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Management of Helicobacter pylori (H. pylori) infection in pediatric patients

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I hereby declare that the submitted thesis entitled "***Management of Helicobacter pylori (H. pylori) infection in pediatric patients***" is my own work. I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

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Table of content

List of abbreviations

AMO	Amoxicillin
CLA	Clarithromycin
BMT	Bismuth-based therapy
CagA	Cytotoxin-associated protein A
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ER	Eradication rate
ESPGHAN	European Society for Pediatric Gastroenterology Hepatology and Nutrition
EuroPedHP-Registry	European Pediatric Helicobacter Pylori Registry
Gastric MALT lymphoma	Gastric mucosa-associated lymphoid tissue lymphoma
GI	Gastrointestinal
H. pylori	Helicobacter pylori
IDA	Iron deficiency anemia
MET	Metronidazole
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
PPI	Proton-pump-inhibitor
PUD	Peptic ulcer disease
SAT	Stool antigen test
SQT	Sequential therapy
STT	Standard triple therapy
TTT	Tailored triple therapy
UBT	13C-urea breath test
WHO	World Health Organization

List of publications

Publication I:

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1. Contribution to the publications

1.1 Publication I

For the publication I, my contribution includes performing the data analysis, interpreting the data, drafting the manuscript, revising it critically for important intellectual content, and reviewing and giving final approval of the manuscript.

Explanation for the shared first authorship:

Together with Dr. Michal Kori and Dr. Katharina Werkstetter, I serve as a joint first author with equal contribution since we, three authors, had worked together on a publication and equally contributed to different work packages of a project including a high number of pediatric patients over four years from 2013 to 2016. Dr. Michal Kori and Dr. Katharina Werkstetter contributed to the conception and design of the registry and acquisition of patient data, while my contribution was the data analysis and interpretation of analysis results and writing the manuscript together with Dr. Michal Kori.

1.2 Publication II

For publication II, my contribution includes developing the registry's conception and design, setting up the survey questions in the data platform, managing the registry, monitoring participating centers, acquiring data, and data quality assurance. In addition, I performed data analysis, interpreted evaluation results, drafted the manuscript, revised it critically for important intellectual content, and reviewed and gave final approval of the manuscript.

2. Introductory summary

2.1 *Helicobacter pylori* infection in children

2.1.1 Background

Helicobacter pylori (H. pylori) is considered as the most common bacterial pathogen in humans worldwide (1, 2). *H. pylori* infections are predominantly acquired in children in early ages (3-9), and may present with or without symptoms. Transmission occurs predominantly within the family (10), especially the infected mother, who plays a crucial role in transmitting *H. pylori* to their children (5, 11).

H. pylori infection is a high-risk factor for developing three serious upper gastrointestinal diseases (12): gastric and duodenal peptic ulcer disease (PUD) (13-17), gastric cancer (12, 18-20), and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (21, 22). *H. pylori* was classified as a class I carcinogen in 1994 by WHO and as an infectious agent in the recent Kyoto consensus (23). Nevertheless, the vast majority if *H. pylori*-infected persons do not or will not show any clinically significant complications (12).

H. pylori infection can be cured. Indication for diagnostic work-up and treatment was first introduced in the Maastricht Consensus Report in 1997 (24). Since then, the standard triple therapy (STT), including a proton pump inhibitor and two antibiotics, commonly clarithromycin (CLA), has been widely used as first-line therapy worldwide (24-28). Eradication of *H. pylori* infection was proven to improve gastric inflammation, heal gastritis, cure PUD and reduce the risk of gastric cancer (23, 29-32). A spontaneous eradication without applying a specific treatment regimen is unlikely (33). After successful eradication, reinfection is rare in Western countries (33, 34).

H. pylori infection in children is different than in adults in many aspects: the infection prevalence, the immunological response (35), type and prevalence of complications, age-specific diagnostic tests, antibiotic resistance rate, available drugs, and available options for treatment (13, 14, 36-38).

This introductory summary addresses the specific characteristics of *H. pylori* infection in children and its knowledge gaps. This doctoral thesis aims to fill some of these gaps by data analysis of collected long-term data via the European Pediatric *Helicobacter pylori* Registry (EuroPedHp Registry).

2.1.2 Prevalence

Compared to adults, the prevalence of *H. pylori* infection in children is lower due to a globally observed cohort effect. This cohort effect in a pediatric population has been nicely demonstrated in two cross-sectional serological studies performed in Russia 10 years apart, including children and adolescents from 1 to 19 years of age. In all age groups, an approximately 25% to 30% higher seropositive rate was found in the cohort assessed in 1995 compared to the cohort measured in 2005 (39). It is estimated that about 30% of children and adolescents globally is or has been infected with *H. pylori* (40, 41). The recently published systematic review and meta-analysis of Yuan et al. 2022 of cohort studies obtaining non-invasive diagnostic tests (serology, urea breath tests, or stool antigen tests) demonstrated that pediatric *H. pylori* infection was significantly associated with older age, more siblings, or children living in the same household, room sharing, lower economic status, limited access to a clean water system, consuming un-boiled or non-treated water, and having an infected mother or siblings (41).

The prevalence of *H. pylori* infection in children and adolescents living in Europe was estimated at 21.8% (95% CI: 16.1 – 28.9) (41) and has decreased over time. The

declining trend is explained by improved living conditions, socioeconomics, and having fewer children per family. In addition, early diagnosis and treatment in adults, respective mothers, fathers, or grandparents reduce the risk of *H. pylori* infection in the offspring (13, 42).

In Northern, Western, and central European countries, the prevalence of pediatric *H. pylori* infection is as low as ≤ 10% and increases with age (40, 43-46). A higher prevalence of 32% was reported in 844 Portuguese children aged <15 years and with higher frequencies in older age groups (20% under five years, 37% in 6-10 years, and 52% in 11-15 years of age (47).

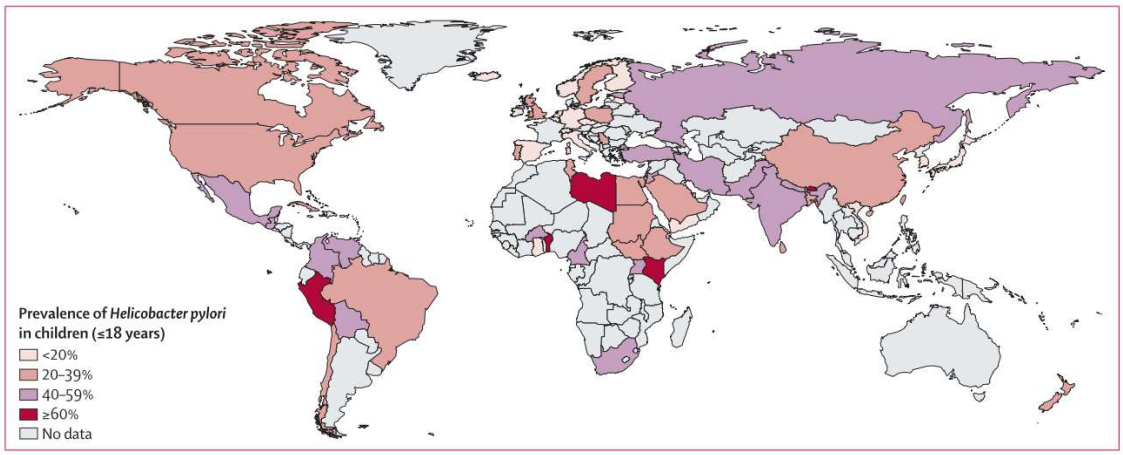

Figure 1: Prevalence of *Helicobacter pylori* infection in children and adolescents worldwide (41)

Adapted from Figure 3 of Yuan C, Adeloye D, Luk TT, et al. *The global prevalence of and factors associated with Helicobacter pylori infection in children: a systematic review and meta-analysis.* Lancet Child Adolesc Health. 2022;6(3):185-194. doi:10.1016/S2352-4642(21)00400-4

Recent results from a cross-sectional cohort study in Heidelberg, Germany, demonstrated an *H. pylori* seroprevalence of 12% in children <15 years (44). In the Ulm Birth Cohort Study, an infection rate of 3% was reported in 2009 at the age of 4 years (5), while 13% of 945 preschool children in Ulm were found *H. pylori* positive in a study back in 1996 (8). A cross-sectional study in the Aschaffenburg area in 1997/1998 revealed an infection in 9% of 540 school-aged children and adolescents (48). However, the prevalence of *H. pylori* infection enormously varied among children living in

Germany, depending on whether their parents were of German or foreign origins with recent immigration to Germany (8, 48). Reflecting the migration from high-prevalence countries of the Middle East, Asia, or Africa (49), children migrated from these areas are more likely to be infected with *H. pylori*.

2.1.3 Clinical complications

2.1.3.1 Gastrointestinal manifestations

In *H. pylori*-infected children, symptoms such as abdominal pain, nausea, vomiting, bloating, heartburn, diarrhea, constipation, or metallic taste were frequently documented. However, these abdominal complaints are nonspecific, occur very common in children, and can be a symptom of functional gastrointestinal disorders or various organic diseases (14, 36, 50, 51). Furthermore, several studies, systematic reviews, and meta-analyses did not confirm a significant association between abdominal pain and *H. pylori* infection in childhood and adolescence (37, 52-56).

Peptic ulcer disease in children is less common compared to adults. Koletzko et al. 2006 reported gastric or duodenal ulcers in less than 5% of young children ≤ 12 years and 10% of teenagers in a large multicentric cohort enrolling 1233 European children and adolescents, who showed symptoms, undergone an upper endoscopy and had a proven *H. pylori* infection (46). In a prospective case-control study including 732 European children, *H. pylori* infection remains a risk factor for duodenal ulcers and duodenal erosions but not for gastric lesions in children (57). Data from endoscopic findings in children over 25 years in Belgium confirmed that *H. pylori* infection is not a risk factor for gastric ulcers but was significantly related to duodenal ulcers and gastric or duodenal erosions (58).

Furthermore, no causal association was shown between *H. pylori* infection and gastric cancer in the pediatric population (36, 59). Only a few cases of gastric MALT lymphoma in teenagers infected with *H. pylori* have been recorded (36, 60).

2.1.3.2 Extra-gastrointestinal manifestations

No conclusive evidence supports the causal association between *H. pylori* and extra gastrointestinal manifestations such as iron deficiency and chronic or refractory iron deficiency anemia (IDA) in pediatrics. *H. pylori* infection as the only cause of iron deficiency anemia is rare in children and adolescents (61, 62). RCTs confirmed the causal relationship between *H. pylori* and iron deficiency anemia (63, 64). A comparative observational study in 2005 demonstrated that recovery from iron deficiency or iron deficiency anemia could be obtained with eradication in pediatric patients with *H. pylori* infection who had not received any iron supplementation (65). A study on young Bangladeshi children concluded that *H. pylori* infection was not a cause of iron deficiency with or without anemia (66). A recent study in low-income settings demonstrates that *H. pylori* infection in children without symptoms was not associated with fractional iron absorption from iron-fortified foods (67).

H. pylori-eradication may have a beneficial health effect in children with chronic idiopathic thrombocytopenic purpura (ITP) (68-73), with recurrent Schönlein-Henoch purpura (74, 75) or chronic urticaria (76, 77). However, these diseases are very rare in children, and *H. pylori* infection is less prevalent in children with these conditions than in affected adults (68, 73, 76). Due to the small number of infected children suffering from these rare conditions and short follow-up, evidence is lacking or very low for a beneficial effect of *H. pylori* eradication in childhood-onset chronic ITP, Schönlein-Henoch purpura, or chronic urticaria (36, 68, 75).

2.1.3.3 Potential beneficial health effects of *H. pylori*

There is some evidence from epidemiological and animal studies that *H. pylori* infection at younger ages has beneficial effects (78). Epidemiological studies demonstrated a negative relationship between *H. pylori* infection in early life, immune-mediated disease, particularly childhood asthma and atopy (45, 79-84), and inflammatory bowel disease (85, 86). *H. pylori* infection, particularly infection with CagA(+) *H. pylori* strain, induces T-Reg cells and may have a protective role in developing childhood asthma (87-93). A study from Israel, a high-prevalence population, confirmed the inverse relation (94). Evidence suggests that *H. pylori* infection was associated significantly with a reduced risk for atopy and allergy.

A negative association between *H. pylori* infection and inflammatory bowel disease has been shown in Europe and East Asia, with a stronger effect on Crohn's disease compared to ulcerative colitis (85, 95, 96). In addition, in children diagnosed with celiac disease, *H. pylori* infection was less common than in the background population or non-celiac control group (97-99). However, in humans, evidence was primarily based on observational studies, i.e., case-control studies, which do not prove a causal relation and a long-term health benefit of early *H. pylori* infection and should be interpreted cautiously for a specific population. In contrast, the interventional animal studies using a mouse model comparing neonatal infected mice with uninfected, later infected, or treated ova-sensitized mice showed a significant decrease in bronchial hypersensitivity and asthma (83, 100). The transfer of T-Reg cells and certain *H. pylori* extracts from neonatal infected to uninfected mice protected the latter ones and atopy and asthma. In other mouse models, the same group could show that *H. pylori* infection could reduce the risk for DSS-induced colitis, with no risk reduction against multiple

sclerosis or Type 1 diabetes (101).

In summary, *H. pylori* infection has fewer harmful complications in children than in adults and may even reduce the risk for some immune-mediated disorders through immunomodulatory properties. Therefore, when eradication therapy is prescribed in pediatrics, it should have a clear benefit for this individual child, e.g., healing peptic ulcers and reducing the risk of recurrence. In the absence of ulcer disease, possible beneficial health effects of an *early H. pylori* infection must be weighed against the potential risks of peptic ulcer disease or its consequent gastric cancer later in life. These risk/benefit considerations are particularly important in children in whom *H. pylori* gastritis was an incidental finding during upper endoscopy of other indications. Postponing the treatment into early adulthood with more treatment options available is an option in such a situation and should be discussed with the patient and their parents. Moreover, pediatricians should also consider that antibiotic resistance develops after a failed therapy in two-thirds of the patients (46, 102, 103), resulting in a higher burden and cost of repeated investigations and treatments (36).

2.1.4 Antibiotic resistance

Compared to adults, surveillance of the resistance rate of *H. pylori* strains to the commonly used drugs, i.e., clarithromycin (CLA) and metronidazole (MET), in children has been limited. Reported resistance rates vary significantly from country to country. In children, they reflect a primary infection with an antibiotic-resistant strain (e.g., from the mother) or acquired antibiotic resistance in a child with *H. pylori* gastritis which was with, e.g., a macrolide monotherapy for respiratory tract infection, which did not clear the *H. pylori* from the stomach but induced a CLA resistance in gastric bacteria. In the latter scenario, only part of the *H. pylori* strains may become resistant, resulting in mixed

infection with different strains. Therefore, the prescription habits of physicians treating children in a particular country may influence the prevalence of antibiotic resistance in *H. pylori* strains obtained from pediatric patients (104-110).

Between 1999 to 2002, the *H. pylori* working group of the ESPGHAN conducted the first international survey reporting the antibiotic resistance rates in *H. pylori* strains obtained from 1233 pediatric patients from 14 countries undergoing endoscopy because of symptoms (46). In this large European multicenter survey, the primary resistance rate to CLA was much higher than in adults reported for this period. The rate doubled once treatment failed (table 1). Double resistance to both drugs was found in 5% of treatment naïve patients but tripled in patients after treatment failed. In the absence of reserve antibiotics for children, this high level of antibiotic resistance was alarming for pediatric gastroenterologists. Children from Southern European countries had two times increased risk for primary CLA resistance. This phenomenon can be explained by the high prescription rates of macrolides in Italy, Spain, and Portugal (46).

Table 1: Antibiotic resistance rate of *H. pylori* strains in children and adolescents in Europe from 1999 to 2002 (46)

Factors	All patients	Group A before treatment	Group B after treatment failed	p-value
Metronidazole resistance, n=1216	25% (300/1216)	23% (233/1024)	35% (67/192)	<0.001
Clarithromycin resistance, n=1181	24% (278/1181)	20% (199/991)	42% (79/190)	0.001
MET- and CLA resistant, n=1181	7% (82/1181)	5.3% (53/992)	15.3% (29/189)	<0.001
Amoxicillin resistance, n=1094	0.6% (7/1094)	0.6% (6/1037)	1.8% (1/57)	n.a.

Adapted from Table 1 of Koletzko S, Richy F, Bontems P, et al. ***Prospective multicentre study on antibiotic resistance of Helicobacter pylori strains obtained from children living in Europe***. Gut. 2006;55(12):1711-1716. doi:10.1136/gut.2006.091272

In a cross-sectional multicentre study performed eight years later, Megraud et al. 2013 showed a significantly higher primary resistance rate to CLA (>30%) but lower

for MET (26%) than those obtained from adults (Table 2) (111). The rate of CLA resistance was related to prescribed doses per 1000 inhabitants per year in the respective countries. The resistance data of *H. pylori* strains from 311 children in this survey should be interpreted cautiously since the study preferentially included children living in countries with a known high CLA consumption (Table 2).

Antibiotic resistance of *H. pylori* strains has become a critical element in the treatment of *H. pylori* infection (103, 112, 113). In the past decades, the high consumption of antibiotics and especially inappropriate therapy regimens have led to a rapid increase in antibiotic resistance of CLA and MET and, as a consequence, a decrease in the efficacy of standard treatment regimens (38).

Table 2: Antibiotic resistance rate of *H. pylori* strains across European countries (1893 adults, 311 children) from 2008 to 2009 (111)

Antibiotic	N (%) resistant adults	N (%) resistant children*
Clarithromycin	332 (17.5)	99 (31.8)
Levofloxacin	267 (14.1)	8 (2.5)
Amoxicillin	14 (0.7)	1 (0.3)
Tetracycline	17 (0.9)	0 (0)
Rifabutin	22 (1.1)	1 (0.3)
Metronidazole	661 (34.9)	80 (25.7)

*Children from Austria, France, Germany, Greece, Italy, Poland, Portugal and Spain only were included.

Adapted from Table 2 of Megraud F, Coenen S, Versporten A, et al. ***Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption***. Gut. 2013;62(1):34-42. doi:10.1136/gutjnl-2012-302254

In a comprehensive systematic review and meta-analyses published by Savoldi et al. 2018, primary and secondary resistance rates to CLA, MET, and levofloxacin were estimated at above 15% and have increased over the past ten years in all WHO regions (112). Resistance to CLA was significantly associated with seven times increased risk for treatment failure of therapy regimens containing CLA (OR=6.97; 95% CI: 5.23-9.28) (112). Other studies came to the same conclusion since previous high consumption of macrolides is associated with an increasing rate of *H. pylori*-resistant strains (111, 114).

In contrast, MET resistance more than doubled the risk for eradication failure (OR=2.52; 95% CI: 1.83-3.48), though resistance to MET is the most prevalent resistance pattern worldwide (112). This phenomenon may be explained since in vitro susceptibility results to MET may not accurately reflect in vivo situations (102, 115). Though MET resistance significantly decreases *H. pylori* eradication rates (102, 116, 117), the negative impact of MET resistance can be largely overcome by prescribing higher doses, longer duration, and adding PPI (102, 118).

In recent years, the success rate of *H. pylori* eradication decreased in children, primarily related to the increasing resistance rate of *H. pylori* strains. Moreover, inappropriate regimens and their consequent failed treatments have contributed to antibiotic resistance development (36, 119, 120).

In the era of rising antibiotic resistance, any *H. pylori* therapy should ideally be based on antimicrobial stewardship to optimize the effect of antibiotics while reducing antibiotic resistance (121-123). Graham & Liou et al. 2021 pointed out the importance of therapy tailored to antibiotic susceptibility. Only antibiotics susceptible to the infection strains should be used in the treatment regimen (122, 123).

The heterogeneity of *H. pylori* strains (124) and the globally wide range of prevalence and diverse resistance patterns call for surveillance of antibiotic resistance of *H. pylori* strains to support the therapeutic choice of appropriate treatment regimens. Koletzko et al. 2006 was the first surveillance that obtained reliable data in pediatrics, including a large number of treatment naïve *H. pylori*-infected children. It addresses an urgent need to build surveillance with the same scope to survey antibiotic resistance to improve the eradication rate and limit the burden of *H. pylori* infection in children.

2.1.5 Treatment

Treatment in pediatrics is different from adults, not only regarding indication for treatment and risk-benefit-considerations but also regarding treatment regimen and dosing and the important availability of licensed drugs for primary therapy and after treatment failure (36). Several drugs that can be used in adults but not in children are restricted, particularly bismuth-based combination drugs, like Pylera® (125-127), which is considered first-line therapy in adults according to the most recent German evidenced-based guidelines for adults (128). Second-line antibiotics, like levofloxacin or rifabutin, are not licensed for children; tetracycline is contraindicated in younger children. Additionally, treatment regimens evaluated in adults were less effective when applied in children (129-131). A survey in 2007 on the applied treatment of pediatric patients in Europe revealed 27 different regimens regarding drug combination, dosing, and duration of therapy (131). The eradication rate was unacceptably low (131).

In the absence of reserve antibiotics and antibiotic resistance after failed therapy in two-thirds of patients, a primary eradication of at least 90% is important in children (102, 103). This will reduce the risk of spreading resistant strains within families, and populations will decrease the burden of repeated endoscopies and therapies to the individual patient and costs for society and caregivers (36, 132).

