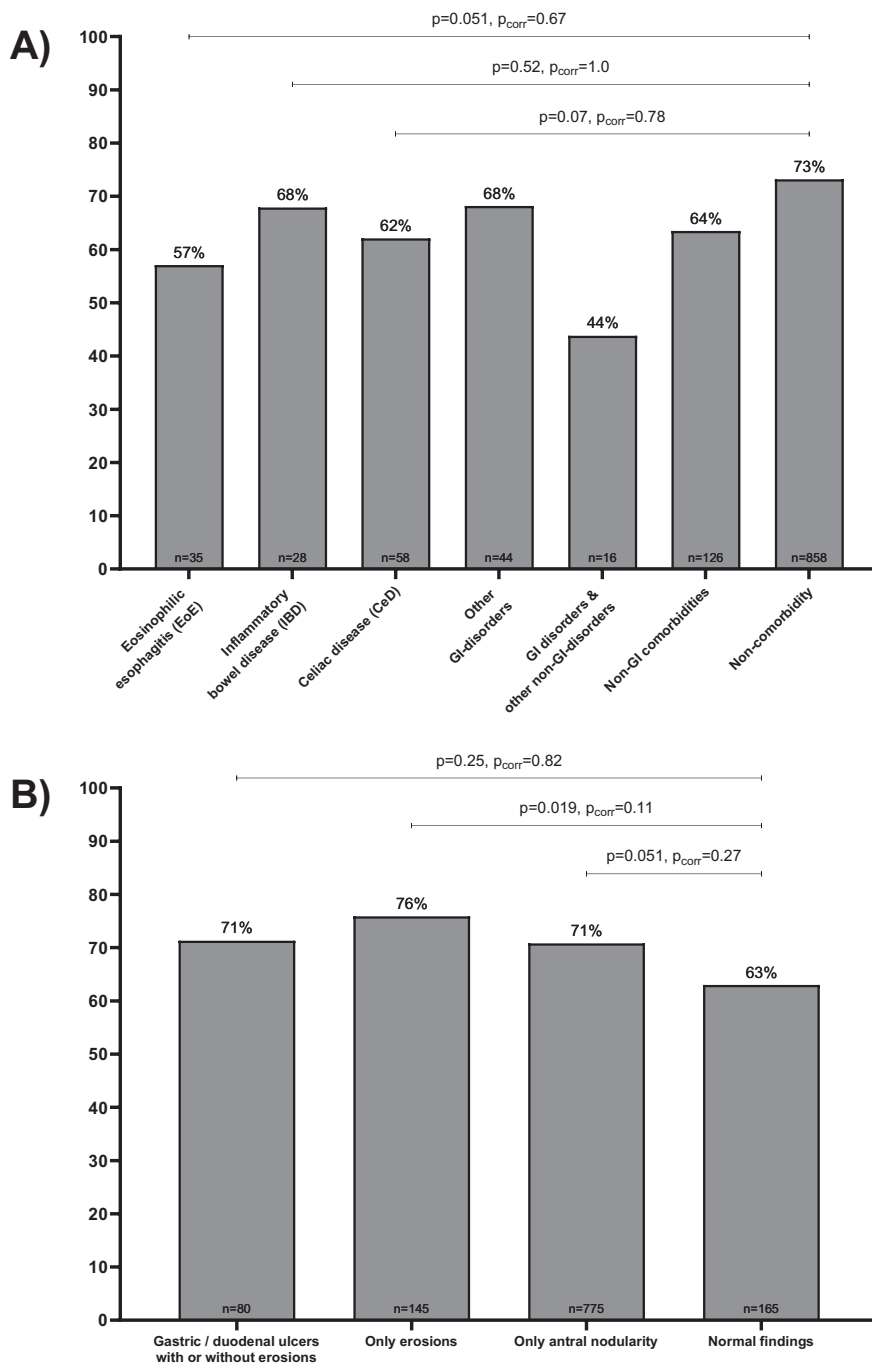
FIGURE 2 | Factors associated with the decision for therapy in treatment-naïve *H. pylori*-infected patients ($N = 1165$): (A) abdominal pain reported in *H. pylori*-infected children with/without comorbidities, (B) abdominal pain reported in *H. pylori*-infected children detected with gastric/duodenal ulcers, erosions, antral nodularity, and those with normal findings at endoscopy. Results were presented in proportion (%) of patients who were reported with abdominal pain within a specific group (*n*). P-values obtained from Fisher's exact test were corrected by applying Sidak's correction approach (Pcorr). GI, gastrointestinal; EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; CeD, Celiac disease.

