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Therapeutic eradication choices in *Helicobacter pylori* infection in children

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***Abstract*:** Current recommendations on *Helicobacter pylori* (*H. pylori*) eradication in children differ from adults. In *H. pylori*-infected adults, the eradication is always recommended because of the risk to develop gastrointestinal and non-gastrointestinal associated diseases. Instead, before treating infected children, we should consider all the possible causes and not merely focus on *H. pylori* infection. Indeed, pediatric international guidelines do not recommend the *test and treat strategy* in children. Therefore, gastroscopy with antimicrobial susceptibility testing by culture on gastric biopsies should be performed before starting the eradication therapy in children to better evaluate all the possible causes of the symptomatology and to increase the eradication rate. Whether antibiotic susceptibility testing is not available, gastroscopy is anyway recommended to better set any possible cause of symptoms and not simply focus on the presence of *H. pylori*. In children the lower antibiotics availability compared to adults forces to treat based on antimicrobial susceptibility testing to minimize the unsuccessful rates. The main antibiotics used in children are amoxicillin, clarithromycin, and metronidazole in various combinations. In empirical treatment, triple therapy for 14 days based either on local antimicrobial susceptibility or on personal antibiotic history is generally recommended. Triple therapy with high dose of amoxicillin is a valid alternative choice, either in double resistance or in second-line treatment. Moving from therapeutic regimens used in adults, we could also select quadruple therapy with or without bismuth salts. However, all the treatment regimens often entail unpleasant side effects and lower compliance in children. In this review, the alternative and not yet commonly used therapeutic choices in children were also analyzed.

Keywords: adjuvants, children, combination therapy, eradication treatment, *Helicobacter pylori*, susceptibility testing

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Introduction

Helicobacter pylori (*H. pylori*) is a helical-shaped, gram-negative bacterium, the first time isolated by Warren and Marshall in 1983 that colonizes gastric mucosa and could produce urease-dependent ammonia locally.[1] *H. pylori* infection can cause gastritis, gastric or duodenal ulcers, atrophic gastritis, mucosa-associated lymphoid tissue lymphoma, and gastric cancer especially adenocarcinoma, as well as extra-digestive disorders including iron deficiency anemia and chronic immune thrombocytopenic purpura.[2–5]

The global prevalence of *H. pylori* infection is approximately around 50%, but infection rates vary between developed and developing countries, often ranging between 20% and 80%.[6] According to an epidemiological study conducted by Zamani *et al.*, *H. pylori* infection was more prevalent in developing (50.8%) compared to developed (34.7%) countries. Furthermore, the prevalence of the infection is higher in adults than children (48.6% *versus* 32.6%, respectively).[3]

Considering the increase in the frequency of this infection over the last years, indications for

treating *H. pylori* have been amplified. Unfortunately, the proportion of strains resistant to certain antibiotics has increased too, making eradication more difficult, especially in pediatric age.[2,7,8]

European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN), Latin American Society of Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN), and Japanese Society of Pediatric Gastroenterology Hepatology and Nutrition (JSPGHAN) guidelines recommend searching for *H. pylori* in children only in cases in which the expected benefits outweigh the costs and risks of testing and subsequent treatments. Moreover, before deciding to investigate *H. pylori* infection in children with abdominal pain, we should carefully evaluate whether upper gastrointestinal endoscopy is needed to better study all the possible causes and not merely focus on *H. pylori* infection. Furthermore, the main pediatric international guidelines are against a 'test and treat' strategy in children. Again, if *H. pylori* infection is incidentally diagnosed during gastroscopy performed for an unrelated clinical suspicion, the subsequent eradication treatment should be considered only after a careful discussion of the risks and benefits with parents.[8–10]

Also Korean children under the age of 10 years should be managed by the updated ESPGHAN/NASPGHAN guidelines. Noninvasive as well as invasive diagnostic test and treatment strategy for *H. pylori* infection are not recommendable in children younger than 10 years of age or children with body weight under 35 kg, except in cases of clinically suspected or endoscopically identified peptic ulcers.[11]

Standard *H. pylori* eradication treatments differ worldwide among regions and countries, due to the differences in drugs availability and antimicrobial resistance of the bacterium. Indeed, because of always more treatment failures, the eradication of *H. pylori* is becoming increasingly challenging. On the one hand, this could be linked to host factors, such as metabolic changes, gut microbiota modifications after treatment, rapid metabolism of proton pump inhibitors (PPIs), inactivation of antibiotics at low gastric pH, or even more to poor compliance.[12,13] Conversely, it may be due to insufficient dose or duration of eradication therapy or *H. pylori* virulence factors, including point mutations, natural transformation, quorum sensing signaling modulators, and efflux pumps, which can result in the multidrug resistant (MDR) *H. pylori* phenotype.[14]