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) jointly provided their guidelines on the investigation and treatment strategies for pediatric gastroenterologists in 2011 (36) and updated their recommendations in 2016 (120). Following the ESPGHAN/ NASPGHAN guidelines, some minor country-specific adaptions of the guidelines on the diagnosis, prevention, and

treatment of *Helicobacter pylori* infection in pediatrics were developed for Latin America (133), Japan (134), Spain (135), Germany (128, 136) and other countries.

According to the ESPGHAN/ NASPGHAN guidelines in 2011 (36) and 2016 (120), endoscopy should be limited to children suffering from signs and symptoms severe enough to justify an upper endoscopy to search for the cause of the symptoms but not only to diagnose *H. pylori* infections. When gastric or duodenal peptic lesions are present, a clear recommendation to treat this child is provided (36, 120). There is no evidence that children with *H. pylori*-induced gastritis and symptoms of functional gastrointestinal disorders have an immediate benefit from the treatment (84). In these cases, it is an option to postpone therapy to prevent complications of *H. pylori* infection into early adulthood (25, 36). This option should be discussed with the caregivers and the patients if old enough, providing the potential risks and benefits of immediate or later therapy.

If *H. pylori* infection is confirmed by invasive methods and therapy is expected, the eradication should be tailored to antibiotic susceptibility since the primary resistance against CLA and MET in *H. pylori* strains is high from infected children. Two antibiotics should be administered for 14 days with a proton pump inhibitor (PPI); this combination is known as tailored triple therapy (TTT) (36, 120).

CLA should not be prescribed if cases with CLA resistance because of a high failure rate (102, 103, 112, 114). The impact of MET resistance on treatment failure in a regimen containing MET is less pronounced, and increasing the dose, duration, and higher PPI doses can overcome the impact of MET resistance in most cases (102, 118). Performing antibiotic susceptibility testing is essential before prescribing first-line therapy to optimize drug choice and thus avoid foreseeable treatment failure (118, 122,

123, 137). Furthermore, TTT was not only more effective than standard triple therapy in the first attempt to treat *H. pylori* infection but also more cost-efficient (132).

The updated guidelines in 2017 recommend a duration of anti–*H pylori* therapy of 14 days. Studies in adults confirmed that increasing therapy duration from 7 to 14 days significantly improved eradication (85% vs. 70%, p≤0.001) (138).

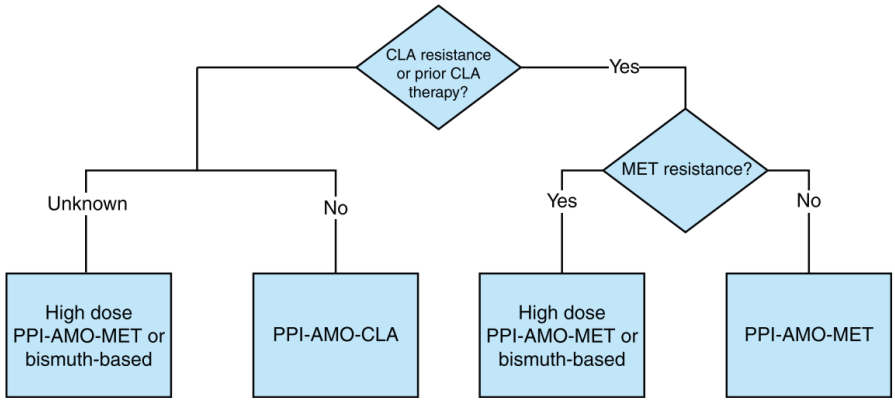

Figure 2: Algorithm to select eradication therapy for *H. pylori*-infected children based on knowledge of antibiotic susceptibility (120)

Adapted with permission from Jones NL, Koletzko S et al.; ESPGHAN, NASPGHAN. ***Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents*** (Update 2016). J Pediatr Gastroenterol Nutr. 2017 Jun;64(6):991-1003.

To achieve a primary eradication rate of at least 90%, the PPI dose used in the TTT regimen was increased from a maximum daily dose of 60mg to 80mg (table 4) (120). A high PPI dose more reliable increases the pH in the stomach. The bacteria enter their growing phase at high pH and become more susceptible to amoxicillin (AMO) and CLA (118). Because children at an early age until puberty have a higher CYP2C19 enzyme activity to break down PPIs such as (es)- omeprazole, they need a higher PPI dose per kg bodyweight to reach the same sufficient acid suppression compared to adults (139, 140). The updated guidelines recommend increasing PPI doses for all treatment regimens (120). Evidence showed that several factors might impair the acid-suppression capacity of PPIs, such as under-dosing, intake after meals instead of fasting state, dosing intervals

of 12 instead of 8 hours (two versus three intakes per day), and genetic polymorphism of the hepatic CYP2C19 enzyme activity (139). The latter one, which determines whether a person belongs to fast metabolizers, about 70% of the Caucasian population, intermediate (about 25%), or low metabolizers (<5%) (141). In fast metabolizers, esomeprazole achieves a higher and more predictable acid-inhibitory effect than, for example, pantoprazole (141). Further research is required to investigate the role of PPI type and different PPI doses on eradication success of triple therapy tailored to antibiotic susceptibility for two-weeks.

In patients infected with strains resistant to both CLA and MET or patients after eradication failure, a higher dose of AMO should be used with a maximum daily dose of 3000 mg instead of 2000 mg (table 4). The high-dose AMO regimen combined with MET and PPI for 14 days has been proven with an ER of 66% (95%CI: 54-78) to be an appropriate treatment option in children infected with double-resistant to *H. pylori* strains when second-line therapy in pediatrics is limited (142).

Table 3: Dosing regimens recommended in the updated ESPGHAN/NASPGHAN guidelines (e-publication in 2016)

A. Standard dosing regimen				
Drug	**Bodyweight range**	**Morning dose, mg**	**Evening dose, mg**	**Daily total dose, mg**
PPI Es(omeprazole)	15 - 24 kg	20 mg	20 mg	40 mg
	25 - 34 kg	30 mg	30 mg	60 mg
	> 35 kg	40 mg	40 mg	80 mg
Amoxicillin (AMO)	15 - 24 kg	500 mg	500 mg	1000 mg
	25 - 34 kg	750 mg	750 mg	1500 mg
	> 35 kg	1000 mg	1000 mg	2000 mg
Clarithromycin (CLA)	15 - 24 kg	250 mg	250 mg	500 mg
	25 - 34 kg	500 mg	250 mg	750 mg
	> 35 kg	500 mg	500 mg	1000 mg
Metronidazole (MET)	15 - 24 kg	250 mg	250 mg	500 mg
	25 - 34 kg	500 mg	250 mg	750 mg
	> 35 kg	500 mg	500 mg	1000 mg
B. High-dosing regimen for amoxicillin				
Drug	**Bodyweight range**	**Morning dose, mg**	**Evening dose, mg**	**Daily total dose, mg**
Amoxicillin (AMO)	15 - 24 kg	750 mg	750 mg	1500 mg
	25 - 34 kg	1000 mg	1000 mg	2000 mg
	> 35 kg	1500 mg	1500 mg	3000 mg

Adapted with permission from Jones NL, Koletzko S et al.; ESPGHAN, NASPGHAN. ***Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents*** (Update 2016). J Pediatr Gastroenterol Nutr. 2017 Jun;64(6):991-1003.

In the updated guidelines (120), sequential therapy containing PPI with AMO for five days, followed by PPI with CLA and MET for five days (143) is only recommended in patients infected with fully susceptible strains (144, 145). Sequential therapy should not be given to children infected with single resistant strains (either to MET or CLA) or if susceptibility testing results are unknown (120). Studies of non-bismuth concomitant quadruple therapy showed a high eradication rate in adults (146), but data for pediatric patients are not available. Both sequential and concomitant quadruple therapy should

be abandoned in pediatrics because these regimens involve at least one of the three antibiotics, which does not contribute to treatment success (122, 123).

Management of *H. pylori* infection in pediatric patients remains a challenge. One challenge has emerged in high-prevalence countries (147), where abdominal pain is the most frequently recorded primary indication for endoscopy, and no causes of these symptoms were detected but the presence of *H. pylori*. The use of non-invasive diagnostic tests in children with abdominal pain will also identify in these countries a high proportion of infected children. The knowledge that the child harbors the bacteria induces anxiety in the child and the parents and may lead to investigations and anti-*H. pylori* treatment, even repeated ones, if therapy fails.

Low compliance with guidelines on the management of *H. pylori* infection has been addressed, not only in regions where antibiotic susceptibility testing is not assessable or available (148). Lack of antibiotic susceptibility testing increased the likelihood of treatment failure.

Children with abdominal pain are first seen by primary-care pediatricians or general practitioners (149), with many of them still practicing “test and treat”. Inadequate dosing and duration of treatments with an antibiotic combination not tailored to antibiotic susceptibility and not monitoring for clearance of the infection is common practice in many countries (150, 151). Loss of follow-up or not performing monitoring visits to confirm treatment outcomes is a challenge in the management of *H. pylori* infection in both children and adults (151). Longer duration and higher antibiotic doses will increase the rate of adverse events, increasing the risk of low compliance, therapy discontinuation, and treatment failure.

In patients harboring more than one *H. pylori* strain in their stomach with

different resistance profiles (mixed infections), the resistant strain may be missed by sampling error, particularly if only one biopsy is used for culture. Mixed infections have been proven in >10% of *H. pylori*-positive children; this leads to a resistance underestimation of about 5% (152). In addition, Brennan et al. 2022 demonstrated that the culturing of *H. pylori* succeeded in a significantly higher number of children when gastric tissues were taken in the antrum and corpus than only in the antrum (153). Feydt-Schmidt et al. 2002 also revealed that the detection rate of resistant strains increases with biopsies from different sites of the antrum (152). Children with simultaneous infection with different *H. pylori* strains might be misinterpreted as susceptible or single-resistant and will receive inappropriate therapy regimens.

Treatment failure can be caused by inappropriate drug doses, in particular low PPI doses leading to ineffective acid suppression, but also too low antibiotic doses. Clinicians are encouraged to increase the PPI dose to a maximum daily dose of 80 mg and use antibiotic doses according to the updated guidelines (120). However, in some countries, high PPI doses cannot be prescribed because of national regulations for drug accessibility and availability for pediatrics. High-dose AMO prevents or reduces the emergence of resistance to other antibiotics used in the same regimen (123, 154).

Finally, poor adherence to therapy is a significant risk factor for eradication failure (155). Physicians should take the time to explain the importance of medication intake as prescribed for treatment success. Therapy-related adverse events are common but mostly mild and not harmful. They need to be described to patients and their parents to avoid therapy discontinuation.

In summary, surveillance of antibiotic resistance, prescribing adequate therapy tailored to antibiotic susceptibility testing, and follow-up data are essential to ensure

that the current treatment regimens remain effective. The EuroPedHp-Registry was established to generate real-life data to identify deficits and to adapt and improve guidance for the management and quality of care in *H. pylori*-infected pediatric patients.

2.2 Design of the EuroPedHp Registry

In 2013, the international multicentre EuroPedHp registry was established. The inclusion and exclusion criteria were as follows:

Inclusion criteria	Exclusion criteria
• age > 3 to ≤ 18 years • Helicobacter pylori infection - diagnosed according to the guidelines	• no endoscopy or biopsies done

From 2017 to 2020, we extended the data collection to treatment and follow-up data. The inclusion criteria of the EuroPedHp registry from 2017 to 2020 were wider to enhance, considering all *H. pylori* cases in children independent of endoscopy, treatment, and follow-up. Different from the EuroPedHp registry of the past period, patients with *H. pylori* infection without treatment were included. In addition, we included *H. pylori*-infected patients who were treated but without biopsies. Inclusion and exclusion criteria are as follows:

Inclusion criteria
• age > 3 to ≤ 18 years • *Helicobacter pylori* (*Hp*) infected patients diagnosed with **at least** stool test (SAT), breath test (UBT) **or** biopsies.

Participating pediatric gastroenterologists from 17 European countries, including Israel and Turkey (figure 2), prospectively and anonymously submitted data on *H. pylori*-infected pediatric patients in several sections:

- Demographics include age, gender, country of birth of the patient and their parents, weight, height, previous *H. pylori*-eradication, number of therapies, and year and month of the last eradication if known.

- Co-morbidities include eosinophilic esophagitis (EoE), inflammatory bowel disease (IBD), celiac disease, other GI-disease, liver disease, kidney disease, heart disease, lung disease, autoimmune disease, and malignancy.
- Assessed symptoms include abdominal pain, bloating, nausea, metallic taste, vomiting, diarrhea, and constipation.
- Endoscopy: Date of endoscopy (month/year) if performed at presenting center, the primary indication for endoscopy, and endoscopic findings in the esophagus, stomach, and duodenum. Number of biopsies taken in the stomach, the purpose of biopsies, results of histology, and RUT, if performed.
- Non-invasive tests (UBT, SAT, or serology) for diagnosis: If a non-invasive test(s) had been performed for diagnostic work-up inside or outside the reporting center, we recorded the date, type, and results.
- Antibiotic susceptibility testing: if disk diffusion, E-test, and/or PCR-based testing were performed, their results on susceptibility against the following antibiotics were recorded: CLA, MET, AMO, tetracycline, levofloxacin, and rifampicin reflecting rifabutin. If E-test was applied, we asked for MIC in µg/ml for each antibiotic if applicable.
- Therapy: If no anti-*H. pylori* therapy was prescribed, a reason for not prescribing therapy should be indicated. In treated patients, we asked for the applied regimen: dual therapy, triple therapy, quadruple therapy, or sequential therapy; type and the total daily dose of used PPI, CLA, MET, or other antibiotics in mg; whether AMO and PPI were taken in two or three divided doses, PPI intake and any use of probiotics and their specification as

well as concomitant medication. If bismuth-based therapy was used, the total daily dose in mg and number of intakes was asked.

- Monitoring assessment: date of the follow-up visit, adverse events during and after treatment, and assessment of eradication success, compliance to therapy, reasons for low/no compliance; results of follow-up tests, i.e., UBT, SAT, culture, or histology to confirm the eradication success at least 4 to 6 weeks after completed treatment, and if patient/caregiver had received the ESPGHAN *pylori* leaflet.

H. pylori infection was confirmed by either two positive biopsy-based tests (histopathology & rapid urease test) or by culture, or by two positive non-invasive tests (^{13}C-urea breath test (UBT) or stool antigen test (SAT)). Participating gastroenterologists were invited to submit records of all *H. pylori* patients independent of ethnicity, gender, country of birth of the parents, co-morbidities, with or without endoscopy, with or without prescribed treatment, applied regimens, or if the eradication succeeded or failed.

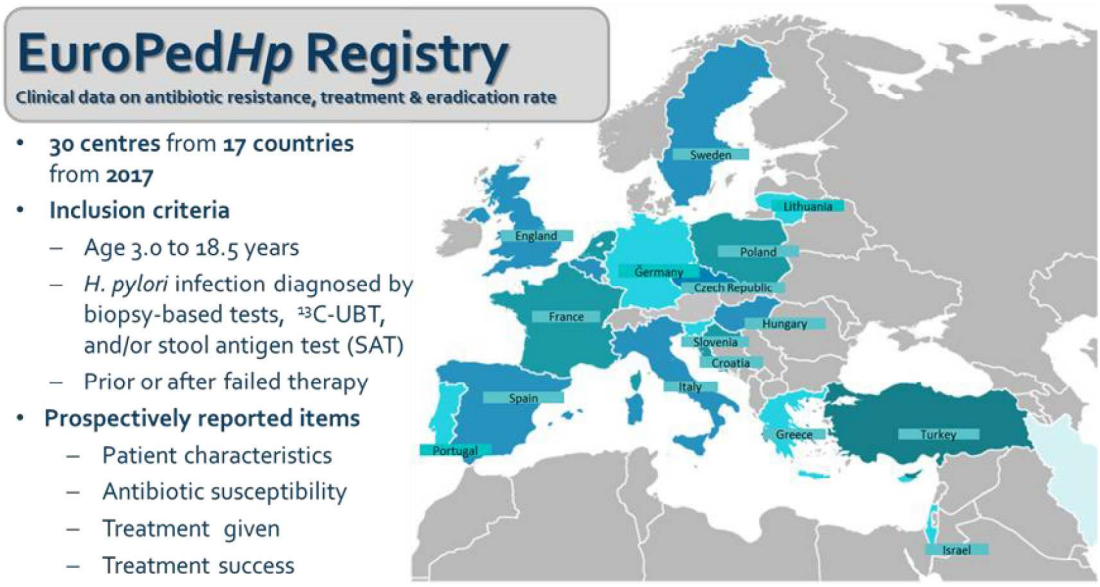

Figure 3: Participating countries in the EuroPedHp Registry 2017 - 2020

From 2013 to 2016, the EuroPedHp registry was established and hosted at the Helmholtz Zentrum München, Germany. Dr. med Andrea Sustmann and Dr. Katharina Werkstetter were appointed as data managers.

From 2017 to 2020, patient records were submitted anonymously as eCRF in Castor EDC, a secure online electronic data capture platform. Ms. Thu Giang Le Thi was appointed as the data manager.

Using a professional Castor platform allows us to generate an algorithm that double-checks the antibiotic testing results in the therapy section, i.e., researchers received a warning if they prescribed resistant antibiotics, the dose was insufficient, or the therapy duration was shorter than the recommended 14 days. The platform also cross-checked the duration of the monitoring assessment until the eradication test was performed. Researchers received a warning if the duration was too short or too long or a reminder if the eradication test was not performed.

Data evaluation was performed twice per year. Queries were sent by the data manager directly to the participating centers or automatically after double-checking on the platform to improve the data quality. Comments and remarks from participating centers were carefully reviewed with the principal investigator.

At yearly meetings of the *H. pylori* working group of the ESPGHAN, interim results of the EuroPedHp registry were discussed and critically reviewed. Pediatric gastroenterologists of participating centers, not only ESPGHAN members but also non-members of small hospitals, received newsletters twice a year with interim results and practical implications for clinical routine to improve treatment success according to the most recent guidelines (120).

Interim results of the EuroPedHp registry were presented at international

conferences over the years to promote the recent guideline for the management of *H. pylori* infection in children for pediatricians and pediatric gastroenterologists (36, 120).

2.3 Objectives of the thesis

This present thesis is based on data of the EuroPedHp registry covering the period from 2013 to 2016 (publication I) and after the extension of the questionnaires focusing on treatment outcomes after implementing the updated guidelines (120), covering the period from 2017-2010 (publication II). The following aims were fulfilled:

- To prospectively collect demographic, clinical, treatment, and follow-up data from *H. pylori*-infected children
- To survey the primary and secondary antibiotic resistance in *H. pylori* strains in pediatric patients concerning the country of living and country of birth of the patient and parents
- To identify risk factors for *H. pylori* antibiotic resistance against CLA, MET, and double resistance against both drugs
- To identify risk factors for gastric and duodenal peptic ulcers and erosions
- To assess clinical practice, compliance, and success of two-week tailored triple therapy (TTT) given according to the current guidelines in the treatment naïve patients
- To investigate factors related to treatment failure by applying a two-week TTT
- To observe the cure rate of bismuth-based therapy (BMT) and its potential in treating patients with double resistance to CLA and MET or after failed therapy.

- **Publication I:** *Kori M, **Le Thi TG**, Werkstetter K, et al. Helicobacter pylori Infection in Pediatric Patients Living in Europe: Results of the EuroPedHP Registry 2013 to 2016. Published in: J Pediatr Gastroenterol Nutr. 2020;71(4):476-483. doi:10.1097/MPG.0000000000002816 (119)*
- **Publication II:** ***Le Thi, T.G.,** Werkstetter, K., Kotilea, K. et al. Management of Helicobacter pylori infection in pediatric patients in Europe: results from the EuroPedHp Registry. Published in: Infection 2022. https://doi.org/10.1007/s15010-022-01948-y*

In the first paper, we focused on the surveillance of antibiotic resistance of *H. pylori* strains obtained during upper endoscopy from pediatric patients living all over Europe and compared the current results with those obtained in the first large survey during four years 15 years ago (46). In the second paper, we focused on evaluating the implementation and success rate of treatment recommendations given by the evidence-based updated guideline to treat *H. pylori*-infected children prior to first and after failed therapy.

2.4 Summary of results

Over eight years - from 2013 to 2020 - we recruited almost 3000 *H. pylori*-infected pediatric patients in our European registry. We accumulated a large and unique data set on patient characteristics, history, clinical presentation, endoscopic findings, antibiotic susceptibility of obtained *H. pylori* strains, applied treatment, adverse events, therapy compliance, and eradication success. We included both patients prior first anti-*H. pylori* therapy ("treatment naïve") and those after at least one failed therapy.

In publication I, our registry data confirmed with 5% a very low rate of peptic or

gastric ulcers considering that the children underwent endoscopy because of symptoms, mostly abdominal pain. This low ulcer rate in *H. pylori*-infected pediatric compared to adult patients is at least in part explained to be the lower exposure of children to additional ulcerogenic factors like tobacco, alcohol, and non-steroid-anti-inflammatory drugs (NSAID). The surveillance of antibiotic resistance over four years allows us to assess the evolution of antibiotic resistance compared to the first survey conducted almost 15 years ago (46). Of more than a thousand treatment naïve children, 25% harbored CLA-resistant strains (156) compared to 20% reported in 2006 (46). In contrast, MET resistance had slightly decreased over time. Primary antibiotic susceptibility showed considerable differences between European regions but was also significantly related to migrant status taking the child's and mother's country of birth into account (156).