the EUROKIDS Registry (*n* = 582), the rate of gastric (18%) or duodenal (17%) involvement including ulcerations or erosions was high (18% and 17%, respectively), but no data are available on how many of these patients had *H. pylori* infection [41]. Most of the IBD patients included in our cohort were already treated, which explains the lower rate of ulcerations compared to the EUROKIDS Registry data. It is unknown whether an additional chronic or active *H. pylori* gastritis will increase the risk of these lesions or hamper healing during IBD-related

therapy. In a large cohort of 663 newly diagnosed unselected pediatric patients with CeD, mucosal lesions (erosions, ulcers) were identified during initial endoscopy in 21 (3.2%) in the stomach and in 41 (6.3%) in the duodenum, but only 3 of 61 children with ulcers or erosions tested positive for *H. pylori* [42]. Even if we can assume, that most of the lesions in IBD and CeD patients are related to the underlying GI disease, in an individual *H. pylori*-infected patient a causal relationship between erosions or ulcerations and the infection and
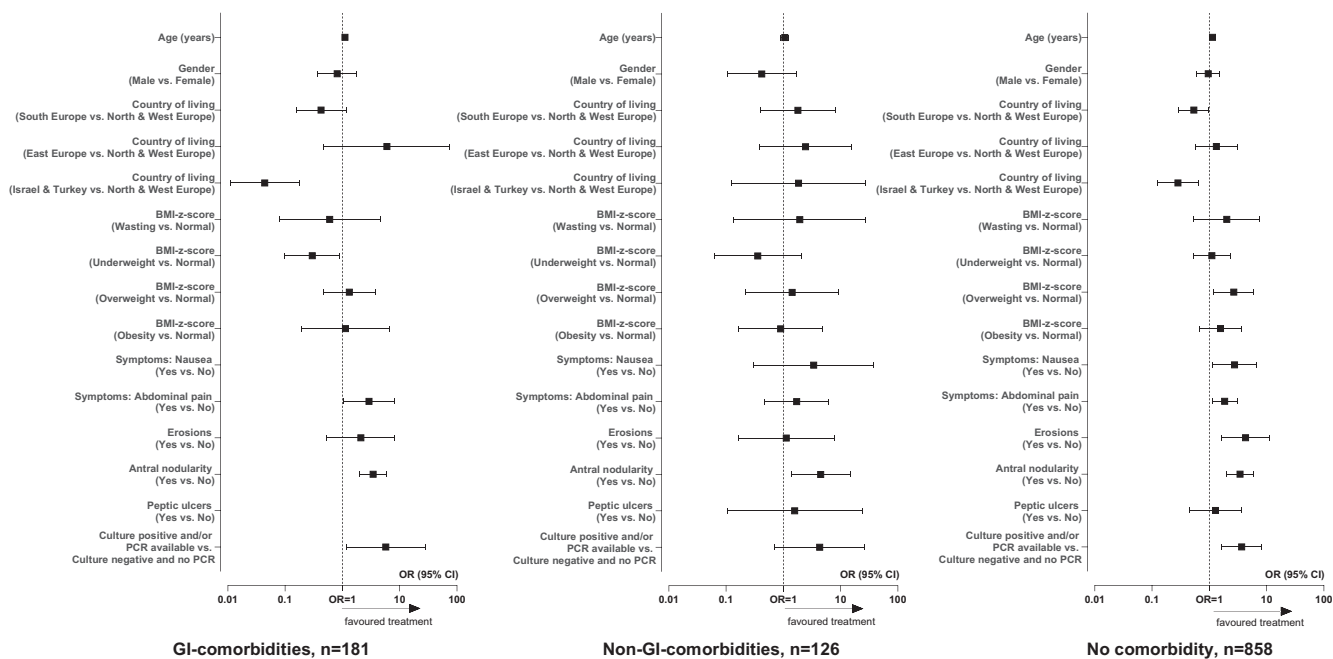
FIGURE 3 | Factors associated with the decision for therapy in treatment-naïve *H. pylori*-infected patients, stratified in three comorbidity groups, ($N = 1165$). Odds ratios with 95% confidence intervals (95% CI) were obtained from the final multivariable logistic regression adjusted for gender, age, region of residence, and the availability of antibiotic susceptibility results. P-values were determined using the Wald chi-square test to access the significance of the odds ratio (OR). BMI, Body Mass Index; GI, gastrointestinal; PCR, polymerase chain reaction; OR, odd ratio.

an increased risk for short- or medium-term complications, if kept untreated, cannot be excluded. Most likely, we will not have an answer to this question, since it would not be feasible and unethical to conduct such randomized intervention trials in these patient groups.