Karbalaei *et al.*, in a systematic review and meta-analysis conducted on 19 studies, found that the prevalence of primary MDR *H. pylori* infection in children was approximately 6.0%.[4] They also detected that the prevalence of primary MDR *H. pylori* infection is significantly higher among Asian children compared to children in Western countries ($p < 0.05$), concluding that it depends on several factors such as national antibiotic consumption, individual comorbidities, and genomic characteristics of *H. pylori* strains. Thus, *H. pylori* treatment regimen should be adjusted based on drugs susceptibility test to reduce the risk of treatment failure.[14]

Therefore, the most recent literature on *H. pylori* treatment regimens in pediatric population was collected to evaluate the effectiveness of these regimens, moreover analyzing the possible alternative combinations for the future.

Methods

We searched related articles in PubMed database using terms containing (*Helicobacter* OR *Helicobacter pylori* OR *H. pylori*) AND (children OR pediatric) AND (treatment OR therapy OR eradication) and (*Helicobacter* OR *Helicobacter pylori* OR *H. pylori*) AND (children OR pediatric) AND [(probiotics) OR (phytotherapy) OR (synbiotics) OR (natural)] for all relevant abstracts, manuscripts, and guidelines published in the last 5 years (2018–2022). Regarding the first choice, we selected randomized controlled trial (RCT), meta-analysis, guidelines, systematic reviews, and narrative/comprehensive reviews. Instead, regarding phytotherapy and probiotics, since data are clearly heterogeneous, we selected only reviews and meta-analysis/systematic reviews. In any case, only articles in English language were selected. The non-human studies and manuscripts that did not involve children or adolescents were excluded.

Treatment options

Eradication treatment of *H. pylori* infection depends on a combination of antisecretory drugs and antimicrobial agents. The firsts are essential because, beyond to raising the gastric pH thus getting *H. pylori* more susceptible to antibiotics, PPIs have a direct antimicrobial activity against the bacterium.[2]

For many years, the standard triple therapy (TT), including PPIs, amoxicillin (AMO) and clarithromycin (CLA) or metronidazole (MET), has been represented the cornerstone therapy in children. However, recently, the widespread use/abuse of antibiotics, particularly for respiratory tract infections, has significantly increased the antibiotic resistances, which however, vary among regions and countries. In northern Italy, for example, it has been observed an increase in CLA resistance, while MET resistance has been reducing in children during last years.[15] On the contrary, AMO susceptibility has been confirmed very rare.[8,15]

As this combination of antimicrobial and antisecretory drugs cannot always get a good eradication rate, some researchers have been used alternative compounds, such as phytomedicines, probiotics, prebiotics, and lactoferrin to improve eradication rates, although their exact mechanism of action is not yet fully understood.

Alternative drugs

Antimicrobial drugs and PPIs represent the main agents used in *H. pylori* eradication, but the increasing development of antibiotic resistance has caused a decrease in successful rate. Moreover, antibiotics alter the intestinal composition of microbiota, causing unpleasant side effects.

For these reasons, there is a crucial need for developing a more effective treatment; in this regards, alternative therapies have been developed and studied.

Probiotics

Although the impact of *H. pylori* infection on gastric and intestinal microbiota diversity is known, it is still far from being elucidated.[16] Probiotics are defined by the World Health Organization as 'live microorganisms which, when administered in adequate amounts confer a health benefit on the host'.[17]

The effect of probiotics in *H. pylori*-infected patients is complex with heterogeneous results in children. Probiotics seem to act in two primary ways: they compete with *H. pylori* in the binding to surface receptors of intestinal epithelial cell inhibiting adhesion to the gastric mucosa resulting in a decrease of inflammation, in secreting antimicrobial substances, with reduction in the bacterial loads, and strengthening of the intestinal biological barrier. Furthermore, decreasing the related-polyantibiotic therapy side effects, probiotics will favor patients' compliance.[18,19] Lastly, probiotics have also an antimicrobial effect by inhibiting urease activity of *H. pylori*, but also by producing short-chain fatty acids resulting a pH reduction and therefore an unsustainable environment for the bacterium.[20]

Most of the strains were studied in single trials only, with no strain specifications, so it remains not known which probiotic strain achieves the best results since no comparative trial was performed. Furthermore, studies use different antibiotics and PPIs, with different dosages and different duration; hence, we do not have adequate standardization because of evident heterogeneity.[20]