The results of EuroPedHp registry from 2013 to 2016 revealed an eradication success in treatment naïve patients of only 80% of patients treated with triple therapy tailored to antibiotic susceptibility for 7 to 14 days (156). These unexpectedly poor results significantly impacted the updated guidelines published in 2017. The new guidelines recommend as first-line treatment a triple therapy guided by antibiotic susceptibility testing for a longer duration of two weeks, with higher doses of PPI (maximum daily dose 80mg) and antibiotics (120) than the previous guidelines (36). In patients infected with double resistance strains or patients with previous treatment failure, a higher dose of amoxicillin (AMO) was recommended, with a maximum dose of 3000 instead of 2000 mg/d (120).

In publication II, the focus was to evaluate the implementation and treatment success of the changed treatment in a large number of pediatric patients. A primary

eradication rate of 90% or higher, as suggested by the updated guidelines, was shown to be feasible with a guideline conform two weeks triple therapy tailored to antibiotic susceptibility with higher drug doses. (157). Treatment failure with this regimen was significantly associated with low treatment compliance and an infecting strain found to be single resistance to CLA or MET. The latter finding was surprising since tailored triple therapy should overcome the problem of antibiotic resistance in single-resistant strains. Based on our results, we hypothesize that we underestimate antibiotic resistance if a child is infected with two or more H. pylori strains with different antibiotic susceptibility profiles. Since multiple *H. pylori* strains are not evenly distributed in the gastric mucosa of different regions, one strain may be missed by taking only one biopsy for culture, or biopsies were taken at only one location. Consequently, we assume a lower antibiotic resistance rate in a considerable number of patients with a single resistance in the presence of double resistance or full susceptibility in the presence of antibiotic resistance. Therefore, we conclude from our findings that eradication success can be improved in clinical practice by taking at least two gastric biopsies from different locations (antrum and corpus) for culture in treatment naïve patients. Even more biopsies should be obtained in patients with failed therapies having a higher risk of these mixed infections. Since a sampling error cannot be excluded even with more biopsies, it should be considered to treat patients with fully susceptible strains with PPI, AMO & MET (PAM) instead of PPI, AMO & CLA (PAC). The rationale for this recommendation is that a missed CLA resistance resulting in the prescription of a CLA-containing regimen has a stronger negative effect on the cure rate than missing MET resistance.

Although the registry data could show that the goal of primary treatment success of 90% or higher can be reached, we identified some deficits in the implementation of

the updated guideline. For example, PPI and antibiotics, particularly AMO after treatment failure, were often prescribed in lower doses than recommended (table 1). Whether overcoming these deficits may result in an even higher success rate should be further investigated in future research.

Our findings also emphasized the importance of educating and empowering patients and their caregivers to improve adherence to therapy since compliance showed the strongest significant risk factor for treatment failure. A new approach is needed for pediatric patients to enable a simple,- low-cost, and patient-friendly treatment.

Because of limited randomized control trials in *H. pylori-infected* children, our registry remains a unique and comprehensive real-life data set obtained in different European regions. The knowledge gained from the pediatric registry will benefit not only children and adolescents. However, it may also be useful for adults with *H. pylori* infection, especially in countries where antibiotic resistance is high, and a bismuth-based fixed combination is not available.

Helicobacter pylori Infection in Pediatric Patients Living in Europe: Results of the EuroPed*HP* Registry 2013 to 2016

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ABSTRACT

Objectives: The aim of the study was to assess clinical presentation, endoscopic findings, antibiotic susceptibility and treatment success of *Helicobacter pylori (H. pylori)* infected pediatric patients.

Methods: Between 2013 and 2016, 23 pediatric hospitals from 17 countries prospectively submitted data on consecutive *H. pylori*-infected (culture positive) patients to the EuroPed*HP*-Registry.

Results: Of 1333 patients recruited (55.1% girls, median age 12.6 years), 1168 (87.6%) were therapy naïve (group A) and 165 (12.4%) had failed treatment (group B). Patients resided in North/Western (29.6%), Southern (34.1%) and Eastern Europe (23.0%), or Israel/Turkey (13.4%). Main indications for endoscopy were abdominal pain or dyspepsia (81.2%, 1078/1328). Antral nodularity was reported in 77.8% (1031/1326) of patients, gastric or duodenal ulcers and erosions in 5.1% and 12.8%, respectively. Primary resistance to clarithromycin (CLA) and metronidazole (MET) occurred in 25% and 21%, respectively, and increased after failed therapy. Bacterial strains were fully susceptible in 60.5% of group A, but in only 27.4% of group B. Primary CLA resistance was higher in Southern and Eastern Europe (adjusted odds ratio [OR_{adj}] = 3.44, 95% confidence interval [CI] 2.22–5.32, $P < 0.001$ and 2.62, 95% CI: 1.63–4.22, $P < 0.001$, respectively) compared with Northern/Western Europe. Children born outside Europe showed higher primary MET resistance ($OR_{adj} = 3.81$, 95% CI: 2.25–6.45, $P < 0.001$). Treatment success in group A reached only 79.8% (568/712) with 7 to 14 days triple therapy tailored to antibiotic susceptibility.

Conclusions: Peptic ulcers are rare in dyspeptic *H. pylori*-infected children. Primary resistance to CLA and MET is markedly dependent on geographical regions of birth and residence. The ongoing survey will show whether implementation of the updated ESPGHAN/NASPGHAN guidelines will improve the eradication success.

Key Words: abdominal pain, clarithromycin, endoscopy, *Helicobacter pylori*, metronidazole, pediatric gastroenterology, peptic ulcer disease (*JPGN* 2020;71: 476–483)

What Is Known

- Antibiotic susceptibility and treatment adherence are crucial for successful *Helicobacter pylori* eradication.
- In 2006, we reported antibiotic resistance in 1233 infected children (1033 treatment-naïve) living in 14 European countries. Primary resistance rates to clarithromycin and metronidazole were 20% and 23%, respectively.

What Is New

- This second survey in 1333 culture-positive children revealed increasing primary resistance for clarithromycin (25%), but not for metronidazole (21%). Antibiotic resistance significantly depended on geographical regions and migration status, questioning country-based recommendations.
- Prescribed drug doses were too low, particularly for protein pump inhibitors (PPI). Improved eradication rates can be expected if current European Society of Pediatric Gastroenterology, Hepatology and Nutrition/North American Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines are followed.

Helicobacter pylori (H. pylori) infection is acquired in early childhood in high and low prevalence countries and persists in most cases, unless treated (1–4). The incidence and prevalence of *H. pylori* infection decreased worldwide (5–9). Infection rates

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remain high in populations residing in or immigrating from Africa, South and Middle America, and many Asian, Middle East, Eastern and Southern European countries (9–12).

Chronic *H. pylori* infection causes gastric inflammation, but in children compared with adults, gastritis is mostly antrum-dominant with lower degree of chronicity and activity and predominant regulatory cell infiltrate (13,14). Epidemiological and animal studies revealed an inverse relationship between early *H. pylori* infection and immune-mediated disease (15–17). Most infected children are asymptomatic (18). Recurrent abdominal pain is not associated with the infection considering age, sex and socioeconomic characteristics (19). Despite rare development of peptic lesions in children, many children with abdominal pain or dyspepsia are investigated for *H. pylori* infection and treated if tested positive.

Efficacy of *H. pylori* eradication therapy in children decreased. Success rates depend on the choice of antibiotics, dose and duration of therapy, antibiotic susceptibility (20,21), and adherence to therapy (22).

Between 1999 and 2002, we performed the first international survey investigating antibiotic resistance rates in 1233 infected children living in Europe (23). Fifteen years later, we initiated the EuroPed*HP* registry to study clinical presentation, endoscopic findings, antibiotic susceptibility, and treatment success. The interim results had major impact on the updated management guidelines of the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) (24).

METHODS

Design of the Prospective Registry

Between 2013 and 2016, members of the *H. pylori* working group of ESPGHAN from 23 centers in 17 countries submitted anonymized demographical and clinical data on *H. pylori* culture-positive patients. Participating centers were from Northern (Sweden), Western (Belgium, France, Germany, The United Kingdom, The Netherlands), Eastern (Slovenia, Poland, Croatia, Lithuania, Hungary), Southern Europe (Portugal, Spain, Greece, Italy), and the Middle East (Israel, Turkey). The ethical committee of the leading center at the Ludwig Maximillian's University of Munich approved the protocol of the anonymous data collection. In the other centers, the respective local ethical committees granted approval whenever required. Physicians were encouraged to follow the *H. pylori* management guidelines published in 2012 (25). After interim analysis in May 2015, higher dosing and longer duration (14 days) of treatment were recommended.

Bacterial Culture and Antibiotic Susceptibility Testing

Antibiotic susceptibility testing was locally performed for metronidazole, clarithromycin, and amoxicillin using E-test or disk diffusion. Minimal inhibitory concentrations (MIC) for resistance were defined as follows: metronidazole at least 16 μg/ml, clarithromycin at least 1.0 μg/ml, and amoxicillin at least 0.5 μg/ml. A strain was considered double resistant if results for metronidazole and clarithromycin were above breakpoints.

Statistical Analysis

The distribution of resistance to metronidazole, clarithromycin, or both was compared in different strata of variables in relation to geographical regions (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). A univariate logistic analysis was performed including all subjects with no missing of considered variables except for "mother's country of birth." Odds were calculated for antibiotic resistance and presence

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The details on the members of the *Helicobacter pylori* working group of ESPGHAN are provided in the Appendix.

Guarantors of the article: T.G.L.T. and S.K.

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Sibylle Koletzko is senior author of the manuscript.

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of mucosal lesions. All statistically significant variables associated with resistance or the presence of peptic ulcer or erosions ($P \leq 0.25$) in the univariate analysis were considered in the multivariate logistic regression. Using the same samples as in the univariate analysis, the final multivariate logistic models were adjusted for sex and age (below and above 12 years) after applying backward elimination. Estimated risks (odds ratio, OR) and 95% confidence intervals (95% CI) were reported. Data were analyzed using SAS (Statistical Analysis Software 9.4, SAS Institute Inc., Cary, NC).

RESULTS

Study Population and Patient Characteristics

Between 2013 and 2016, data on 1460 patients with biopsy-proven, culture-positive *H. pylori* infection were submitted to the EuroPed*HP* Registry; 127 patients were excluded because of failing inclusion criteria or missing data (Supplemental Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Of the remaining 1333 children (55.1% girls, median age 12.6 years), 87.6% were treatment-naïve (group A), whereas 165 (12.4%) had failed treatment at least once (group B). Twenty-two percentage of the children, but 34.7% (n = 329) of the mothers were born outside of Europe, Turkey, or Israel (Table 1). There was an equal distribution of *H. pylori*-infected patients reported to the registry each year.

Indications for Endoscopy and Endoscopic Findings of Ulcers and Erosions

Abdominal pain and dyspepsia were the indication for endoscopy in 81.2% of patients (Table 1). Antral nodularity was observed during endoscopy in 77.8% of patients, gastric or duodenal ulcers and erosions in 5.1% and 12.8% of children, respectively. Erosions were significantly more prevalent than ulcers, with no significant differences between group A and group B (Table 1).

Among treatment-naïve children (group A), boys had a higher risk of having ulcers or erosions than girls (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Children older than 12 years were more likely to have ulcers than younger children (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Children living in Northern/Western Europe were 4 times more frequently reported to have peptic ulcers compared to children living in Southern Europe or Israel and Turkey (OR = 0.26, 95% CI: 0.13–0.55, $P = 0.0004$ and OR = 0.24, 95% CI: 0.08–0.70, $P = 0.009$, respectively) (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B866*).

Antibiotic Susceptibility

Antimicrobial susceptibility was tested with the E-test in 771 (57.8%), with disk diffusion in 546 (41.0%), and RT-PCR in 16 (1.2%) patients.

Antibiotic Resistance in Treatment-naïve Patients (Group A)

Metronidazole

Resistance to metronidazole was detected in 20.9% (95% CI: 18.4–23.5) of the strains obtained from treatment-naïve children (primary resistance) (Table 1). In the univariate analysis, the following risk factors were identified for a primary metronidazole resistance: age older than 12 years, country of residence, and birth of the child (Table 2). Children born outside of Europe had a 3.8 times higher risk (95% CI: 2.25–6.45, $P < .0001$) of being resistant to MET than children born in Northern/Western Europe (Table 3).

Clarithromycin

Primary resistance to clarithromycin was detected in 24.8% (95% CI: 22.1–27.5) of the strains (Table 1). The univariate analysis identified 2 important risk factors for primary clarithromycin resistance: region of residence and region of birth of the child (Table 2). Children living in Southern or Eastern Europe had a 3.4 and 2.6 times increased risk for primary clarithromycin resistance, respectively, compared with children living in Northern/Western Europe (Table 4).

Double Resistance

Primary resistance against both, clarithromycin and metronidazole, was found in 5.8% of the strains (57/976) (Table 1).

Amoxicillin

Resistance to amoxicillin (AMO) was a rare event (1.2%) in the cohort, with a slight increase in group B compared with group A patients ($P = 0.024$) (Table 1).

Antibiotic Resistance After Failed Treatment (Group B)

Out of 165 patients with treatment failure, the majority were born and lived in Southern Europe, whereas their mothers were also more likely to be born in Southern Europe (Table 1). The proportion of patients infected with strains susceptible to both CLA and MET was significantly lower in group B (27.4%) compared with group A (60.5%) ($P < 0.0001$) (Table 1). The chance to harbor a resistant strain increased after failed treatment, for amoxicillin from 0.9% to 3.3% ($P = 0.024$), for metronidazole from 20.9% to 52.4% ($P < 0.0001$), for clarithromycin from 24.8% to 47.6% ($P < 0.0001$), and for double resistance from 5.8% to 27.4% ($P < 0.0001$) (Table 1).

Factors Associated With Antibiotic Resistance in Treatment-naïve Patients

The comparison of antibiotic susceptibility in the 4 geographical regions demonstrated marked differences in the primary antibiotic resistance for both CLA and MET. CLA had the highest primary resistance rate in Southern Europe (36.7%) and the lowest in Northern/Western Europe (13.6%) (Supplemental Figure 3, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). MET had the highest primary resistance rate in children residing in Israel or Turkey (44.1%), whereas in the other regions, resistance ranged from 14.2% to 20.5%. After failed therapy (group B), antibiotic resistance increased for both antibiotics in all regions, but because of the small numbers in some of the subgroups, interpretations should be done with caution.

Treatment

Treatment regimens were prescribed tailored to antibiotic susceptibility. The majority of the patients received standard triple therapy ranging from 7 to 14 days' duration, whereas 14% (116/828) were treated with sequential therapy for 10 days. A small proportion received other therapy regimens. During the 4-year period, the median daily dose of protein pump inhibitors (PPI)

TABLE 1. Patient characteristics and clinical presentation (N = 1333)

Factors	All patients (N = 1333) No. (%)	Group A before treatment (n = 1168) No. (%)	Group B after treatment failed (n = 165) No. (%)	*P*-value†
Demographical characteristics				
Female	735 (55.1)	646 (55.3)	89 (53.9)	0.741
Age group (years), N = 1333				0.492
Age <12	605 (45.4)	526 (45.0)	79 (47.9)	
Age ≥12	728 (54.6)	642 (55.0)	86 (52.1)	
Country of residence*, N = 1333				0.0015
Northern/Western Europe	394 (29.6)	343 (29.4)	51 (30.9)	
Southern Europe	455 (34.1)	384 (32.9)	71 (43.0)	
Eastern Europe	306 (23.0)	287 (24.6)	19 (11.5)	
Israel & Turkey	178 (13.4)	154 (13.2)	24 (14.5)	
Country of birth*, N = 1118				0.0001
Northern/Western Europe	240 (21.5)	206 (21.2)	34 (23.3)	
Southern Europe	399 (35.7)	331 (34.1)	68 (46.6)	
Eastern Europe	226 (20.2)	216 (22.2)	10 (6.8)	
Asia, Africa, America & Middle East	253 (22.6)	219 (22.5)	34 (23.3)	
Mother's country of birth*, N = 947				<.0001
Northern/Western Europe	50 (5.3)	38 (4.6)	12 (10.4)	
Southern Europe	347 (36.6)	290 (34.9)	57 (49.6)	
Eastern Europe	221 (23.3)	213 (25.6)	8 (7.0)	
Asia, Africa, America & Middle East	329 (34.7)	291 (35.0)	38 (33.0)	
Diagnostic year, N = 1333				0.199
2016	335 (25.1)	299 (25.6)	36 (21.8)	
2015	342 (25.7)	302 (25.9)	40 (24.2)	
2014	325 (24.4)	288 (24.7)	37 (22.4)	
2013	331 (24.8)	279 (23.9)	52 (31.5)	
Endoscopic findings				
Indication for endoscopy, N = 1328				0.225
Abdominal pain	793 (59.7)	679 (58.4)	114 (69.1)	
Dyspepsia incl. nausea, vomiting	285 (21.5)	252 (21.7)	33 (20.0)	
Anemia	54 (4.1)	51 (4.4)	3 (1.8)	
Celiac disease	31 (2.3)	28 (2.4)	3 (1.8)	
GI-bleeding	28 (2.1)	27 (2.3)	1 (0.6)	
GERD, reflux	21 (1.6)	19 (1.6)	2 (1.2)	
IBD	9 (0.7)	8 (0.7)	1 (0.6)	
Eosinophilic esophagitis	6 (0.5)	5 (0.4)	1 (0.6)	
Others: weight loss, diarrhea etc.	101 (7.6)	94 (8.1)	7 (4.2)	
Antral nodularity, N = 1326	1031 (77.8)	898 (77.3)	133 (80.6)	0.346
Ulcers, N = 1325	67 (5.1)	60 (5.2)	7 (4.2)	0.610
Erosions, N = 1325	170 (12.8)	152 (13.1)	18 (10.9)	0.430
Results of antibiotic susceptibility testing				
Metronidazole resistance, N = 1126	282 (25.0)	205 (20.9)	77 (52.4)	<.0001
Clarithromycin resistance, N = 1131	314 (27.8)	244 (24.8)	70 (47.6)	<.0001
Amoxicillin resistance, N = 1000	12 (1.2)	8 (0.9)	4 (3.3)	0.024
Metronidazole and Clarithromycin resistance - Susceptibility subgroups, N = 1122				<.0001
MET-S/CLA-S	630 (56.1)	590 (60.5)	40 (27.4)	
MET-S/CLA-R	212 (18.9)	183 (18.8)	29 (19.9)	
MET-R/CLA-S	183 (16.3)	146 (15.0)	37 (25.3)	
MET-R/CLA-R	97 (8.6)	57 (5.8)	40 (27.4)	

N represents total number of available data for each factor in the cohort.
*Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.
†*P*-values refer to comparison between group A (before treatment) and group B (after treatment failed) obtained by the Pearson's Chi-square test.

had increased from 1.05 mg/kg body weight (2013) to 1.24 mg/kg (2016) and of amoxicillin from 46.6 mg/kg (2013) to 57.8 mg/kg (2016) (Supplemental Figure 4, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). There was a minor increase in the median dose of clarithromycin and metronidazole over the 4 years. The duration of treatment increased from 7 to 10 to 14 days in the majority of patients throughout the study, particularly after the interim analysis in May 2015 (Supplemental Figure 5, Supplemental Digital Content, *http://links.lww.com/MPG/B866*).

Eradication Success

Treatment outcome was available in 76.2% (1016/1333) of all patients. Among treatment-naïve patients infected with fully

TABLE 2. Univariate analysis of factors associated with metronidazole and clarithromycin resistance among pediatric patients not previously treated for *Helicobacter pylori* infection

Factors	MET susceptibility, N = 797				CLA susceptibility, N = 801			
	MET resistant (n = 180)	OR	(95% CI)	*P*-value†	CLA resistant (n = 210)	OR	(95% CI)	*P*-value†
Gender								
Female	103	1			116	1		
Male	77	0.92	(0.66 to 1.29)	0.642	94	1.03	(0.75 to 1.42)	0.847
Age group (years)								
Age <12	64	1			79	1		
Age ≥12	116	1.45	(1.03 to 2.04)	0.035	131	1.33	(0.96 to 1.84)	0.084
Country of residence*								
Northern/Western Europe	52	1			35	1		
Southern Europe	39	0.61	(0.39 to 0.97)	0.035	100	3.48	(2.25 to 5.38)	<.0001
Eastern Europe	45	1.15	(0.73 to 1.82)	0.538	58	2.66	(1.66 to 4.27)	<.0001
Israel & Turkey	44	2.79	(1.70 to 4.60)	<.0001	17	1.18	(0.63 to 2.23)	0.603
Country of birth*								
Northern/Western Europe	27	1			25	1		
Southern Europe	37	0.87	(0.51 to 1.50)	0.623	96	3.43	(2.10 to 5.61)	<.0001
Eastern Europe	47	1.71	(1.01 to 2.89)	0.046	63	2.86	(1.70 to 4.80)	<.0001
Asia, Africa, America & Middle East	69	4.01	(2.40 to 6.72)	<.0001	26	1.17	(0.65 to 2.13)	0.604
Mother's country of birth*								
Northern/Western Europe	6	1			9	1		
Southern Europe	30	0.69	(0.27 to 1.81)	0.455	94	2.04	(0.92 to 4.54)	0.080
Eastern Europe	50	1.68	(0.66 to 4.30)	0.280	58	1.33	(0.59 to 3.00)	0.495
Asia, Africa, America & Middle East	64	1.93	(0.76 to 4.88)	0.166	30	0.47	(0.20 to 1.11)	0.084
Diagnostic year								
2016	54	1			57	1		
2015	34	0.54	(0.33 to 0.87)	0.012	50	0.79	(0.51 to 1.24)	0.304
2014	49	0.79	(0.51 to 1.23)	0.296	51	0.76	(0.49 to 1.18)	0.221
2013	43	0.88	(0.55 to 1.40)	0.592	52	1.01	(0.64 to 1.57)	0.983
Ulcers								
No	169	1			199	1		
Yes	11	1.48	(0.72 to 3.06)	0.290	11	1.20	(0.58 to 2.48)	0.619

Odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the univariate analysis are given. Analyses were performed with complete datasets with no missing values in covariates, excepted the variable ''mother's country of birth.''

*Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.

†*P*-values obtained from the Wald Chi-Square Test for the significance of OR.

susceptible strains, triple therapy for 14 days showed a higher eradication success than for a shorter duration of 7 to 10 days (85% vs 75.6% respectively, $P = 0.03$) (Supplemental Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). No significant difference was detected by comparing triple therapy with different duration in other susceptibility groups. The eradication success did not achieve the treatment goal of 90% eradication rate in any subgroup (Supplemental

TABLE 3. Final logistic regression model for metronidazole resistance among pediatric patients not previously treated for *Helicobacter pylori* infection and no missing data for all of the factors considered in the univariate analysis (n = 797)

Factors	Unadjusted OR	Adjusted OR	(95% CI)	*P*-value†
Gender (Male vs. Female)	0.92	0.93	(0.65 to 1.32)	0.682
Age (Age ≥ 12 vs. Age <12)	1.45	1.18	(0.82 to 1.70)	0.374
Country of birth* (vs. Northern/Western Europe)				
Southern Europe	0.87	0.85	(0.50 to 1.46)	0.551
Eastern Europe	1.71	1.66	(0.98 to 2.81)	0.061
Asia, Africa, America & Middle East	4.01	3.81	(2.25 to 6.45)	<.0001

Unadjusted odds ratios (OR) were obtained from the univariate analysis.

Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the multivariate logistic regression model with sex and age group (below or above 12 years old) are given. Analyses were performed with complete datasets with no missing values in covariates.

*Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.

†*P*-values obtained from the Wald chi-square test for the significance of adjusted OR.

TABLE 4. Final logistic regression model for clarithromycin resistance among pediatric patients not previously treated for *Helicobacter pylori* infection and no missing data for all of the factors considered in the univariate analysis (n = 801)

Factors	Unadjusted OR	Adjusted OR	(95% CI)	*P*-value[†]
Gender (Male vs. Female)	1.03	1.15	(0.83 to 1.60)	0.407
Age (Age ≥12 vs. Age <12)	1.33	1.34	(0.96 to 1.88)	0.091
Country of residence[*] (vs. Northern/Western Europe)				
Southern Europe	3.48	3.44	(2.22 to 5.32)	<.0001
Eastern Europe	2.66	2.62	(1.63 to 4.22)	<.0001
Israel & Turkey	1.18	1.11	(0.59 to 2.10)	0.749

Unadjusted odds ratios (OR) were obtained from the univariate analysis.

Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the multivariate logistic regression model with gender and age group (below or above 12 years old) are given. Analyses were performed with complete datasets with no missing values in covariates.

[*]Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.

[†]*P*-values obtained from the Wald chi-square test for the significance of adjusted OR.

Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B866*).

DISCUSSION

Our analysis of the EuroPed*HP* survey data collected over 4-years disclose problems in the management of *H. pylori*-infected children and allow suggestions for improvement. The number of children included in this survey (n = 1333) is comparable with the previous 15 years ago (n = 1233) (23). The primary antibiotic resistance rates are high with large differences between geographical regions. Resistance rates are also related to migrant status. The rate of peptic ulcers in our cohort was low (5.1%). Prescribed treatments markedly differed, and the anticipated eradication rate of 90% was not reached, even in treatment-naïve children. The causes are multifactorial and other factors, such as adherence to therapy, dosing of the drugs, number of biopsies taken to capture strains with different antibiotic susceptibility in the stomach should be addressed.

With respect to antibiotic susceptibility, our cohort is representative of infected children residing in Europe including Israel and Turkey (Istanbul area). To account for the uneven distribution of patients from different countries, the study population was clustered in 4 geographical regions, which are similar in the accessibility and prescription behavior of antibiotics (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Patients from Southern Europe contributed a slightly higher percentage whereas there were fewer patients from Israel and Turkey. Selection and reporting bias are unlikely, as all centers prospectively reported every child with culture-positive *H. pylori* infection. Reliable data on previous eradication therapy were obtained from parents and referring physicians. The low ulcer rate argues against a selection bias with preferential testing children with abnormal endoscopic findings. Most European pediatric gastroenterologist take routine gastric and duodenal biopsies during upper endoscopy. Indication for endoscopy were unspecific symptoms, such as abdominal pain and dyspepsia in 4 out of 5 patients, whereas objective alarm signs, such as bleeding or anemia were rare (6.2%).

Compared with our previous survey (23), this registry included more detailed and structured reporting of endoscopic findings. The high rate of antral nodularity (78%) confirms previous pediatric series (26). Antral nodularity is almost pathognomonic to *H. pylori*-infected children, but not related to the presence of symptoms (27). The ulcer rate of 4% in children below 12 years of age was equal to the previous survey, whereas the current rate in teenagers was lower than 15 years back (6% vs 10%, respectively) (23). Teenage boys were more likely to have ulcers than girls pointing to either a lower threshold for endoscopy in girls or a higher exposure to environmental risk factors like tobacco, alcohol, or ulcerogenic drugs in adolescent boys. Our finding that children living in Northern/Western Europe had a 4 times increased chance of ulcer diagnosis may be because of the small number of ulcers found. Also, indication for endoscopy differs between countries depending on expectations of parents, reimbursement systems, use of noninvasive tests and referral for endoscopy based on a positive test result. In Northern/Western countries, children born to immigrant mothers were overrepresented, and immigrant status was related to peptic ulcer disease. This association could be related to different extrinsic or intrinsic factors, like referral for endoscopy or differences in genetic host or bacterial virulence factors.

With respect to primary antibiotic susceptibility, we noticed that metronidazole resistance decreased over the last 15 years in Eastern Europe (from 23.8% to 20.4%) (23) and Southern Europe (from 22.3% to 14.2%) (23). Clarithromycin resistance in Southern Europe, however, further increased, from 32.6% to 36.7% (23). In Eastern Europe, the clarithromycin resistance rate increased by 9% (from 17.5% to 26.3%) (23). Israel and Turkey showed a distinct pattern with a high metronidazole resistance rate (44.1%) but moderate rates for clarithromycin (16.5%).

As in the previous survey, being born outside of Europe was associated with an almost 4 times higher risk of harboring a metronidazole-resistant strain (OR = 3.81 in this vs OR = 2.42 in the previous survey). As the mother is the main source of infection (28), this finding is likely explained by the high use of metronidazole in Africa, the Middle East, and Asia. For clarithromycin resistance, there was a trend for a lower risk in younger children. The strongest association with clarithromycin resistance was the country of residence, confirming the positive relationship between a macrolides prescribed for benign infections and increasing resistant rates in Southern and Eastern Europe in adults (29). Restricting prescriptions for macrolides in Belgium resulted in the decreased clarithromycin resistance rates of *H. pylori* strains from children 10 years later (30). This indicates that intervention programs to reduce antibiotic use in common colds (31) or the antibiotic stewardship initiative may decrease antibiotic resistance within a population including *H. pylori*-infected children.

Treating *H. pylori* in pediatric patients is a challenge as bismuth-based combination drugs and second line antibiotics including levofloxacin and rifabutin are not licensed. Therefore,

a high primary success rate is even more important in children compared with adults. To avoid repeated antibiotic exposures and spreading of resistant strains after failed treatment, pediatric guidelines recommended against the test and treat strategy (24,25,32). The clear recommendation for treating infected children is given when gastric or duodenal peptic lesions are present. There is no evidence that symptomatic children with gastritis only have an immediate benefit of being treated (15). Applying the test and treat strategy to a pediatric population with an assumed *H. pylori* prevalence rate of 10%, would require noninvasive testing in 200 children and exposure to triple therapy in 20 of them in order to benefit 1 child with ulcer. Recent consensus reports recommend for adults to search for infected persons and treat them prior development of intestinal metaplasia and dysplasia to prevent gastric cancer (33,34). This does not apply to Pediatrics (35). In children, endoscopy should be restricted to those with symptoms suggesting organic disease. If *H. pylori* infection is detected during endoscopy and therapy is anticipated, the choice of antibiotics should be tailored to susceptibility testing (24,25). This strategy is superior and more cost effective compared with empiric therapy (36) with less burden to patients and their families by avoiding further endoscopies and antibiotic usage in this vulnerable population.

The strength of our study is the prospective recruitment of a large number of unselected patients with culture-proven infection from different European countries, the structured reporting of birthplace of child and mother, indications for endoscopy, macroscopic findings, antibiotic susceptibility, and outcome data. No such data are available from North America where susceptibility testing prior therapy is rare. The collection period of 4 years and application of the same analysis as in the previous survey allowed comparison of findings almost 15 years apart.

This survey has several limitations: *An uneven distribution of patients from different countries* due to the multicentric method, allowing only an evaluation by geographic regions. *Susceptibility testing was not performed in a central laboratory* due to financial restrictions (29). *Two methods (E-test and disc diffusion)* were used for susceptibility testing, and centers (country of residence) confounded the difference between the two methods. *Local antibiotic resistance breakpoints may not have been unified* over years. However, they were adjusted to the guidelines of the European Committee of Antibiotic Susceptibility Testing (EUCAST) (37) with AMO 0.5 μg/ml or 0.12 μg/ml, CLA 1.0 μg/ml or 0.5 μg/ml and MET 8.0 μg/ml or 16 μg/ml, respectively (38). Nonetheless, by comparing different breakpoints, we might overestimate a few cases of AMO resistance, but not for MET or CLA resistance (38). *Only one biopsy* was recommended for culture. This might underestimate antibiotic resistance, since mixed infections with multiple strains are likely to be missed (39). *A large range of different drug regimens and doses* were used for treatment not allowing solid data on treatment outcomes. *Patients after failed treatment* consisted only a small portion, 12.4% of the registry. Selection bias in this sub cohort cannot be excluded.

CONCLUSIONS

In conclusion, our results demonstrate the importance on continuous surveillance of antibiotic susceptibility of *H. pylori* strains from children considering country of living and migrant background. We also recommend the surveillance of eradication rates in relation to the drug regimen prescribed. Based on our data we suggest obtaining at least two gastric biopsies (antrum and corpus) for culture. We also suggest increasing drug doses, in particular PPI dose, and prolonging therapy to 14 days according to guidelines (24). We recommend improving adherence by providing written information to caregivers (40). The ongoing registry will show whether these measures increase eradication rates of tailored triple therapy to at least 90%.

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APPENDIX

Appendix 1 List of all members of the Helicobacter pylori working group of ESPGHAN in 2016

Supplemental Digital Content (SDC):

Supplemental table legends

Supplemental Table 1: Country distribution

Supplemental Table 2: Final logistic regression model for the presence of ulcers or erosions among pediatric patients not previously treated for *H. pylori* infection and country of residence

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Supplemental Figure 3: Antibiotic resistance of *H. pylori* strains obtained from pediatric patients residing in four regions of Europe, Israel and Turkey

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Supplemental Figure 5: Therapy duration over four years from 2013 to 2016, N=811

Supplemental Table 1: Country distribution

Country regions	Countries
Northern/Western Europe	
Northern Europe	Sweden, Norway, Finland
Western Europe	UK, England, Ireland, Scotland, France, Netherlands, Belgium, Germany, Austria, Switzerland, Luxembourg
Southern Europe	Portugal, Spain, Italy, Greece
Eastern Europe	Albania, Bosnia, Kosovo, Serbia, Macedonia, Romania, Slovenia, Moldova, Ukraine, Russia, Chechnya, Lithuania, Poland, Hungary, Czech Republic, Slovakia, Croatia, Azerbaijan, Moldavia, Rumania
Asia, Africa, America and Middle East	Angola, Guinea, Somalia, Senegal, Ghana, Cabo to Verde, Guinea, Guinea to Bissau, Madagascar, South Africa, Libya , Morocco, Tunisia, Algeria, Ethiopia, Eritrea, Republic Dominican, China, Mongolia, Thailand, Vietnam, New Guinea, Iran, Iraq, Iraq, Syria, Egypt, Turkey, Israel, Armenia, Bangladesh, Afghanistan, Afghanistan, Kazakhstan, Kazakhstan, Azerbaijan, India, Nepal, Azerbaijan, Canada, USA, US, Colombia, Chile, Peru, Ecuador, Bolivia Argentina, Brazil, Uruguay, Paraguay, Argentina, Australia.

Supplemental Table 2: Final logistic regression model for the presence of ulcers or erosions among pediatric patients not previously treated for *H. pylori* infection and country of residence

	Presence of ulcers, N=1160			Presence of erosions, N=1160		
	Adjusted OR	**(95% CI)**	**P-value‡**	**Adjusted OR**	**(95% CI)**	**P-value‡**
Gender (Male vs. Female)	3.18	(1.79 to 5.65)	<.0001	1.80	(1.27 to 2.57)	0.001
Age (Age ≥ 12 vs. Age <12)	1.83	(1.05 to 3.19)	0.034	1.07	(0.75 to 1.53)	0.704
Country of residence† (vs. Northern/Western Europe)						
Southern Europe	0.26	(0.13 to 0.55)	0.0004	0.48	(0.30 to 0.78)	0.003
Eastern Europe	0.49	(0.25 to 0.94)	0.033	0.82	(0.51 to 1.31)	0.398
Israel & Turkey	0.24	(0.08 to 0.70)	0.009	1.81	(1.12 to 2.92)	0.015

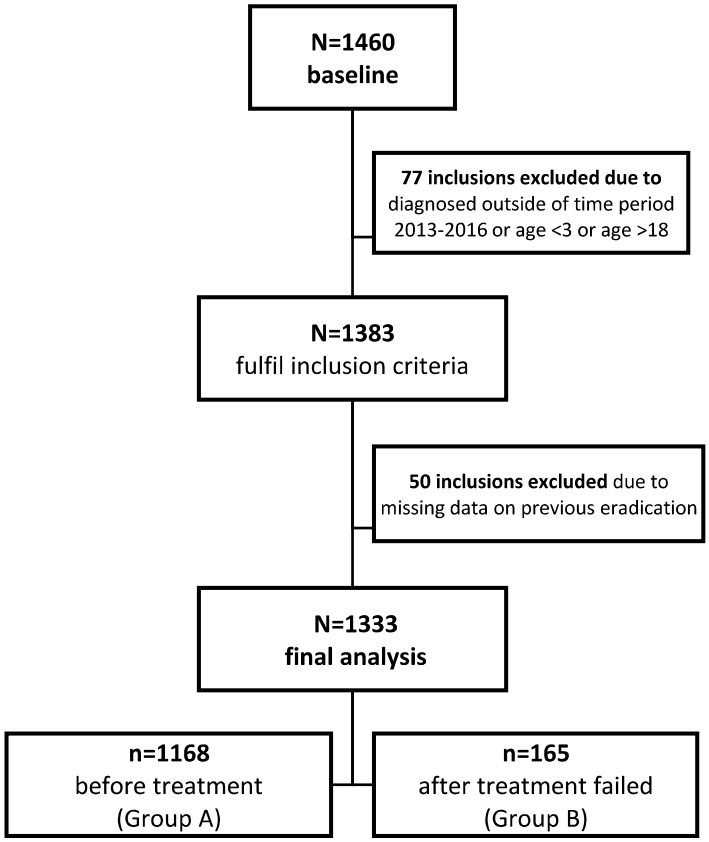
Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the multivariate logistic regression model with gender and age group are given.
Analyses were performed with complete datasets with no missing values in covariates.
† Country distribution was given in Supplemental Table 1.
‡ P-values obtained from the Wald Chi-Square Test for the significance of adjusted OR.

Supplemental Table 3: Eradication success of tailored triple therapy (TTT) for 7 (n=55) or 10 day (n=196) and TTT for 14 days (n=342) stratified in different susceptibility groups among pediatric patients not previously treated for *H. pylori* infection (group A)

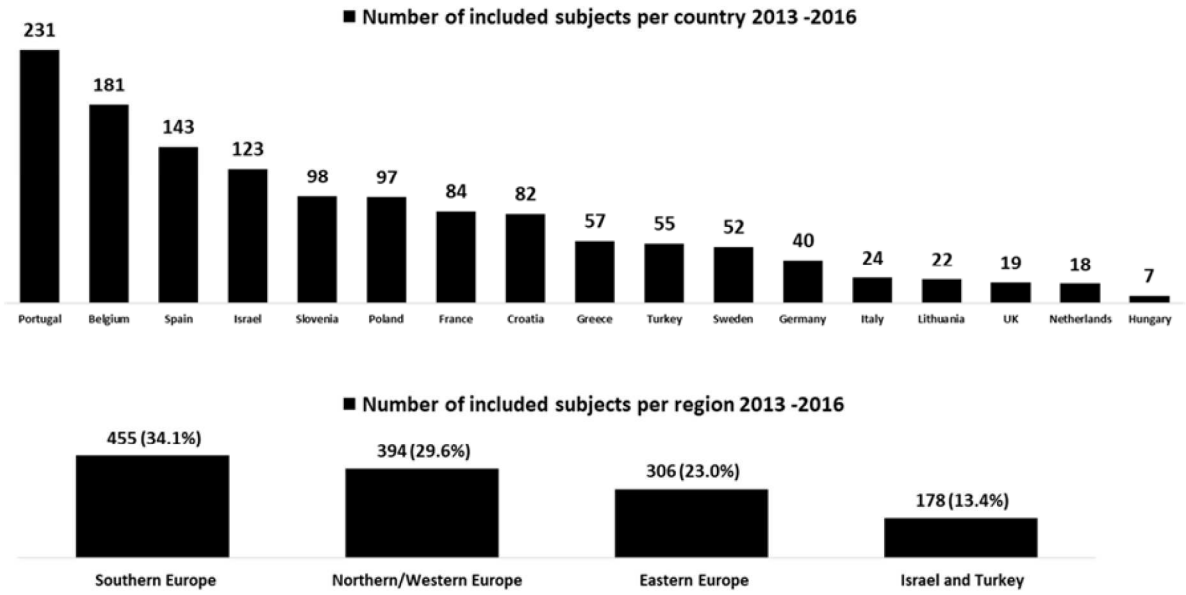
Metronidazole and clarithromycin resistance - Susceptibility subgroups	**TTT (7 or 10 days) E% (E/N)**	**TTT (14 days) E% (E/N)**	**P-value†**
MET-S/CLA-S, n=350	75.6 (124/164)	85.0 (158/186)	0.031
MET-S/CLA-R, n=133	75.0 (33/44)	85.4 (76/89)	0.157
MET-R/CLA-S, n=89	69.4 (25/36)	73.6 (39/53)	0.811
MET-R/CLA-R, n=21	85.7 (6/7)	57.1 (8/14)	0.337

TTT, Tailored triple therapy.
E% represents eradication success in percent as the proportion of all patients treated successfully (E) relative to all patients received a specific standard triple therapy (N) stratified in different susceptibility subgroups.
† P-values refer to comparison between TTT (7 or 10 days) and TTT (14 days) obtained by the Fisher Exact Test for each susceptibility subgroup.