The intake of certain drugs used in patients with IBD, EoE, and other eosinophilic GI disorders (EGID) may also increase the risk of complications in *H. pylori*-infected patients compared to non-infected patients. Thiopurines are commonly used in patients with IBD, but have been associated with the development of malignancies in both, adults and children [43]. In a large French nationwide cohort study including 19,486 IBD patients, those treated with thiopurine had a five times higher risk for developing lymphoproliferative disorders [44]. To our knowledge, no data exist on the relation of thiopurine therapy and the risk for mucosa-associated lymphoid tissue (MALT) lymphoma in *H. pylori*-infected patients [45–47].

Long-term intake of PPI, as reported in 43% of the EoE patients in our cohort (Data S3), alters the topography of *H. pylori* gastritis with the spread from antrum-predominant to corpus-predominant pattern, results in increased gastrin levels, and is associated with atrophic gastritis in the corpus, and therefore may increase the risk for later gastric cancer [14]. *H. pylori* eradication improves gastritis in long-term PPI users [14]. Therefore, eradication therapy seems beneficial and is recommended in *H. pylori*-infected patients with planned or ongoing long-term PPI therapy [15].

Once therapy was prescribed, eradication success rates were high with a trend toward better compliance in patients with GI comorbidities and lower rates of adverse effects during therapy compared to those without comorbidities (Data S8). Antibiotic

therapy may have negative medium- or long-term effects on the microbiome and may cause a flare of the disease. *H. pylori* eradication therapy did not alter short-term disease activity in adult patients with IBD [48]. In our cohort, adverse events or abdominal symptoms were reported in only 4%–5% of the cohort 4–6 weeks after anti-*H. pylori* therapy, including in patients with GI comorbidity, making a relapse within this time frame unlikely.

Our study's strengths lie in the prospective reporting and comprehensive data of a large number of *H. pylori*-infected children, including symptoms, primary indications for upper endoscopy, endoscopic findings, antibiotic resistance, prescribed therapy, and comorbidities. We also assessed and compared adherence to therapy and adverse effects in children with and without comorbidities undergoing anti-*H. pylori* therapy, which to our knowledge has not been reported before. Our study has several limitations. We did not gather detailed medical information on children with comorbidities, such as ongoing disease activity, and detailed previous and current drug therapy, since this was not the primary goal of our registry. This information is usually considered by physicians when deciding the treatment of *H. pylori* infection in children with GI comorbidities. Our study also lacks details on whether the upper endoscopy was performed during the initial diagnostic workup or during follow-up for disease monitoring or observing therapy response. This may influence the findings regarding mucosal lesions and treatment decisions.

5 | Conclusion

In our cohort of 1165 pediatric patients with endoscopically confirmed treatment-naïve *H. pylori* infections, children with

GI comorbidities were less likely to be treated than children without any comorbidity, particularly in countries with a high *H. pylori* prevalence in the background population. Patients with GI comorbidities, particularly with IBD, CeD, or EoE, did not differ from children with no comorbidity regarding abdominal pain, ulcers or erosions, and adherence to anti-*H. pylori* therapy and the rate of adverse events, when treated. Weighing the benefits versus risks of not initiating therapy for a proven *H. pylori* infection may differ in children with GI comorbidities. Considerations should include age, type, and activity of the disease, current or planned drug therapy and—like in otherwise healthy children—psychological aspects of inducing anxiety by leaving a known infection untreated. For several reasons, eradication therapy in children with comorbidities may be deferred at a later time point. However, our data do not provide any evidence supporting different management strategies in patients in whom *H. pylori* infection was found incidentally during diagnostic endoscopy for suspected or proven GI disorders compared to otherwise healthy children reporting abdominal pain who were found to be *H. pylori* infected during upper endoscopy.