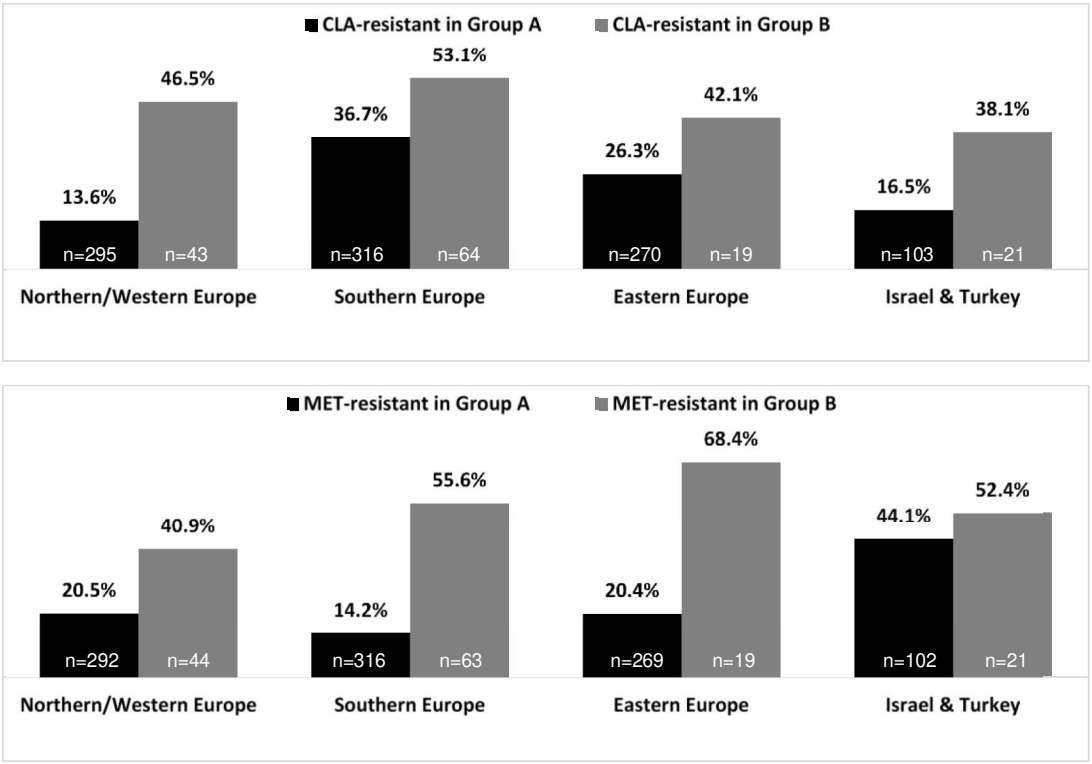
Supplemental Figure 1: Flow chart of the study population



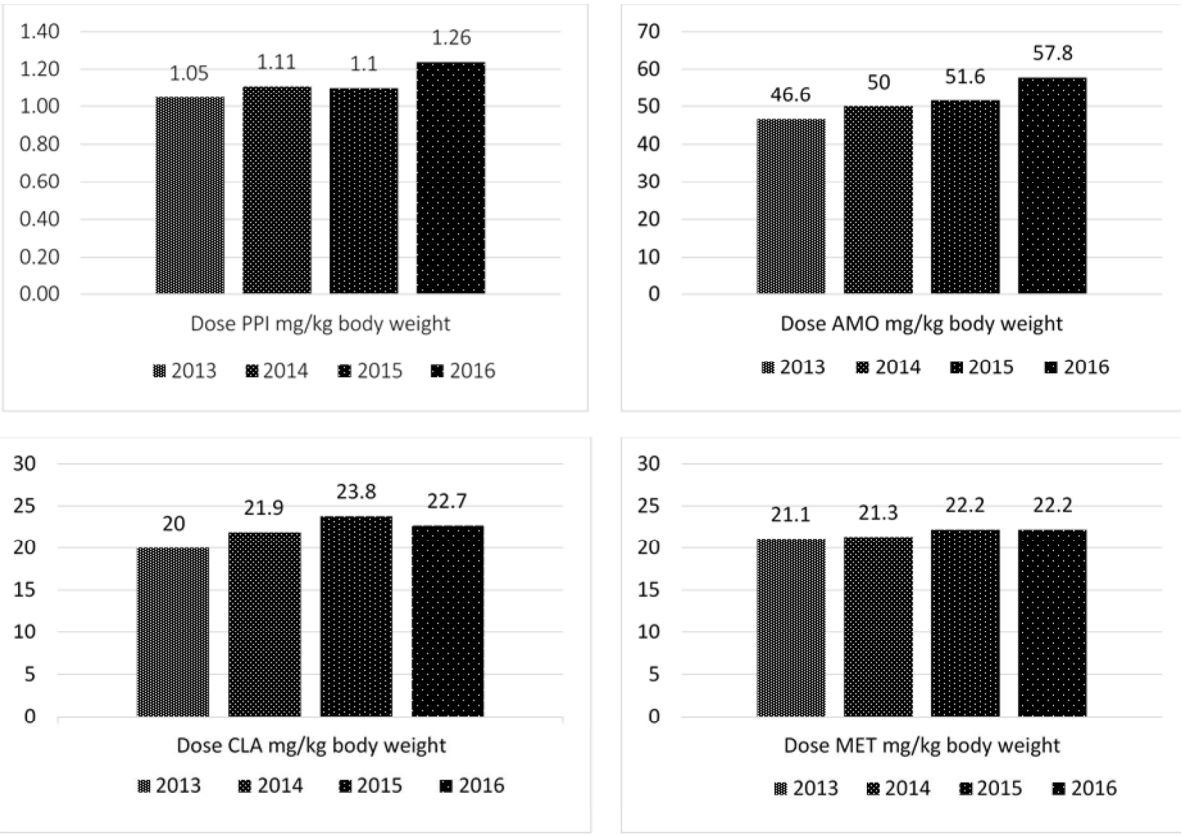
Supplemental Figure 2: Number of included subjects per country and per region from 2013 to 2016, N=1333



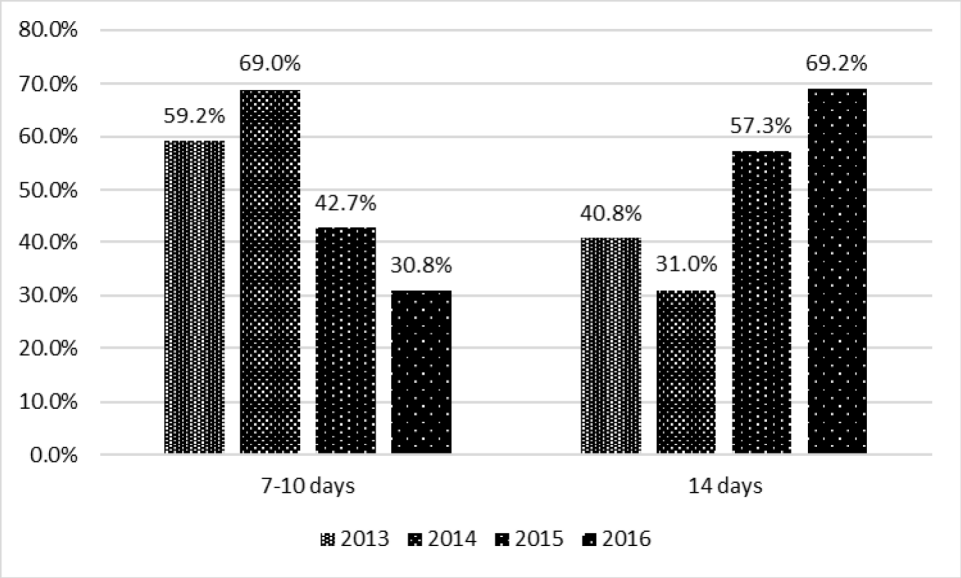
Supplemental Figure 3: Antibiotic resistance of *H. pylori* strains obtained from pediatric patients residing in four regions of Europe, Israel and Turkey



Supplemental Figure 4: Median daily dose given as mg/kg bodyweight of prescribed drugs over four years from 2013 to 2016 – Proton pump inhibitor (PPI), amoxicillin (AMO), clarithromycin (CLA) and metronidazole (MET)



Supplemental Figure 5: Therapy duration over four years from 2013 to 2016, N=811



RESEARCH

Management of *Helicobacter pylori* infection in paediatric patients in Europe: results from the EuroPedHp Registry

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Abstract

Purpose The EuroPedHp-registry aims to monitor guideline-conform management, antibiotic resistance, and eradication success of 2-week triple therapy tailored to antibiotic susceptibility (TTT) in *Helicobacter pylori*-infected children.

Methods From 2017 to 2020, 30 centres from 17 European countries reported anonymized demographic, clinical, antibiotic susceptibility, treatment, and follow-up data. Multivariable logistic regression identified factors associated with treatment failure.

E-Poster at the 34th Workshop of the European Helicobacter and Microbiota Study Group (2021) with the title: "Treatments after failed therapy in H. pylori-infected children in Europe: Results of the EuroPedHp Registry".

Oral presentation at the UEG Week Virtual (2020) with the title: "Excellent performance of 2-weeks tailored triple therapy in H. pylori-infected children: Interim results of the new EuroPedHp Registry".

E-presentation at the 33rd Workshop of the European Helicobacter and Microbiota Study Group (2020) with the title: "Excellent performance of 2-weeks tailored triple therapy in H. pylori-infected children: Interim results of the new EuroPedHp Registry".

Oral presentation at the 32nd Workshop of the European Helicobacter and Microbiota Study Group (2019) with the title: "Current treatment of *Helicobacter pylori*-infected children and adolescents in Europe: Interim results of the new EuroPedHp Registry".

Oral presentation at the 52nd ESPGHAN Annual Meeting (2019) with the title: "Interim analysis from the new EuroPedHp Registry of *Helicobacter pylori*-infected children in Europe".

Oral presentation to update the EuroPedHp Registry at the Annual Meeting of the *H. pylori* Special Interest Group of the ESPGHAN from 2017 to 2022.

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Extended author information available on the last page of the article

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Results Of 1605 patients, 873 had follow-up data (53.2% female, median age 13.0 years, 7.5% with ulcer), thereof 741 (85%) treatment naïve (group A) and 132 (15%) after failed therapy (group B). Resistance to metronidazole was present in 21% (*A*: 17.7%, *B*: 40.2%), clarithromycin in 28.8% (*A*: 25%, *B*: 51.4%), and both in 7.1% (*A*: 3.8%, *B*: 26.5%). The majority received 2-week tailored triple therapy combining proton pump inhibitor (PPI), amoxicillin with clarithromycin (PAC) or metronidazole (PAM). Dosing was lower than recommended for PPI (*A*: 49%, *B*: 41%) and amoxicillin (*A*: 6%, *B*: 56%). In treatment naïve patients, eradication reached 90% ($n=503$, 95% CI 87–93%) and 93% in compliant children ($n=447$, 95% CI 90–95%). Tailored triple therapy cured 59% patients after failed therapy ($n=69$, 95% CI 48–71%). Treatment failure was associated with PAM in single clarithromycin resistance (OR = 2.47, 95% CI 1.10–5.53), with PAC in single metronidazole resistance (OR = 3.44, 95% CI 1.47–8.08), and with low compliance (OR = 5.89, 95% CI 2.49–13.95).
Conclusions Guideline-conform 2-weeks therapy with PPI, amoxicillin, clarithromycin or metronidazole tailored to antibiotic susceptibility achieves primary eradication of ≥ 90%. Higher failure rates in single-resistant strains despite tailored treatment indicate missed resistance by sampling error.

Keywords *Helicobacter pylori* · *Helicobacter pylori*—in children · Antibiotic therapy · Drug resistance · Paediatric gastroenterology

Background

Helicobacter pylori (H. pylori) infections are mostly acquired in early childhood [1]. *H. pylori* infection causes chronic gastritis, although most children remain asymptomatic [2, 3]. Eradication of *H. pylori* infection improves gastric inflammation and reduces the risk for recurrent peptic ulcer disease (PUD) and malignancies [4]. *H. pylori* treatment should aim to reach a high primary eradication rate of at least 90% [5–8].

In the past years, the unnecessary and inappropriate use of antibiotics has led to high antibiotic resistance, including those used for *H. pylori* treatment (e.g. clarithromycin, metronidazole, and levofloxacin) [9–11]. In 2017, the World Health Organization designated clarithromycin-resistant *H. pylori* as a high-priority bacterium for antibiotic research and development [10]. In the era of increasing antibiotic resistance and decreasing eradication success, *H. pylori* therapies should be based on antimicrobial stewardship principles optimizing antibiotic use while reducing antibiotic resistance [5, 6]. Graham and Liou 2021 emphasized the importance of treatment tailored to antibiotic susceptibility regardless of age. Only antibiotics susceptible to infecting strains should be prescribed [5, 6], acknowledging that at least two-thirds of the *H. pylori* strains become resistant after treatment failure [12, 13].

In 2016, the European and North American Societies of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, NASPGHAN) updated guidelines to reach an eradication success of at least 90% in treatment naïve patients. They recommend first-line triple therapy with body weight-adjusted dosing combining proton-pump-inhibitor (PPI) at a higher dose (maximum 80 mg/day (es)-omeprazole or equivalent) plus two antibiotics tailored to susceptibility testing for 2 weeks [7, 8]. Sequential therapy is restricted to fully susceptible strains [3, 8, 14]. A higher daily amoxicillin (AMO) dose (maximum 3000 mg instead of 2000 mg) is recommended for infections with double-resistant strains or after treatment failure [8]. In children, a high initial eradication rate is crucial to avoid repetitive courses of antibiotics with the risk of inducing dysbiosis and antibiotic resistance. A high initial success rate will decrease repeated investigations (e.g. endoscopies), therapies and, consequently, costs and burdens for the patient, their families, and society [7].

Data on antibiotic resistance and treatment outcomes in children and adolescents living in Europe are sparse, and most are restricted to single centres [15, 16]. The *H. pylori* working group of the ESPGHAN initiated the EuroPedHp registry to survey antibiotic resistance, compliance to guideline-conform treatments, and eradication rate (ER) of the recommended treatment regimen. The data gathered from 2017 to 2020 allow us to investigate factors associated with treatment failure of tailored triple therapy (TTT). Furthermore, in countries with available bismuth-based therapy (BMT), we survey the cure rate of BMT in patients with double resistance to clarithromycin and metronidazole or after failed therapy.

Methods

Design and data collection

The EuroPedHp registry started in 2013 with the main aim of surveillance of antibiotic resistance [17]. From January 2017 onwards, data collection was extended for clinical and endoscopic findings, prescribed treatment, compliance, and

therapy success. Participating centres from 17 European countries, including Israel and Turkey, anonymously submitted information on *H. pylori*-infected paediatric patients on demographics (age, gender, country of birth from patient and their parents), symptoms and other indications leading to upper-endoscopy, previous anti-*H. pylori* therapies, comorbidities, endoscopic findings, antibiotic susceptibility testing, prescribed therapy and compliance with drug intake, adverse events during and after treatment and assessment of treatment success. Regarding country of living or country of birth, we assigned countries to four European geographical regions (Northern, Western, Southern, and Eastern) and outside Europe, including Israel, Turkey, the Middle East, Asia, Africa, and America (Supplementary File 1). *H. pylori* infection was confirmed according to guidelines [7, 8] by a positive culture or positive results of two other tests, either biopsy-based (histopathology, rapid urease test, or RT-PCR) or noninvasive [^{13}C-urea breath test (UBT) or monoclonal stool antigen test (SAT)].

Antibiotic susceptibility of *H. pylori* strains for clarithromycin, metronidazole, amoxicillin and second-line antibiotics like tetracycline, levofloxacin, and rifampicin was assessed at the local centres by using epsilometer test (E-test) or disc diffusion, occasionally real-time polymerase chain reaction (RT-PCR).

The local paediatric gastroenterologist decided on the treatment regimen, type, dose (mg/kg) and duration of applied PPI and antibiotics. Participating centres were encouraged to follow the evidence-based guidelines for the management of *H. pylori* infection in children and adolescents published in 2011 [7] and updated in 2017 (online available in 2016) [8] by the ESPGHAN/NASPGHAN and to prescribe the recommended dosing regimens according to body weight (Supplementary File 2).

Eradication success was assessed by noninvasive tests (UBT or monoclonal SAT) or gastric biopsies at least 4 weeks after completed treatment. Eradication rate (ER) was evaluated as the proportion of all patients treated successfully with a confirmed negative test relative to all treated patients with follow-up results.

Strict monitoring of treatment success was highly recommended. In cases of failed treatment, therapeutic regimens were chosen based on antibiotic susceptibility results, patient age, and availability of bismuth-containing drugs or other reserve antibiotics.

Data reporting and centre monitoring

Patient records were anonymously submitted in an electronic case report form (e-CRF) (Castor EDC, Amsterdam, The Netherlands). At the annual meetings of *H. pylori* working group of the ESPGHAN, interim data of the EuroPedHp registry were critically reviewed. Participating centres received newsletters providing practical recommendations to improve treatment success.

The protocol for irreversibly anonymized data collection was approved by the Ethical Committee of the LMU University Hospital Munich, Germany (project number: 105–13). Participating centres 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-Klinikum Munich, Germany.

Statistical analysis

Descriptive statistics for demographical and clinical characteristics are presented in two groups: patients prior to first anti-*H. pylori* therapy (treatment naïve) (group A) and after at least one failed therapy (group B).

The final analysis set (FAS) contains all paediatric patients with proven *H. pylori* infection, who received anti-*H. pylori* therapy, took at least one treatment dose and completed follow-up. Per-protocol (PP) analysis included all patients in the final analysis set who took at least 90% of prescribed drugs. Drug doses calculated by three weight classes (Supplementary File 2) were classified as "conform with guidelines" or "lower than recommended" [8].

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. All statistical tests were assessed with two-sided significance levels of 5%.

A univariate logistic analysis was performed to determine potential risk factors for treatment failure. Using the same samples as in the univariate analysis, the final multivariable logistic models were selected using backward elimination and adjusted for gender and age (in years) (Supplementary File 3). Estimated odds ratio (OR) and 95% confidence interval (CI) were reported.

To determine the difference between the real-life data and data including only cases treated with guideline-conform choices of antibiotics, we performed a sensitivity analysis after excluding cases where physicians falsely prescribed antibiotics to patients whose strains were resistant to.

Statistical analyses were performed using the SAS program (Statistical Analysis Software 9.4, SAS Institute Inc., Cary, North Carolina, USA) and Prism 9.3 (GraphPad Software).

Results

Study population

From 2017 to 2020, 1543 valid records of 1605 patients were reported by 30 centres from 17 European countries,

thereof all but 15 children had undergone upper endoscopies with biopsies in the reporting centres. Treatment against *H. pylori* infection was prescribed to 1263 patients, and thereof 873 completed follow-up (Supplementary File 4). Reasons for untreated cases include detection of *H. pylori* infection by chance at endoscopy for other disorders, no symptoms, young age, or parents' refusal. One-third of treated patients did not return for monitoring the success of therapy.

The baseline characteristics of the final analysed cohort are presented in Table 1 (53.2% female, median age: 13.0 years) with 741 of 873 (85%) treatment naïve patients (group A) and 132 (15%) patients after failed therapy (group B). A high proportion of reported patients live in Southern Europe, predominantly in Spain and Portugal (Table 1, Supplementary File 5).

Clinical presentation

Endoscopy was performed in almost all cases (99.1%, $n=873$). Abdominal pain was the primary indication for endoscopy in 66.8% ($n=865$, Table 1). Macroscopic findings disclosed antral nodularity in 85.4% of infected children, while 7.5% showed gastric and/or duodenal peptic ulcers and 16.4% erosions. Macroscopic signs of eosinophilic esophagitis were observed in 5.4% (Table 1).

Antibiotic susceptibility results

Antibiotic susceptibility results were available in 710 of 727 with positive culture and in 131 patients from RT-PCR testing. Primary resistance (group A) to metronidazole or clarithromycin was found in 17.7% ($n=604$, 95% CI 14.7–20.8%) and 25.0% ($n=651$, 95% CI 21.7–28.4%) of strains, respectively (Table 1). Once patients had failed *H. pylori* therapy (group B), the resistance rate increased to 40.2% ($n=102$, 95% CI 30.7–49.7%) against metronidazole and to 51.4% ($n=109$, 95% CI 42.0–60.8%) against clarithromycin. Strains susceptible to both clarithromycin and metronidazole were present in 57.5% (*A*: 61.3%, *B*: 35.3%), while double resistance to both clarithromycin and metronidazole was reported in treatment naïve patients 3.8% ($n=604$, 95% CI 2.3–5.3%), but increased in patients after failed therapy to 26.5% ($n=102$, 95% CI 17.9–35.0%). Resistance to amoxicillin was rare ($n=662$, *A*: 1.0%, *B*: 4.9%).

The primary resistance rate to levofloxacin and rifampicin was found in 5.4% ($n=571$) and 8.5% ($n=142$), respectively, with few cases having documented resistance to tetracycline (Table 1).

Eradication success of common treatment regimens

Two weeks of tailored triple therapy with PPI, amoxicillin, clarithromycin (PAC) or PPI, amoxicillin, metronidazole (PAM) were prescribed to 80.4% (702/873), 10% each received sequential ($n=86$) or other therapy regimens ($n=85$). Tailored triple therapy cured the infection in 90% of treatment naïve children ($n=503$, 95% CI 87–93%) and in 93% in naïve patients adhering to therapy (per-protocol analysis) ($n=447$, 95% CI 90–95%) (Table 2). Eradication rate was higher in compliant patients than in less compliant patients (ER = 93% vs ER = 63%, $p<0.0001$). Infected children with fully susceptible strains achieved a significantly higher eradication rate than those harbouring single-resistant strains, both in the final analysis set and the per-protocol population (Fig. 1).

PAM showed a trend for higher success than PAC, in both fully susceptible (ER = 95% vs ER = 91%, $p=0.241$) and single-resistant strains (ER = 88% vs ER = 83%, $p=0.383$) (Table 2, Supplementary 6). Sequential therapy (SQT), although mostly used in fully susceptible patients, did not reach the 90% goal (ER = 86%, $n=51$, 95% CI 77–96%).

Tailored triple therapy in patients with previously failed therapy (group B) performed poorly (ER = 59%, $n=69$, 95% CI 48–71%), while bismuth-based therapy was successful in 80% ($n=15$), including in eight of ten children harbouring double-resistant strains (Table 2).

The most commonly prescribed PPIs were omeprazole or esomeprazole (92%) and the remaining lansoprazole (2%) or pantoprazole (6%). The PPI dose was lower than recommended in the guidelines [8] in half of all patients (Table 3, Supplementary File 7). Antibiotic doses were prescribed according to guidelines in 80% of the patients, except in patients after failed therapy, in which more than half received lower amoxicillin doses than recommended (Supplementary File 7).

Factors associated with treatment failure

Among treatment naïve patients receiving 2-weeks tailored triple therapy ($n=503$), we identified in the univariate analysis only antibiotic susceptibility and therapy compliance associated with treatment failure. Other factors, including gender, age, drug dose, number of drug intakes per day, use of probiotics during therapy or reported adverse events, were not significantly associated with treatment failure (Table 3). The multivariable logistic regression showed that eradication failure of tailored triple therapy is three times more likely if the infecting strains are resistant to metronidazole or clarithromycin compared to fully susceptible strains (Fig. 2). Children taking < 90% of prescribed drugs over 14 days had a six times higher risk (OR = 5.89, 95% CI 2.49–13.95,

Table 1 Basic characteristics of *H. pylori*-infected paediatric patients in the EuroPedHp registry from 2017 to 2020 for the total cohort with follow-up data (final analysis set, FAS, $N=873$) (*IQR* interquartile range, *MET* metronidazole, *CLA* clarithromycin)

Factors, *n* (%)	All patients $N=873$ (100%)	Group A treatment naïve patients, $n=741$ (85%)	Group B patients after failed therapy, $n=132$ (15%)	*p* value[a]
Demographics				
Gender—female	464 (53.2)	390 (52.6)	74 (56.1)	0.467
Age (years), median (IQR)	13.0 (10.3–15.2)	13.0 (10.3–15.1)	12.8 (10.2–15.4)	0.352
Age group (years), $n=873$				0.573
Age < 12	351 (40.2)	295 (39.8)	56 (42.4)	
Age ≥ 12	522 (59.8)	446 (60.2)	76 (57.6)	
Weight, $n=863$, median (IQR)	45.5 (34.0–57.5)	45.8 (34.0–57.5)	45.0 (33.0–57.3)	0.712
Weight groups (kg), $n=863$				0.916
< 25	85 (9.8)	72 (9.8)	13 (9.9)	
25–34	141 (16.3)	118 (16.1)	23 (17.6)	
> 35	637 (73.8)	542 (74.0)	95 (72.5)	
Country of living[b], $n=873$				**< 0.0001**
Northern/Western Europe	232 (26.6)	204 (27.5)	28 (21.2)	
Southern Europe	419 (48.0)	364 (49.1)	55 (41.7)	
Eastern Europe	164 (18.8)	140 (18.9)	24 (18.2)	
Israel and Turkey	58 (6.6)	33 (4.5)	25 (18.9)	
Country of birth[b], $n=777$				**0.002**
Northern/Western Europe	173 (22.3)	153 (23.4)	20 (16.4)	
Southern Europe	317 (40.8)	273 (41.7)	44 (36.1)	
Eastern Europe	175 (22.5)	148 (22.6)	27 (22.1)	
Asia, Africa, America and Middle East	112 (14.4)	81 (12.4)	31 (25.4)	
Mother's country of birth[b], $n=719$				0.371
Northern/Western Europe	35 (4.9)	28 (4.6)	7 (6.0)	
Southern Europe	260 (36.2)	223 (37.0)	37 (31.9)	
Eastern Europe	189 (26.3)	162 (26.9)	27 (23.3)	
Asia, Africa, America and Middle East	235 (32.7)	190 (31.5)	45 (38.8)	
Symptoms associated with *H. pylori* infection				
Abdominal pain	667 (76.6)	552 (74.7)	115 (87.1)	**0.002**
Nausea	137 (15.7)	112 (15.2)	25 (18.9)	0.271
Vomiting	134 (15.4)	111 (15.0)	23 (17.4)	0.481
Bloating	46 (5.3)	39 (5.3)	7 (5.3)	0.99
Diarrhoea	34 (3.9)	30 (4.1)	4 (3.0)	0.574
Constipation	29 (3.3)	28 (3.8)	1 (0.8)	0.108
Metallic taste	4 (0.5)	3 (0.4)	1 (0.8)	0.482
Endoscopic findings				
Endoscopy at presenting centre, $n=873$	865 (99.1)	733 (98.9)	132 (100)	0.230
Year of endoscopy, $n=865$				0.506
2017	336 (38.8)	279 (38.1)	57 (43.2)	
2018	300 (34.7)	256 (34.9)	44 (33.3)	
2019 and 2020	229 (26.5)	198 (27.0)	31 (23.5)	
Primary indication for endoscopy, $n=865$				**< 0.0001**
Abdominal pain	578 (66.8)	476 (64.9)	102 (77.3)	
Dyspepsia incl. nausea, vomiting	93 (10.8)	76 (10.3)	17 (13)	
Anaemia	36 (4.2)	35 (4.8)	1 (0.8)	
GastrointestinaI-bleeding	18 (2.1)	18 (2.5)	0	
Celiac disease	27 (3.1)	27 (3.7)	0	
Eosinophilic esophagitis	24 (2.8)	21 (2.9)	3 (2.3)	
Inflammatory bowel disease	10 (1.2)	10 (1.4)	0	

Table 1 (continued)

Factors, *n* (%)	All patients *N* = 873 (100%)	Group A treatment naïve patients, *n* = 741 (85%)	Group B patients after failed therapy, *n* = 132 (15%)	*p* value[a]
Others: weight loss, diarrhoea, etc	68 (7.9)	65 (8.9)	3 (2.3)	
Only positivity in noninvasive tests	11 (1.3)	5 (0.7)	6 (4.5)	
Number of biopsies, *n* = 843, median (IQR)	4 (4–6)	4 (4–6)	5 (4–6)	**0.012**
Antral nodularity, *n* = 863	737 (85.4)	622 (84.9)	115 (88.5)	0.283
Suspected eosinophilic esophagitis, *n* = 862	47 (5.4)	36 (4.9)	11 (8.4)	0.107
Ulcers, *n* = 862	65 (7.5)	57 (7.8)	8 (6.2)	0.532
Erosions, *n* = 862	141 (16.4)	117 (16.0)	24 (18.6)	0.454
Positive rapid urease test (RUT), *n* = 342	310 (90.6)	270 (90.3)	40 (93.0)	0.567
Histology confirmed, *n* = 500[c]	465 (93.0)	410 (94.3)	55 (84.6)	**0.017**
Susceptibility testing, *n* = 873				**0.0491**
Culture positive and/or PCR available	775 (88.8)	666 (89.9)	109 (82.6)	
Culture negative and no PCR	37 (4.2)	28 (3.8)	9 (6.8)	
Not applicable or unknown	61 (7.0)	47 (6.3)	14 (10.6)	
Antibiotic resistance profile				
Metronidazole resistance, *n* = 706	148 (21.0)	107 (17.7)	41 (40.2)	**< 0.0001**
Clarithromycin resistance[d], *n* = 760	219 (28.8)	163 (25.0)	56 (51.4)	**< 0.0001**
Amoxicillin resistance, *n* = 662	10 (1.5)	6 (1.0)	4 (4.9)	**0.007**
Tetracycline resistance, *n* = 584	3 (0.5)	2 (0.4)	1 (1.5)	0.227
Levofloxacin resistance[d], *n* = 664	35 (5.3)	31 (5.4)	4 (4.3)	0.652
Rifampicin resistance, *n* = 172	14 (8.1)	12 (8.5)	2 (6.7)	0.745
Metronidazole and clarithromycin resistance—Susceptibility subgroups[e], *n* = 706				**< 0.0001**
MET-Susceptible/CLA-Susceptible	406 (57.5)	370 (61.3)	36 (35.3)	
MET-Susceptible/CLA-Resistant	152 (21.5)	127 (21.0)	25 (24.5)	
MET-Resistant/CLA-Susceptible	98 (13.9)	84 (13.9)	14 (13.7)	
MET-Resistant/CLA-Resistant	50 (7.1)	23 (3.8)	27 (26.5)	

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

[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. Bold *p* values indicate significant differences in the proportion of respective factors between group A (treatment naïve patients) and group B (patients after failed therapy) with a *p* value ≤ 0.05

[b]Country distribution was given in supplementary file 2

[c]Data of histology were collected from 2018 to 2020

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

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

Fig. 3) of treatment failure than children with excellent compliance.

In patients with previously failed therapy (group B), a standard dose compared to the recommended high dose of amoxicillin was associated with five times increased risk for treatment failure (OR = 5.04, 95% CI 1.09–23.28) (Supplementary Files 2 & 8). Low versus high compliance increased the estimated risk for unsuccessful therapy (OR = 12.93, 95% CI 1.93–86.75, Supplementary File 8).

Adverse events during therapy

In the final analysis set, adverse events during therapy were reported in 12% (96/822), mainly abdominal pain (*n* = 54), diarrhoea (*n* = 28), nausea (*n* = 26) and vomiting (*n* = 22). Of those, 19% (18/96) failed therapy (*A*: 12%, *n* = 81; *B*: 53%, *n* = 15).

Sensitivity analysis

In seven (1.4%) of 503 patients, the caring physician chose the wrong antibiotics: twice PAC instead of PAM in single clarithromycin-resistant strains, three times PAM instead of PAC in single metronidazole-resistant strains and twice PAC with high-dose amoxicillin instead of PAM in infections with double-resistant strains. In patients infected with single-resistant strains, the sensitivity analysis revealed marginal differences compared to the real-life situation with

Table 2 Eradication rate (ER) of the most common treatment regimens in relation to antibiotic susceptibility in treatment naïve patients (group A) and patients after failed therapy (group B)

Susceptibility sub-groups/common treatments	All subgroups ER% (*n*/*N*)	MET-S/CLA-S ER% (*n*/*N*)	MET-S/CLA-R ER% (*n*/*N*)	MET-R/CLA-S ER% (*n*/*N*)	MET-R/CLA-R ER% (*n*/*N*)
Group A (treatment naïve patients)					
Tailored triple therapy (TTT) including PAC and PAM	90% (452/503)	92% (279/302)	86% (94/109)	84% (68/81)	100% (11/11)
PPI + AMO + CLA (PAC)	88% (252/285)	91% (185/203)	0% (0/2)	83% (65/78)	100% (2/2)
PPI + AMO + MET (PAM)	92% (200/218)	95% (94/99)	88% (94/107)	100% (3/3)	100% (9/9)
PPI + AMO + CLA + MET sequential	82% (50/61)	86% (44/51)	56% (5/9)	100% (1/1)	N.A
Group B (patients after failed therapy)					
Tailored triple therapy (TTT) including PAC and PAM	59% (41/69)	65% (22/34)	71% (15/21)	30% (3/10)	25% (1/4)
PPI + AMO + CLA (PAC)	52% (14/27)	60% (12/20)	N.A	29% (2/7)	N.A
PPI + AMO + MET (PAM)	64% (27/42)	71% (10/14)	71% (15/21)	33% (1/3)	25% (1/4)
PPI + AMO + other antibiotic(s)	69% (9/13)	N.A	100% (2/2)	100% (1/1)	60% (6/10)
Bismuth-based therapy (BMT)	83% (10/12)	N.A	N.A	100% (2/2)	80% (8/10)

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

ER% represents eradication rate (ER) in per cent (%) as the proportion of all patients treated successfully with a confirmed negative test after completed treatment (*n*) relative to all patients treated (*N*)

Abbreviation: *TTT* tailored triple therapy, *ER* eradication rate, *PPI* proton pump inhibitor, *AMO* amoxicillin, *CLA* clarithromycin, *MET* metronidazole, *PAC* for treatment regimen with proton pump inhibitor, amoxicillin, clarithromycin, *PAM* for treatment regimen with proton pump inhibitor, amoxicillin, metronidazole, *BMT* bismuth-based therapy, *N.A.* not applicable

MET-S/CLA-S: Strains susceptible to both metronidazole and clarithromycin. MET-S/CLA-R: Strains susceptible to metronidazole but resistant to clarithromycin. MET-R/CLA-S: Strains resistant to metronidazole but susceptible to clarithromycin. MET-R/CLA-R: Strains resistant to both metronidazole and clarithromycin

an eradication rate of 86% ($n = 185$) versus 85% ($n = 190$), respectively (Supplementary File 9A and Fig. 1A). The multivariable logistic regression showed that the risk of eradication failure of tailored triple therapy for 2 weeks was still 2.74 times more likely in children infected with *H. pylori* strains resistant to metronidazole or clarithromycin compared to fully susceptible strains, $p = 0.0037$.

Discussion

Our findings confirm that a primary eradication rate of at least 90% is feasible in clinical practice with a 2-week triple therapy tailored to antibiotic susceptibility results giving higher doses as recommended in the recent ESPGHAN/NASPGHAN guidelines [8]. Being infected with an *H. pylori* strain resistant to clarithromycin or metronidazole and an intake of < 90% of prescribed drugs are significant risk factors for primary treatment failure of tailored triple therapy.

Antibiotic resistance of *H. pylori* strains

Our registry data provide a long-term and comprehensive surveillance of antibiotic resistance of *H. pylori* strains in children living in Europe. Our first survey covered 1999–2002 [18], the second 2013–2016 [17], and the current 2017–2020, reporting all consecutive *H. pylori*-infected patients from the paediatric centres. For treatment naïve children, selection bias regarding antibiotic susceptibility is unlikely. Comparing the primary resistance to clarithromycin, we noticed a slight increase over time (20%, 24.8%, and 25%, respectively), while resistance to metronidazole decreased (23%, 20.9% and 17.7%, respectively). Several recent European intervention programmes restricting macrolide consumption, particularly for respiratory tract infections in children [9, 19, 20], may have prevented a further increase in the clarithromycin resistance rate from the second to the third survey. While macrolides are often prescribed to children and may induce resistance to *H. pylori* strains, metronidazole is rarely used in paediatrics. Therefore, children most likely acquire a metronidazole-resistant strain, with their mothers being the main source of infection. In all three periods, resistance to clarithromycin and/or metronidazole was significantly more frequent in strains from children after failed therapy compared to treatment naïve patients [17, 18].

Sampling error and treatment failure

The wide availability of antibiotic susceptibility testing in Europe allows us to evaluate the eradication success of

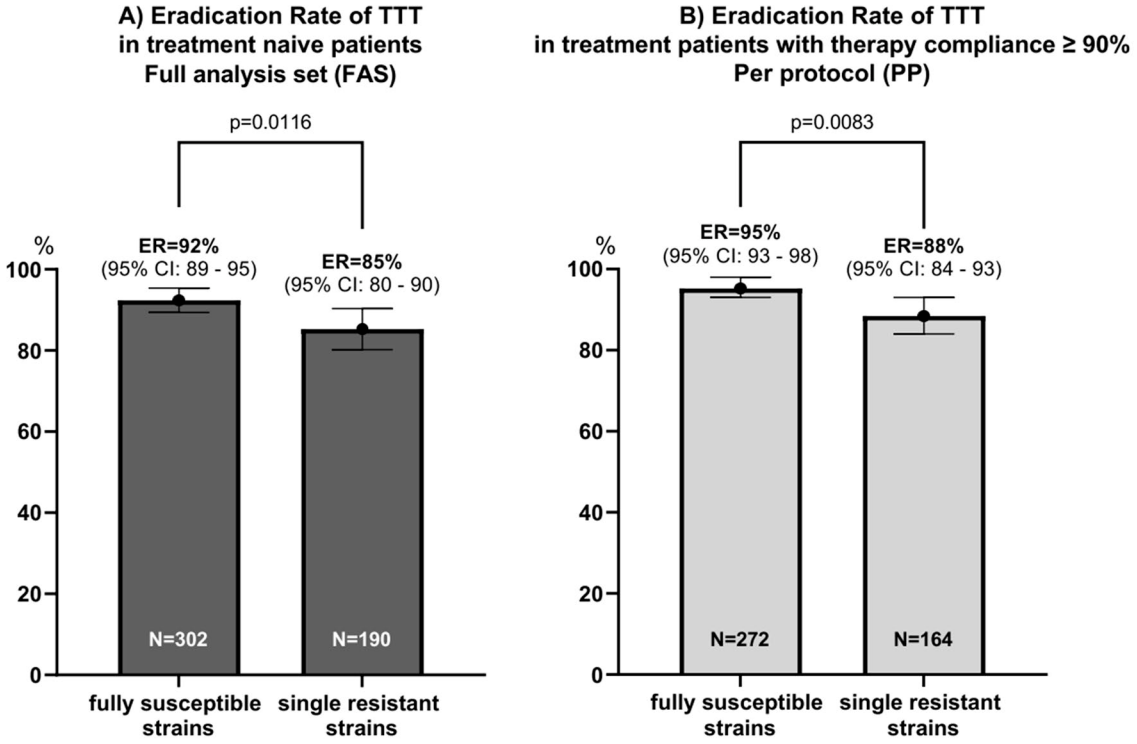

Fig. 1 **A** and **B** Eradication rate (ER) of tailored triple therapy (TTT) in patients with fully susceptible strains vs single-resistant strains. **A** In full analysis set (FAS). **B** Per protocol (PP) population. Abbreviation: *TTT* tailored triple therapy, *ER* eradication rate, *FAS* full analysis set, *PP* per protocol. ER% represents eradication rate (ER) in per cent (%) as the proportion of all patients treated successfully with a confirmed negative test after completed treatment relative to all patients treated in a specific sub-group. *P* values were obtained from Pearson's Chi-square test to determine the significant difference in eradication rate (ER) between patient group infected with fully susceptible strains to both clarithromycin and metronidazole vs patient group infected with single-resistant strains to clarithromycin or metronidazole

2-weeks tailored triple therapy for four antibiotic susceptibility sub-groups: Fully susceptible, single resistant to clarithromycin, single resistant to metronidazole and double resistant. Of children compliant with drugs, 5% failed the first attempt if infected with fully susceptible strains (Fig. 1B), while the failure rate was 12% in children infected with single-resistant strains (Fig. 1B). Children infected with single-resistant strains ($n = 190$) had a two to three times higher risk for treatment failure despite treatment with antibiotics; they were susceptible to compared to those with fully susceptible strains (Fig. 2). This significant difference remained after excluding five cases where the physicians had chosen the wrong antibiotics (Supplementary File 9A). We hypothesize that the main cause of treatment failure despite therapy tailored to antibiotic susceptibility is missed mixed infections. In a previous study on 83 infected children, we evaluated gastric biopsies taken at the same endoscopy, one biopsy each by E-testing in two different laboratories and the third one by in situ hybridisation [21]. In 11 patients (13%), we found discrepant results regarding clarithromycin resistance between the applied methods indicating mixed infections with the co-existence of a clarithromycin-susceptible and a clarithromycin-resistant strain which was obviously not evenly distributed in the stomach [21, 22]. Considering the result of antibiotic susceptibility based on only one biopsy leads to an underestimation of around 5% of clarithromycin resistance in the sub-groups "fully susceptible" and "single metronidazole resistance". Missing a clarithromycin-resistant strain has a higher clinical impact because PAC has a low eradication rate in clarithromycin-resistant infections, while in vitro metronidazole resistance may be overcome in vivo by a higher drug dose and longer duration of therapy [11, 13, 23]. By comparing PAC to PAM, our hypothesis supports the findings of a 4–5% lower eradication rate in children with single resistance and children with fully susceptible strains (Table 2, Supplementary File 6). Moreover, 95% eradication is obtained only in children with fully susceptible strains taking > 90% of prescribed drugs.