References

1. J. K. Y. Hooi, W. Y. Lai, W. K. Ng, et al., "Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis," *Gastroenterology* 153, no. 2 (2017): 420–429.

2. P. Malfertheiner, M. C. Camargo, E. El-Omar, et al., "*Helicobacter pylori* Infection," *Nature Reviews Disease Primers* 9, no. 1 (2023): 19.

3. M. Rowland, L. Daly, M. Vaughan, A. Higgins, B. Bourke, and B. Drumm, "Age-Specific Incidence of *Helicobacter pylori*," *Gastroenterology* 130, no. 1 (2006): 65–72 quiz 211.

4. M. Rowland, M. Clyne, L. Daly, et al., "Long-Term Follow-Up of the Incidence of *Helicobacter pylori*," *Clinical Microbiology and Infection* 24, no. 9 (2018): 980–984.

5. N. Kalach, Z. Misak, P. Bontems, et al., "Systematic Review and Meta-Analysis of Histological Gastric Biopsy Aspects According to the Updated Sydney System in Children," *Journal of Pediatric Gastroenterology and Nutrition* 74, no. 1 (2022): 13–19.

6. Y. Hu, J. H. Wan, X. Y. Li, Y. Zhu, D. Y. Graham, and N. H. Lu, "Systematic Review With Meta-Analysis: The Global Recurrence Rate of *Helicobacter pylori*," *Alimentary Pharmacology & Therapeutics* 46, no. 9 (2017): 773–779.

7. A. Feydt-Schmidt, A. Kindermann, N. Konstantopoulos, et al., "Reinfection Rate in Children After Successful *Helicobacter pylori* Eradication," *European Journal of Gastroenterology & Hepatology* 14, no. 10 (2002): 1119–1123.

8. B. J. Marshall and J. R. Warren, "Unidentified Curved Bacilli in the Stomach of Patients With Gastritis and Peptic Ulceration," *Lancet* 1, no. 8390 (1984): 1311–1315.

9. J. Q. Huang, S. Sridhar, Y. Chen, and R. H. Hunt, "Meta-Analysis of the Relationship Between *Helicobacter pylori* Seropositivity and Gastric Cancer," *Gastroenterology* 114, no. 6 (1998): 1169–1179.

10. K. E. L. McColl, "*Helicobacter pylori* Infection," *New England Journal of Medicine* 362, no. 17 (2010): 1597–1604.

11. W. Fischbach, "Gastric Mucosal-Associated Lymphoid Tissue Lymphoma," *Gastroenterology Clinics of North America* 42, no. 2 (2013): 371–380.

12. K. Sugano, J. Tack, E. J. Kuipers, et al., "Kyoto Global Consensus Report on *Helicobacter pylori* Gastritis," *Gut* 64, no. 9 (2015): 1353–1367.

13. I. J. Choi, M. C. Kook, Y. I. Kim, et al., "*Helicobacter pylori* Therapy for the Prevention of Metachronous Gastric Cancer," *New England Journal of Medicine* 378, no. 12 (2018): 1085–1095.

14. P. Malfertheiner, F. Megraud, T. Rokkas, et al., "Management of *Helicobacter pylori* Infection: The Maastricht VI/Florence Consensus Report," *Gut* 71 (2022): 1724–1762.

15. W. Fischbach, J. Bornschein, J. C. Hoffmann, et al., "Update S2k-Guideline *Helicobacter pylori* and Gastroduodenal Ulcer Disease of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS)," *Zeitschrift für Gastroenterologie* 62, no. 2 (2024): 261–321.

16. N. L. Jones, S. Koletzko, K. Goodman, et al., "Joint ESPGHAN/NASPGHAN Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (Update 2016)," *Journal of Pediatric Gastroenterology and Nutrition* 64, no. 6 (2017): 991–1003.

17. S. Koletzko, N. L. Jones, K. J. Goodman, et al., "Evidence-Based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children," *Journal of Pediatric Gastroenterology and Nutrition* 53, no. 2 (2011): 230–243.

18. L. A. Spee, M. B. Madderom, M. Pijpers, Y. van Leeuwen, and M. Y. Berger, "Association Between *Helicobacter pylori* and Gastrointestinal Symptoms in Children," *Pediatrics* 125, no. 3 (2010): e651–e669.