We conclude from our findings to take at least two biopsies in the antrum and corpus for culture if *H. pylori* infection is macroscopically suspected (e.g. antral nodularity, peptic lesions) or after failed therapy to improve the success rate for culture [24] and to decrease the risk of missing resistant strains. The recent guidelines recommend obtaining

Table 3 Risk factors for eradication failure of tailored triple therapy (TTT) among treatment naïve patients (group A), $N = 503$

Factors, *n* (row percent %)	*N*	ER failed *n* (%)	ER success *n* (%)	*p* value[a]	OR_{crude}[b] (95% CI)	*p* value[c]	OR_{adj}[d] (95% CI)	*p* value[c]
Gender				0.520				
Female	268	25 (9%)	243 (91%)		Ref			
Male	235	26 (11%)	209 (89%)		1.21 (0.68–2.16)	0.520		
Age (years), median (IQR)	503	13 (11–15)	13 (10–15)	0.871	1.03 (0.94–1.13)	0.546		
Country of living[e]				0.288				
Northern/Western Europe	146	11 (8%)	135 (92%)		Ref			
Southern Europe	222	21 (9%)	201 (91%)		1.28 (0.60–2.75)	0.522		
Eastern Europe	113	16 (14%)	97 (86%)		2.02 (0.90–4.55)	0.088		
Israel and Turkey	22	3 (14%)	19 (86%)		1.94 (0.50–7.58)	0.342		
Susceptibility sub-groups[f]				0.053				
MET-S/CLA-S (treated with PAC or PAM)	302	23 (8%)	279 (92%)		Ref		Ref	
MET-S/CLA-R (treated with PAM)	109	15 (14%)	94 (86%)		1.94 (0.97–3.86)	0.061	1.90 (0.94–3.86)	0.074
MET-R/CLA-S (treated with PAC)	81	13 (16%)	68 (84%)		**2.32 (1.12–4.81)**	**0.024**	**2.69 (1.25–5.78)**	**0.011**
MET-R/CLA-R	11	0	11 (100%)		N.A		N.A	
Antibiotic resistance				**0.021**				
Fully susceptibility to MET and CLA	302	23 (8%)	279 (92%)		Ref		Ref	
Single resistance to MET or CLA	190	28 (15%)	162 (85%)		**2.10 (1.17–3.76)**	**0.013**	**2.20 (1.22–3.98)**	**0.009**
Double resistance to MET and CLA	11	0	11 (100%)		N.A		N.A	
Tailored triple therapy				0.221				
PPI + AMO + MET (PAM)	218	18 (8%)	200 (92%)		Ref		Ref	
PPI + AMO + CLA (PAC)	285	33 (12%)	252 (88%)		1.46 (0.80–2.66)	0.223	1.59 (0.85–2.96)	0.146
PPI dose per day[g]				0.650				
According to guidelines 2017	262	25 (10%)	237 (90%)		Ref		Ref	
Lower than recommended	232	25 (11%)	207 (89%)		1.15 (0.64–2.06)	0.650	1.31 (0.70–2.45)	0.397
Amoxicillin dose per day[g]				0.500				
According to guidelines 2017	468	49 (10%)	419 (90%)		Ref		Ref	
Lower than recommended	26	1 (4%)	25 (96%)		0.34 (0.05–2.58)	0.298	0.32 (0.04–2.46)	0.273
Drug intake per day				0.220				
Three times per day	97	6 (6%)	91 (94%)		Ref		Ref	
Two times per day	370	38 (10%)	332 (90%)		1.74 (0.71–4.23)	0.225	1.59 (0.61–4.13)	0.339
Use of probiotics				0.940				
Yes	88	9 (10%)	79 (90%)		Ref		Ref	
No	381	40 (11%)	341 (89%)		1.03 (0.48–2.20)	0.941	1.19 (0.54–2.66)	0.665
Adverse events during therapy				0.634				
No	428	46 (11%)	382 (89%)		Ref		Ref	
Yes	52	4 (8%)	48 (92%)		0.69 (0.24–2.01)	0.498	0.81 (0.25–2.58)	0.716
Therapy compliance				**< 0.0001**				
≥ 90% drug intakes	447	32 (7%)	415 (93%)		Ref		Ref	
< 90% drug intakes	30	11 (37%)	19 (63%)		**7.51 (3.29–17.14)**	**< 0.0001**	**6.51 (2.79–15.19)**	**< 0.0001**

Abbreviation: *TTT* tailored triple therapy, *ER* eradication rate, *OR* odd ratio, *PPI* proton pump inhibitor, *AMO* amoxicillin, *CLA* clarithromycin, *MET* metronidazole, *PAC* for treatment regimen with proton pump inhibitor, amoxicillin, clarithromycin, *PAM* for treatment regimen with proton pump inhibitor, amoxicillin, metronidazole, *N.A.* not applicable, *ref.* reference category

[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. Bold *p* values indicate significant differences in the proportion of respective factors between the patient group with eradication failure and the patient group with eradication success by a *p* value ≤ 0.05

[b] Crude odd ratio (OR_{crude}) with 95% confidence intervals (95% CI) applied from a univariate logistic regression

[c] *P* values obtained from the Wald Chi-Square Test for the significance of the odd ratio (OR)

[d] Adjusted odds ratios (OR_{adj}) with 95% confidence intervals (95% CI) obtained from the multivariable logistic regression adjusted with gender, age in years and country of living

[e] Country distribution was given in supplementary file 2

[f] MET-S/CLA-S: Strains susceptible to both metronidazole and clarithromycin. MET-S/CLA-R: Strains susceptible to metronidazole but resistant to clarithromycin. MET-R/CLA-S: Strains resistant to metronidazole but susceptible to clarithromycin. MET-R/CLA-R: Strains resistant to both metronidazole and clarithromycin

[g] Results were evaluated by comparing the prescribed dose with the standard dosing regimen provided in the updated guidelines 2016 [8]

Factors n (row %)	ER failed 51 (10%)	ER success 452 (90%)	Odd Ratio (OR) (95%CI)	Odd Ratio (OR) (95%CI)	p-value
Gender (Male vs. Female)	26 (11%)	209 (89%)		0.94 (0.47 - 1.86)	0.86
Age (years), median (IQR)	13 (11-15)	13 (10-15)		0.98 (0.88 - 1.09)	0.71
Country of living (Israel & Turkey vs. North & West Europe)	3 (14%)	19 (86%)		2.34 (0.52 - 10.56)	0.27
Country of living (East Europe vs. North & West Europe)	16 (14%)	97 (86%)		2.64 (1.01 - 6.9)	**0.0485**
Country of living (South Europe vs. North & West Europe)	21 (9%)	201 (91%)		1.35 (0.52 - 3.53)	0.54
MET-S/CLA-R vs. MET-S/CLA-S	15 (14%)	94 (86%)		2.47 (1.1 - 5.53)	**0.028**
MET-R/CLA-S vs. MET-S/CLA-S	13 (16%)	68 (84%)		3.44 (1.47 - 8.08)	**0.0045**
Therapy compliance (<90% vs. >=90%)	11 (37%)	19 (63%)		5.71 (2.4 - 13.61)	**<0.0001**

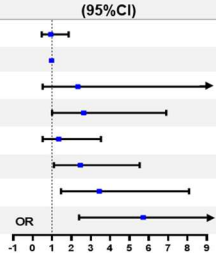

Fig. 2 Risk factors for eradication failure applied from multivariable logistic regression among treatment naïve patients (group A) with known antibiotic susceptibility of clarithromycin (CLA) & metronidazole (MET), who received tailored triple therapy (TTT) and completed follow-up, $N=503$. Abbreviations: *TTT* tailored triple therapy, *ER* eradication rate, *OR* odd ratio, *PPI* proton pump inhibitor, *AMO* amoxicillin, *CLA* clarithromycin, *MET* metronidazole, *MET-S/CLA-S* strains susceptible to both metronidazole and clarithromycin, *MET-S/CLA-R* strains susceptible to metronidazole but resistant to clarithromycin, *MET-R/CLA-S* strains resistant to metronidazole but susceptible to clarithromycin, *MET-R/CLA-R* strains resistant to both metronidazole and clarithromycin. Odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the final multivariable logistic regression are given. *P* values were obtained from the Wald Chi-Square Test for the significance of the odds ratio (OR)

at least six gastric biopsies, thereof four for histopathology and the remaining two for culture and rapid urase test [8]. In our cohort, six biopsies were documented in only 25% of patients, giving room for improvement. Moreover, we suggest preferring PAM over PAC to treat the fully susceptible group in case of missed clarithromycin-resistant strains by sampling error.

Optimized drug dosing regimens

Sufficient acid suppression is crucial for effectiveness because, at high pH, the bacteria enter their replicative state and become susceptible to amoxicillin and clarithromycin [23]. Children around puberty have higher CYP2C19 enzyme activity to metabolize PPIs, including (es)-omeprazole; hence, they may need higher doses per kg body weight than adults for equivalent acid suppression [25, 26]. The updated paediatric guidelines recommend higher PPI doses for all regimens (Supplementary File 2) [8]. For different reasons, this recommendation was followed in only half of the patients (e.g. national regulations or high costs). The acid-suppressive capacity of PPIs may be negatively affected by under-dosing, by taking the drug not prior but with or after meals, by larger dosing intervals (daily dose divided into two versus three intakes), and by genetic polymorphism of the hepatic CYP2C19 enzyme activity [25]. The latter determines fast (70% of Caucasians), intermediate 25–30% of Caucasians) and slow metabolizer (2–5% of Caucasians) [27]. Esomeprazole is less susceptible to degradation by fast metabolizers than pantoprazole, resulting in a higher and better predictable acid-inhibitory effect. Therefore, esomeprazole-based tailored triple therapy was prescribed to 60% of our treatment-naïve patients, followed by omeprazole (32%), while lansoprazole and pantoprazole were used by only 2% and 6%, respectively. Randomized controlled trials may be needed to clarify the role of PPI type and dosing on the success of 2-weeks tailored triple therapy.

In contrast to PPI dosing, we found a four times higher risk of treatment failure using standard compared to a high amoxicillin dose. We could previously show that in children infected with a double-resistant strain, PAM with high-dose amoxicillin was successful in 75% (22/45) of children compliant with the 2-week therapy [28] (Supplementary File 7). The benefit of high-dose amoxicillin in the tailored triple therapy was reported in reducing the emergence of resistance to co-antibiotics [6]. Thus, using a higher amoxicillin dose may further increase the effectiveness of clarithromycin or metronidazole in tailored triple therapy.

Therapy compliance

Poor therapy compliance is a significant risk factor for treatment failure. Kotilea et al. 2017 [16] demonstrated that with high compliance, defined as more than 90% intake of prescribed doses, a success rate of 89.9% was achieved, while patients with lower adherence reached only 36.8%. To improve compliance, the *H. pylori* working group developed an information leaflet for parents and children on the importance of strict drug intake to successfully treat the infection (links: https://www.espghan.org/knowledge-center/education/H-Pylori-Patient-Parent-Guide) [29].

Other therapy regimens

Based on previous publications of our group, a 10-days sequential therapy was given as an option in the current guidelines, but only to treat patients infected with fully susceptible strains [3, 8, 14]. In the present cohort, sequential therapy failed the treatment goal of 90% even in these

patients (Table 2). Furthermore, like in concomitant regimens, sequential therapy contains three antibiotics (amoxicillin, clarithromycin and metronidazole), in which one of them does not contribute to eradication success. According to antibiotic stewardship principles, therapies using antibiotic combinations assuming the infection will be susceptible to at least one [5, 6] should be abandoned. Since we achieve eradication of 90% and higher with 2-weeks triple therapy tailored to antibiotic susceptibility, we suggest that neither sequential therapy nor concomitant regimens should be prescribed to treat *H. pylori* infection in children.

Bismuth-based regimens achieved a high cure rate as second-line therapy, including treatment of patients infected with double-resistant strains. For older adolescents, PPI with a capsule containing bismuth-subcitrate, tetracycline and metronidazole for compassionate use would be an alternative [30].

Strengths and limitations

Our registry attained unique and comprehensive surveillance over four years on a large number of consecutive *H. pylori*-infected paediatric patients in Europe with complete data on demographics, clinical and endoscopic presentation, antibiotic resistance, treatment, and follow-up. The unbalanced number of children included from participating centres and countries reflects the different prevalence of paediatric *H. pylori* infection in European countries and the patient population care in the different centres. This impacts the reported primary antibiotic resistance in treatment naïve patients since we previously showed that country of living and the mother's country of birth has a major impact on the antibiotic resistance rates towards clarithromycin and metronidazole [17]. However, the uneven recruitment should not introduce a bias towards our reported results of treatment success rates because children were treated with 2-weeks antibiotics tailored to antibiotic susceptibility results and with dosing recommended by guidelines [8]. The recommendations are not difficult to follow since in only 7 (1.4%) children, physicians made a mistake by prescribing an antibiotic the child was resistant to (not guideline conform). All children underwent endoscopy because of symptoms or underlying disease (e.g. eosinophilic esophagitis, inflammatory bowel disease, or celiac disease). Therefore, we have an enrichment (7.1%) of these co-morbidities in our cohort compared to the general population, but this should also not introduce a bias with respect to eradication success of tailored triple therapy for 2 weeks. Unlike the European registry on *H. pylori*-infected adults [31], we provided feedback annually to participating centres, including suggestions to improve adherence to guidelines and treatment success.

Our study has several limitations. First, the antibiotic susceptibility testing was performed locally and not in a central laboratory due to the complexity of sample transport and financial restriction. E-test was the most common tool used for susceptibility testing, and antibiotic resistance breakpoints were unified in the laboratories by applying the guidelines of the European Committee of Antibiotic Susceptibility Testing (EUCAST). Second, we cannot exclude recall bias for any previous *H. pylori* eradication treatment, especially in patients with migration backgrounds and language barriers. Third, concerning compliance, we relied on parents' reporting to their physicians: medications completely taken (100% compliance), one day (90%), 2–3 days (70–90%), ≥ 4 days left out (≤ 70%). The estimated therapy compliance in our cohort was high since adherent patients are more likely to return for follow-up visits to monitor the success of therapy than patients not adhering to therapy. Fourth, loss to follow-up occurred in one-third of all treated patients. In some countries or clinical settings, monitoring visits at the outpatient clinic are either impossible or not reimbursed by health insurance; other reasons include long travel distances to the hospital or missed appointments. However, this should not influence the results of per-protocol analysis.

Practical implications for clinical routine

In the absence of bismuth-based combination drugs, triple therapy tailored to antibiotic susceptibility for 2 weeks with drug doses as recommended in the ESPGHAN/NASPGHAN guidelines is currently the best option to treat *H. pylori*-infected children and adolescents with a primary success rate of ≥ 90% following the principles of the antibiotic stewardship program.

Our data suggest that taking two or more biopsies (antrum and corpus) for antibiotic susceptibility testing may increase the chance to detect clarithromycin-resistant bacterial strains in case of mixed infection, having an uneven distribution of clarithromycin-suseptible and clarithromycin-resistant *H. pylori* strains in the stomach. Tailored triple therapy combining PPI, amoxicillin with metronidazole (PAM) should be preferred over the combination with clarithromycin (PAC) to treat patients with fully susceptible strains in regions or populations known for high clarithromycin resistance. Applying recommended PPI and antibiotic dosing regimens [8] (Supplementary File 2) optimizes the effectiveness of tailored triple therapy. Patient education is crucial for high adherence to therapy. These measures improve treatment success and reduce later complications and costs.

Conclusion

In conclusion, 2-weeks triple therapy with PPI, amoxicillin and clarithromycin or metronidazole tailored to antibiotic susceptibility with optimized doses remains highly effective as the first-line therapy in *H. pylori*-infected children and adolescents. An anticipated primary eradication rate of at least 90% will reduce the need for repeated or unnecessary antibiotic exposures, the risk for long-term adverse effects on the child's microbiota, and the development of resistant strains. Whether obtaining two or more gastric biopsies for antibiotic susceptibility testing may further increase eradication rate of tailored triple therapy needs to be investigated in future studies. Guideline-conform management following the antibiotic stewardship program principles will contribute to reducing global antibiotic resistance.

Practical guidance should be provided to paediatric gastroenterologists, paediatricians, and general practitioners, encouraging them to follow guidelines, including consequent noninvasive monitoring for treatment success. Systematic surveillance of antibiotic resistance and continuous centre monitoring is fundamental to improve the quality of care in *H. pylori*-infected patients.

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Author contributions TGLT serves as first author of the manuscript. SK is senior and corresponding author of the manuscript. SK is the principal investigator of the registry and acquired financial support for the project. TGLT and KW programmed the registry and contributed as data manager to the acquisition of the data. TGLT performed data analysis, data presentation and drafted the manuscript. TGLT and SK interpreted data results, revised the manuscript for important intellectual content and gave final approval of the manuscript. All authors contributed to conceptualization, design of the registry, and submission of patient data. All authors reviewed and approved the final version of the manuscript. All collaborators (non-author contributors) acquired data, critically reviewed the manuscript draft, and approved the submitted manuscript.

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Declarations

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Conflict of interest SK reports grants from Mead Johnson, BioGaia, and personal fees from Nestle, Danone, Novalac, AbbVie, Janssen, Sanofi, Takeda outside the submitted work. PB reports speakers' honoraria from AbbVie, Avanos, Biocodex, Danone, Ferring and Nestlé as well as fees for participating in Advisory Board from Biocodex, outside of the submitted work. ZM has received personal fees and travel grants from GlaxoSmithKline, Abbvie, Pharmas, Wurth, outside the submitted work. All authors declare no conflict of competing interest in performing this manuscript.

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Supplementary file legends

Supplementary file 1: Countries assigned to four geographical regions

Country regions	Countries
Northern/Western Europe	
Northern Europe	Sweden, Norway, Finland
Western Europe	UK, England, Ireland, Scotland, France, Netherlands, Belgium, Germany, Austria, Switzerland, Luxembourg
Southern Europe	Portugal, Spain, Italy, Greece
Eastern Europe	Albania, Bosnia, Kosovo, Serbia, Macedonia, Romania, Slovenia, Moldova, Ukraine, Russia, Chechnya, Lithuania, Poland, Hungary, Czech Republic, Slovakia, Croatia, Azerbaijan, Moldavia, Rumania
Asia, Africa, America, and the Middle East	Angola, Guinea, Somalia, Senegal, Ghana, Cabo to Verde, Guinea, Guinea to Bissau, Madagascar, South Africa, Libya, Morocco, Tunisia, Algeria, Ethiopia, Eritrea, Republic Dominican, China, Mongolia, Thailand, Vietnam, New Guinea, Iran, Iraq, Iraq, Syria, Egypt, Turkey, Israel, Armenia, Bangladesh, Afghanistan, Afghanistan, Kazakhstan, Kazakhstan, Azerbaijan, India, Nepal, Azerbaijan, Canada, USA, US, Colombia, Chile, Peru, Ecuador, Bolivia Argentina, Brazil, Uruguay, Paraguay, Argentina, Australia.

Supplementary file 2: Dosing regimens recommended in the updated ESPGHAN/NASPGHAN guidelines; e-publication in 2016 [1]

A. Standard dosing regimen				
Drug	**Bodyweight range**	**Morning dose, mg**	**Evening dose, mg**	**Daily total dose, mg**
PPI Es(omeprazole)	15 - 24 kg	20 mg	20 mg	40 mg
	25 - 34 kg	30 mg	30 mg	60 mg
	> 35 kg	40 mg	40 mg	80 mg
Amoxicillin (AMO)	15 - 24 kg	500 mg	500 mg	1000 mg
	25 - 34 kg	750 mg	750 mg	1500 mg
	> 35 kg	1000 mg	1000 mg	2000 mg
Clarithromycin (CLA)	15 - 24 kg	250 mg	250 mg	500 mg
	25 - 34 kg	500 mg	250 mg	750 mg
	> 35 kg	500 mg	500 mg	1000 mg
Metronidazole (MET)	15 - 24 kg	250 mg	250 mg	500 mg
	25 - 34 kg	500 mg	250 mg	750 mg
	> 35 kg	500 mg	500 mg	1000 mg
B. High dosing regimen for amoxicillin				
Drug	**Bodyweight range**	**Morning dose, mg**	**Evening dose, mg**	**Daily total dose, mg**
Amoxicillin (AMO)	15 - 24 kg	750 mg	750 mg	1500 mg
	25 - 34 kg	1000 mg	1000 mg	2000 mg
	> 35 kg	1500 mg	1500 mg	3000 mg

Abbreviation: PPI proton pump inhibitor

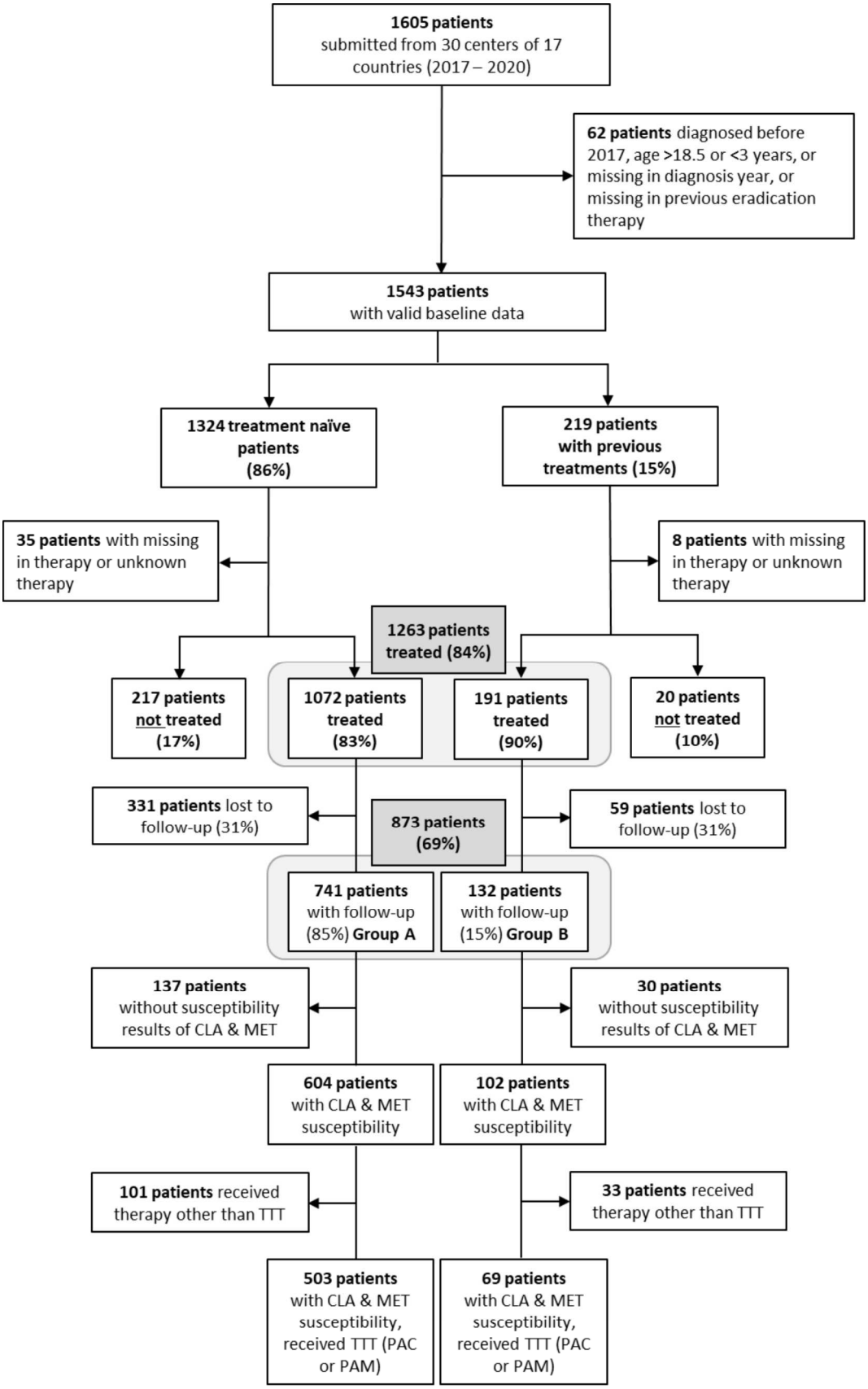
Adapted with permission from Jones NL, Koletzko S et al.; ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr. 2017 Jun;64(6):991-1003.

Supplementary file 3: Detailed explanation of statistical analysis

Results were presented in median and interquartile range (IQR) from 25% quartile to 75% quartile for continuous variables and in frequency (n) and percentage (%) for categorical variables. 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. All statistical tests were assessed with two-sided significance levels of 5%.

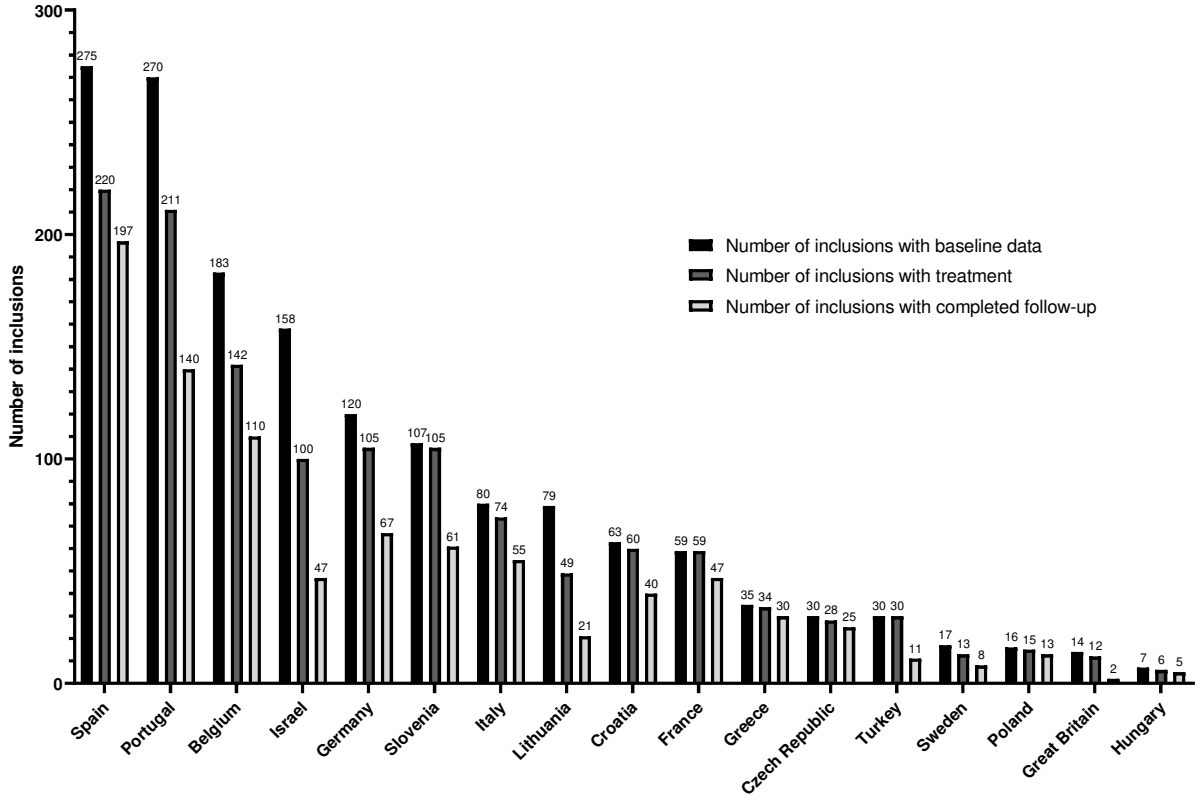
A univariate logistic analysis was performed to determine potential risk factors for treatment failure. Crude odd ratios (OR_{crude}) with 95% confidence intervals (95% CI) applied from a univariate logistic regression were shown. Adjusted odds ratios (OR_{adj}) with 95% confidence intervals (95% CI) were obtained from the multivariable logistic regression adjusted with gender, age in years and country of living.

All variables associated with treatment failure at p-value ≤0.25 in the univariate analysis were considered in the multivariable logistic regression. Using the same samples as in the univariate analysis, the final multivariable logistic models were selected using backward elimination and adjusted for gender and age (in years). Logistic analyses were performed with complete datasets with no missing values in covariates. Interaction and effect modification between considered variables and gender or age were examined parallel to backward elimination. Estimated odds ratio (OR) and 95% CI were reported. P-values from the Wald Chi-Square Test determine the significance of the odd ratio (OR). Statistical significance was considered at $p \leq 0.05$.

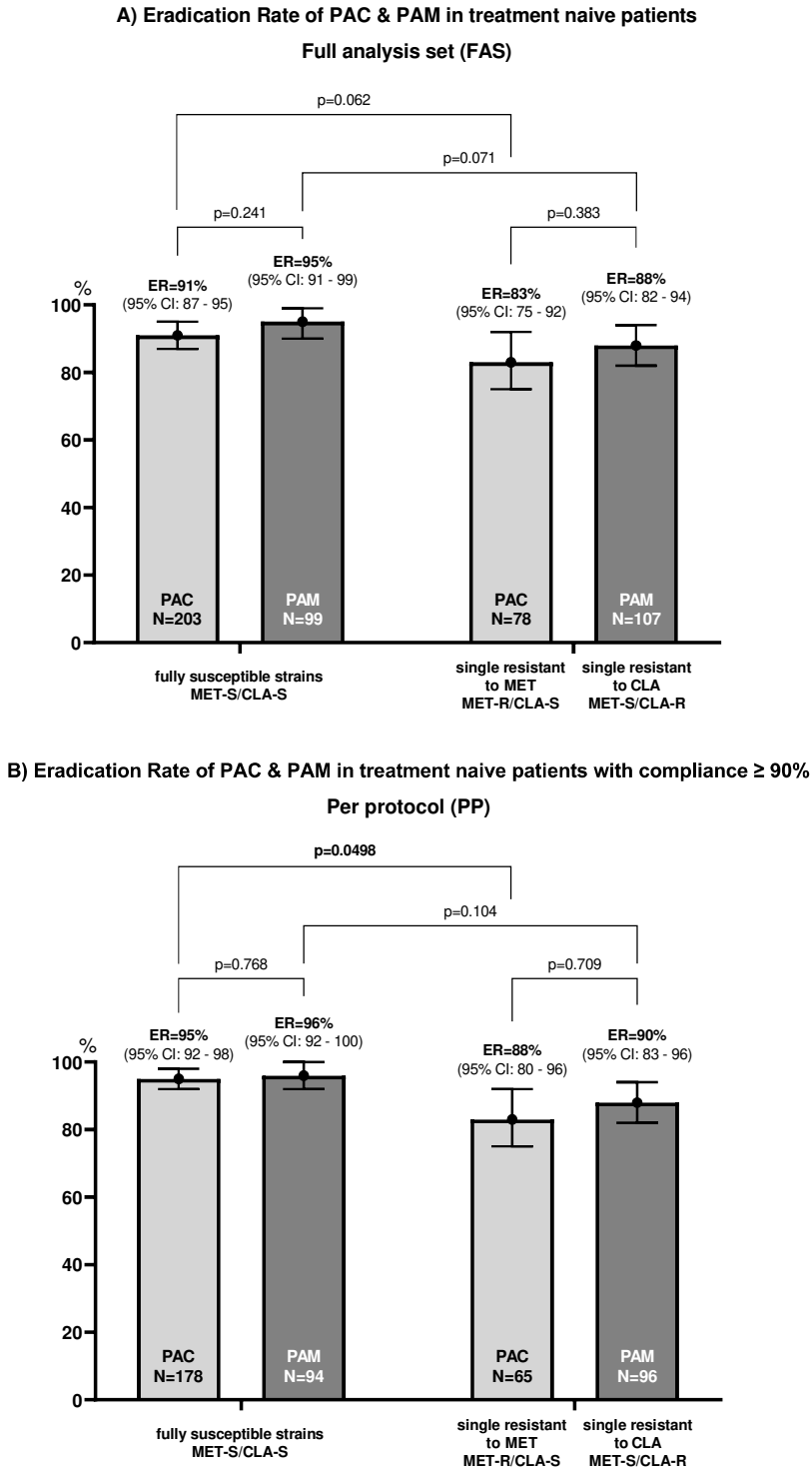


Supplementary file 4: Flowchart of the study population

Abbreviation: TTT tailored triple therapy; CLA clarithromycin; MET metronidazole; PAC for treatment regimen with proton pump inhibitor, amoxicillin, clarithromycin; PAM for treatment regimen with proton pump inhibitor, amoxicillin, metronidazole; Group A (treatment naïve patients) and group B (patients after failed therapy).



Supplementary file 5: Number of included patients per country from 2017 to 2020: of 1543 included patients in the EuroPedHp registry, 1263 were treated, thereof 873 completed follow-up



Supplementary file 6: Eradication rate (ER) of PAC vs PAM in patients with fully susceptible strains & single resistant strains: A) final analysis set (FAS) and B) Per protocol (PP) population

Abbreviation: ER eradication rate; CLA clarithromycin; MET metronidazole; PAC for treatment regimen with proton pump inhibitor, amoxicillin, clarithromycin; PAM for treatment regimen with proton pump inhibitor, amoxicillin, metronidazole.
ER% represents eradication rate (ER) in per cent (%) as the proportion of all patients treated successfully with a confirmed negative test after completed treatment relative to all patients treated in a specific sub-group.
P-values were obtained from Pearson's Chi-square test to determine the significant difference in eradication rate (ER) between the patient group that received PAC vs PAM.

Supplementary file 7: Risk factors for eradication failure of tailored triple therapy (TTT) among patients after failed therapy (group B), N=69

Factors, n (row per cent %)	N	ER failed n (%)	ER success n (%)	p-value [a]	OR_{crude} [b] (95%CI)	p-value [c]	OR_{adj} [d] (95%CI)	p-value [c]
Gender								
Female	44	15 (34%)	29 (66%)	0.145	ref.			
Male	25	13 (52%)	12 (48%)		2.09 (0.77 - 5.71)	0.148		
Age (years), median (IQR)	69	12 (9 - 14)	13 (10 - 15)	0.065	0.91 (0.79 - 1.05)	0.197		
Country of living [e]				0.163				
Northern/Western Europe	15	5 (33%)	10 (67%)		ref.			
Southern Europe	26	9 (35%)	17 (65%)		1.06 (0.28 - 4.06)	0.934		
Eastern Europe	13	4 (31%)	9 (69%)		0.89 (0.18 - 4.38)	0.885		
Israel & Turkey	15	10 (67%)	5 (33%)		4.00 (0.88 - 18.26)	0.074		
Susceptibility sub-groups [f]				0.066				
MET-S / CLA-S (treated with PAC or PAM)	34	12 (35%)	22 (65%)		ref.		ref.	
MET-S / CLA-R (treated with PAM)	21	6 (29%)	15 (71%)		0.73 (0.23 - 2.39)	0.606	1.23 (0.26 - 5.83)	0.791
MET-R / CLA-S (treated with PAC)	10	7 (70%)	3 (30%)		4.28 (0.93 - 19.65)	0.062	**6.36 (1.003 - 40.38)**	**0.0496**
MET-R / CLA-R	4	3 (75%)	1 (25%)		5.50 (0.51 - 58.83)	0.159	**18.07 (1.19 - 274.8)**	**0.037**
Antibiotic resistance				0.355				
Fully susceptibility	34	12 (35%)	22 (65%)		ref.		ref.	
Single resistance	31	13 (42%)	18 (58%)		1.32(0.49 - 3.61)	0.583	2.40 (0.66 - 8.81)	0.187
Double resistance	4	3 (75%)	1 (25%)		5.50 (0.51 - 58.77)	0.159	**15.82 (1.09 - 229.9)**	**0.043**
Tailored triple therapy				0.305				
PPI + AMO + AMO (PAM)	42	15 (36%)	27 (64%)		ref.		ref.	
PPI + AMO + CLA (PAC)	27	13 (48%)	14 (52%)		1.67 (0.63 - 4.47)	0.306	1.03 (0.32 - 3.35)	0.955
PPI dose per day [g]				**0.004**				
According to guidelines 2016	40	22 (55%)	18 (45%)		ref.		ref.	
Lower than recommended	29	6 (21%)	23 (79%)		**0.21 (0.07 - 0.64)**	**0.006**	**0.20 (0.05 - 0.72)**	**0.014**
Amoxicillin dose per day [g]				0.073				
High dose acc. guidelines 2016	24	6 (25%)	18 (75%)		ref.		ref.	
Lower than recommended	45	22 (49%)	23 (51%)		2.87 (0.96 - 8.56)	0.059	**3.94 (1.01 - 15.23)**	**0.048**
Drug intake per day				0.074				
Three times per day	6	0	6 (100%)		N.A.		N.A.	
Two times per day	61	26 (43%)	35 (57%)		N.A.		N.A.	
Use of probiotics				0.691				
Yes	7	2 (29%)	5 (71%)		ref.		ref.	
No	59	25 (42%)	34 (58%)		1.84 (0.33 - 10.25)	0.488	0.94 (0.13 - 6.77)	0.954
Adverse events during therapy				0.436				
No	53	21 (40%)	32 (60%)		ref.		ref.	
Yes	7	4 (57%)	3 (43%)		2.03 (0.41 - 10.01)	0.384	2.56 (0.40 - 16.42)	0.323
Therapy compliance				0.021				
≥ 90% drug intakes	54	17 (31%)	37 (69%)		ref.		ref.	
< 90% drug intakes	9	7 (78%)	2 (22%)		**7.62 (1.43 - 40.59)**	**0.017**	**10.58 (1.41 - 79.28)**	**0.022**

Analyses were performed with complete datasets with no missing values in covariates.

Abbreviation: TTT tailored triple therapy; ER eradication rate; OR odd ratio; PPI proton pump inhibitor; AMO amoxicillin; CLA clarithromycin; MET metronidazole; PAC for treatment regimen with proton pump inhibitor, amoxicillin, clarithromycin; PAM for treatment regimen with proton pump inhibitor, amoxicillin, metronidazole; N.A. not applicable; ref. reference category.

[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. Bold p-values indicate significant differences in the proportion of respective factors between the patient group with eradication failure and the patient group with eradication success by a p-value ≤0.05.

[b] Crude odd ratio (OR_{crude}) with 95% confidence intervals (95% CI) applied from a univariate logistic regression.

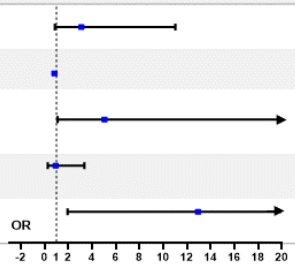
[c] P-values obtained from the Wald Chi-Square Test for the significance of the odd ratio (OR).

[d] Adjusted odds ratios (OR_{adj}) with 95% confidence intervals (95% CI) obtained from the multivariable logistic regression adjusted with gender, age in years and country of living.

[e] Country distribution was given in supplementary file 2.

[f] MET-S/CLA-S: Strains susceptible to both metronidazole and clarithromycin. MET-S/CLA-R: Strains susceptible to metronidazole but resistant to clarithromycin. MET-R/CLA-S: Strains resistant to metronidazole but susceptible to clarithromycin. MET-R/CLA-R: Strains resistant to both metronidazole and clarithromycin. [g] Results were evaluated by comparing the prescribed dose with the standard dosing regimen provided in the updated guidelines 2016 [1].

Factors	ER failed	ER success	Odd Ratio (OR)	Odd Ratio (OR)	p-value
n (row %)	28 (41%)	41 (59%)	(95%CI)	(95%CI)	
Gender (Male vs. Female)	13 (52%)	12 (48%)		3.1 (0.87 - 11.03)	0.08
Age (years), median (IQR)	12 (9 - 14)	13 (10 - 15)		0.82 (0.68 - 0.996)	**0.046**
Low AMO dose (lower than recommended than in the updated guidelines 2016) (Yes vs. No)	22 (49%)	23 (51%)		5.04 (1.09 - 23.28)	**0.038**
Single resistance vs. Fully susceptibility	13 (42%)	18 (58%)		0.92 (0.26 - 3.34)	**0.90**
Therapy compliance(<90% vs. >=90%)	7 (78%)	2 (22%)		12.93 (1.93 - 86.75)	**0.008**

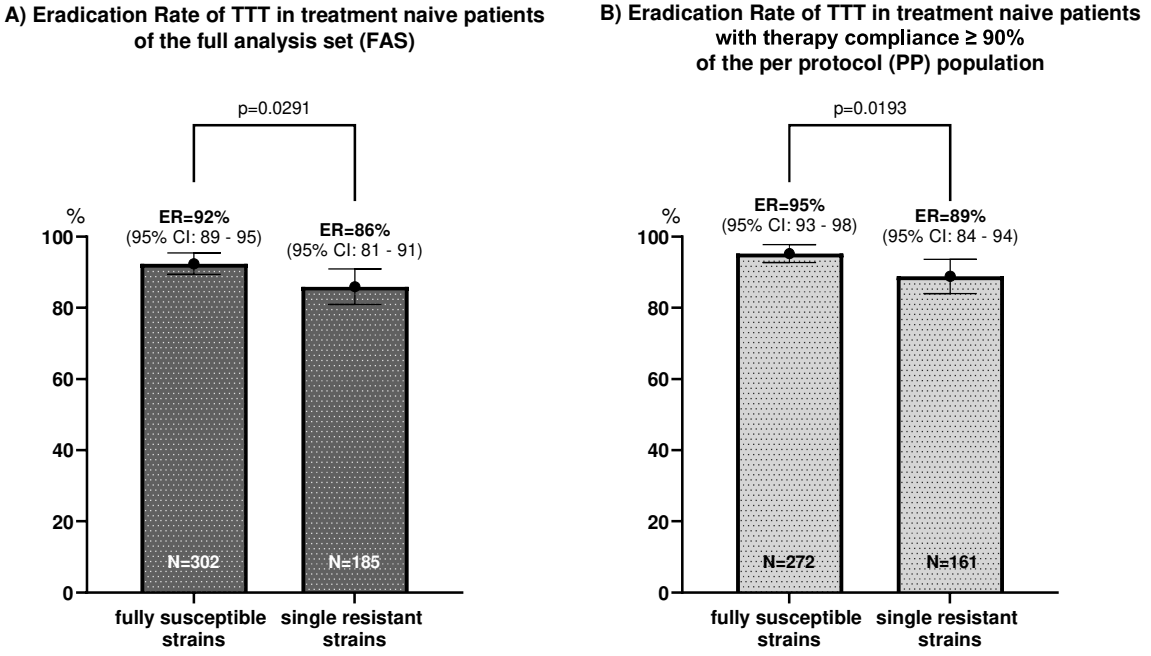


Supplementary file 8: Risk factors for eradication failure applied from multivariable logistic regression in patients after failed therapy (group B) with known antibiotic susceptibility to clarithromycin (CLA) & metronidazole (MET); all received tailored triple therapy (TTT) and completed follow-up, N=69

Abbreviation: TTT tailored triple therapy; ER eradication rate; OR odd ratio; PPI proton pump inhibitor; AMO amoxicillin; CLA clarithromycin; MET metronidazole.

Fully susceptibility represents strains susceptible to both clarithromycin and metronidazole, while single resistance determines strains resistant to clarithromycin or metronidazole.

Odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the final multivariable logistic regression are given. P-values were obtained from the Wald Chi-Square Test for the significance of the odds ratio (OR).



Supplementary file 9 A and B: Eradication rate (ER) of tailored triple therapy (TTT) in patients with fully susceptible vs single resistant strains. A) in full analysis set (FAS) B) Per protocol (PP) population obtained from the sensitivity analysis

Abbreviation: ER eradication rate; CLA clarithromycin; MET metronidazole; PAC for treatment regimen with proton pump inhibitor, amoxicillin, clarithromycin; PAM for treatment regimen with proton pump inhibitor, amoxicillin, metronidazole.
ER% represents eradication rate (ER) in per cent (%) as the proportion of all patients treated successfully with a confirmed negative test after completed treatment relative to all patients treated in a specific sub-group.
P-values were obtained from Pearson's Chi-square test to determine the significant difference in eradication rate (ER) between the patient group that received PAC vs PAM.

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