19. S. Koletzko, F. Richy, P. Bontems, et al., "Prospective Multicentre Study on Antibiotic Resistance of *Helicobacter pylori* Strains Obtained From Children Living in Europe," *Gut* 55, no. 12 (2006): 1711–1716.

20. M. Kori, T. G. Le Thi, K. Werkstetter, et al., "*Helicobacter pylori* Infection in Pediatric Patients Living in Europe: Results of the EuroPedHP Registry 2013 to 2016," *Journal of Pediatric Gastroenterology and Nutrition* 71, no. 4 (2020): 476–483.

21. T. G. Le Thi, K. Werkstetter, K. Kotilea, et al., "Management of *Helicobacter pylori* Infection in Paediatric Patients in Europe: Results From the EuroPedHp Registry," *Infection* 51, no. 4 (2023): 921–934.

22. R. Miyamoto, M. Okuda, Y. Lin, K. Murotani, A. Okumura, and S. Kikuchi, "Rapidly Decreasing Prevalence of *Helicobacter pylori* Among Japanese Children and Adolescents," *Journal of Infection and Chemotherapy* 25, no. 7 (2019): 526–530.

23. I. C. Arnold and A. Muller, "*Helicobacter pylori*: Does Gastritis Prevent Colitis?" *Inflammatory Intestinal Diseases* 1, no. 3 (2016): 102–112.

24. I. C. Arnold, N. Dehzad, S. Reuter, et al., "*Helicobacter pylori* Infection Prevents Allergic Asthma in Mouse Models Through the Induction of Regulatory T Cells," *Journal of Clinical Investigation* 121, no. 8 (2011): 3088–3093.

25. X. Zhang, I. C. Arnold, and A. Muller, "Mechanisms of Persistence, Innate Immune Activation and Immunomodulation by the Gastric Pathogen *Helicobacter pylori*," *Current Opinion in Microbiology* 54 (2020): 1–10.

26. M. J. Blaser, Y. Chen, and J. Reibman, "Does *Helicobacter pylori* Protect Against Asthma and Allergy?" *Gut* 57, no. 5 (2008): 561–567.

27. R. A. Imawana, D. R. Smith, and M. L. Goodson, "The Relationship Between Inflammatory Bowel Disease and *Helicobacter pylori* Across East Asian, European and Mediterranean Countries: A Meta-Analysis," *Annals of Gastroenterology* 33, no. 5 (2020): 485–494.

28. S. C. Shah, A. Tepler, R. M. Peek, Jr., J. F. Colombel, I. Hirano, and N. Narula, "Association Between *Helicobacter pylori* Exposure and Decreased Odds of Eosinophilic Esophagitis-A Systematic Review and Meta-Analysis," *Clinical Gastroenterology and Hepatology* 17, no. 11 (2019): 2185–2198.e2183.

29. N. A. Bayrak, E. Tutar, B. Volkan, et al., "*Helicobacter pylori* Infection in Children With Celiac Disease: Multi-Center, Cross-Sectional Study," *Helicobacter* 25, no. 3 (2020): e12691.

30. F. I. Amlashi, Z. Norouzi, A. Sohrabi, et al., "A Systematic Review and Meta-Analysis for Association of *Helicobacter pylori* Colonization and Celiac Disease," *PLoS One* 16, no. 3 (2021): e0241156.

31. K. M. Riggle, G. Wahbeh, E. M. Williams, and K. J. Riehle, "Perforated Duodenal Ulcer: An Unusual Manifestation of Allergic Eosinophilic Gastroenteritis," *World Journal of Gastroenterology* 21, no. 44 (2015): 12709–12712.

32. C. Deslandres, P. Russo, P. Gould, and P. Hardy, "Perforated Duodenal Ulcer in a Pediatric Patient With Eosinophilic Gastroenteritis," *Canadian Journal of Gastroenterology* 11, no. 3 (1997): 208–212.

33. A. Alper, S. Hardee, D. Rojas-Velasquez, S. Escalera, R. A. Morotti, and D. S. Pashankar, "Prevalence and Clinical, Endoscopic, and Pathological Features of Duodenitis in Children," *Journal of Pediatric Gastroenterology and Nutrition* 62, no. 2 (2016): 314–316.

34. A. Papadopoulou, J. Amil-Dias, M. K. Auth, et al., "Joint ESPGHAN/NASPGHAN Guidelines on Childhood Eosinophilic Gastrointestinal Disorders Beyond Eosinophilic Esophagitis," *Journal of Pediatric Gastroenterology and Nutrition* 78 (2023): 122–152.

35. K. Thakkar, L. Chen, M. E. Tessier, and M. A. Gilger, "Outcomes of Children After Esophagogastroduodenoscopy for Chronic Abdominal Pain," *Clinical Gastroenterology and Hepatology* 12, no. 6 (2014): 963–969.

36. S. Yuan, J. H. Kim, P. Xu, and Z. Wang, "Causal Association Between Celiac Disease and Inflammatory Bowel Disease: A Two-Sample Bidirectional Mendelian Randomization Study," *Frontiers in Immunology* 13 (2022): 1057253.

37. P. S. Ganga-Zandzou, L. Michaud, P. Vincent, et al., "Natural Outcome of *Helicobacter pylori* Infection in Asymptomatic Children: A Two-Year Follow-Up Study," *Pediatrics* 104, no. 2 Pt 1 (1999): 216–221.

38. J. S. Hyams, C. Di Lorenzo, M. Saps, R. J. Shulman, A. Staiano, and M. van Tilburg, "Functional Disorders: Children and Adolescents," *Gastroenterology* 150 (2016): 1456–1468.e2.

39. Y. Dolstra and M. Kori, "*Helicobacter pylori* Found Incidentally During Upper Endoscopy Performed for Diagnosis of Common Pediatric Gastrointestinal Diseases," *Pediatric Infectious Disease Journal* 42, no. 10 (2023): 833–836.

40. K. Kotilea, C. Romano, E. Miele, et al., "*Helicobacter pylori* Infection Found During Upper Endoscopy Performed for the Diagnosis of Celiac, Inflammatory Bowel Diseases, and Eosinophilic Esophagitis: A Multicenter Pediatric European Study," *Helicobacter* 29, no. 3 (2024): e13092.

41. C. I. de Bie, A. Paerregaard, S. Kolacek, et al., "Disease Phenotype at Diagnosis in Pediatric Crohn's Disease: 5-Year Analyses of the EURO-KIDS Registry," *Inflammatory Bowel Diseases* 19, no. 2 (2013): 378–385.

42. K. J. Werkstetter, I. R. Korponay-Szabo, A. Popp, et al., "Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice," *Gastroenterology* 153, no. 4 (2017): 924–935.

43. J. S. Hyams, M. C. Dubinsky, R. N. Baldassano, et al., "Infliximab Is Not Associated With Increased Risk of Malignancy or Hemophagocytic Lymphohistiocytosis in Pediatric Patients With Inflammatory Bowel Disease," *Gastroenterology* 152, no. 8 (2017): 1901–1914 e1903.

44. L. Beaugerie, N. Brousse, A. M. Bouvier, et al., "Lymphoproliferative Disorders in Patients Receiving Thiopurines for Inflammatory Bowel Disease: A Prospective Observational Cohort Study," *Lancet* 374, no. 9701 (2009): 1617–1625.

45. D. S. Kotlyar, J. D. Lewis, L. Beaugerie, et al., "Risk of Lymphoma in Patients With Inflammatory Bowel Disease Treated With Azathioprine and 6-Mercaptopurine: A Meta-Analysis," *Clinical Gastroenterology and Hepatology* 13, no. 5 (2015): 847–858.e4.

46. A. Kandiel, A. G. Fraser, B. I. Korelitz, C. Brensinger, and J. D. Lewis, "Increased Risk of Lymphoma Among Inflammatory Bowel Disease Patients Treated With Azathioprine and 6-Mercaptopurine," *Gut* 54, no. 8 (2005): 1121–1125.

47. M. Lemaitre, J. Kirchgesner, A. Rudnichi, et al., "Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease," *Journal of the American Medical Association* 318, no. 17 (2017): 1679–1686.

48. S. Shinzaki, T. Fujii, S. Bamba, et al., "Seven Days Triple Therapy for Eradication of *Helicobacter pylori* Does Not Alter the Disease Activity of Patients With Inflammatory Bowel Disease," *Intestinal Research* 16, no. 4 (2018): 609–618.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.