A systematic review and network meta-analysis by Feng *et al.* evaluating 29 trials involving 17 probiotic regimens concluded that probiotics added to TT significantly increased *H. pylori* eradication rates with a relative ratio (RR) of 1.19 [95% confidence interval (CI), 1.13–1.25) and reduced side effects with a RR of 0.49 (95% CI, 0.38–0.65). *Lactobacillus casei* and the association of *L acidophilus* and *L. rhamnosus* was the best for eradication rates and for the side effects, respectively.[21]

Another systematic review and meta-analysis by Zhou *et al.*, analyzing 18 trials, demonstrated that *Saccharomyces boulardii* supplementation significantly improved eradication therapy with a RR of 1.09 (95% CI, 1.05–1.113) and reduced the incidence of side effects (mainly diarrhea) with a RR of 0.47 (95% CI, 0.36–0.61), although with moderate- and low-quality evidence, respectively.[22]

Other authors in a meta-analysis of RCT showed that *Lactobacillus*, especially in high dosage and longer duration of supplementation, added to TT in children may increase *H. pylori* eradication rates with a RR of 1.19 (95% CI, 1.07–1.33) and

decrease the incidence of related side effects (mainly the incidence of diarrhea) with a RR of 0.30 (95% CI, 0.10–0.85).[23]

Another network meta-analysis by Wen *et al.* analyzing 17 RCTs showed that the adding of *Bacillus mesentericus* + *Clostridium butyricum* + *Streptococcus faecalis* to a 14-day TT, significantly increased *H. pylori* eradication rates with a RR of 1.16 (95% CI, 1.07–1.26) and reduced side effects with a RR of 0.40 (95% CI, 0.34–0.48) in Asian children.[24]

All things considered, a recent review concluded that the effect of probiotics on *H. pylori* infection is complex and although they cannot eradicate the infection if administered alone, they have the ability to increase the eradication rates by up to 10% when used in combination with standard TT or sequential therapy (ST) and to reduce the secondary adverse events related to eradication therapy.[16]

The recent Maastricht VI/Florence guidelines stated that several probiotic strains such as *Lactobacillus* spp, *Bifidobacterium* spp, and *Saccharomyces boulardii* can improve the eradication rate in adults; but it seems to be a secondary effect, due to the decreasing of adverse events related to eradication therapy. The lesser the side effects, the higher the compliance of eradication therapy, rather than through direct effects on *H. pylori*.[2]

Prebiotics/symbiotics

Prebiotics include a group of nutrients not digestible by the human body, but degraded by bacteria. They can improve health by stimulating the growth or activity of a selection of intestinal bacteria. Instead, symbiotics are the combination of pre- and probiotics.[25]

In literature, there are very few studies about the combination between prebiotics and eradication therapy in children with *H. pylori*.[20]

In 2017, two Turkish studies achieved discordant results regarding the addition of *B. lactis* and inulin in eradication rate of *H. pylori* infection in children. Sirvan *et al.* showed improving in eradication rate of 16% in the group treated with this symbiotic added to standard therapy compared to standard therapy alone. In the same way, these authors achieved also an improving in side effects with significant statistical value regarding abdominal pain, nausea, and diarrhea but not for metallic taste.[26]

Instead, Ustundag *et al.* did not show differences neither in eradication rate ($p = 0.16$ and $p = 0.19$ in intention-to-treat and per-protocol (PP) analyses, respectively), nor in improving side effects (RR: 0.97, 95% CI, 0.14–6.71) in the group treated with *B. lactis* and inulin added to 14-day TT compared to 14-day TT alone.[27]

Again, other studies showed that adding prebiotic to probiotic, then having symbiotic, significantly increased the eradication rate and decreased side effects in adult patients (95% prebiotics, 85.7% probiotic, and 83.3% placebo group, respectively).[28]

Bovine lactoferrin

Bovine lactoferrin (bLf) is an iron-binding glycoprotein present in the milk, body fluids, pancreatic and seminal fluids, and the granules of the polymorphonuclear leukocytes in humans and bovines.[29]

Some studies in adults have reported the role of bLf as an add-on therapy for eradication of *H. pylori* infection, with conflicting results; bLf instead seems ameliorate the unpleasant adverse events related to eradication therapy.[19,30,31]

To our knowledge, bLf has never used in children with *H. pylori* infection, so far.

In conclusion, although probiotics cannot eradicate *H. pylori* infection when administered alone, several authors concluded that in *H. pylori* eradication, probiotics might contribute to increase the eradication rate and decrease the related side effects, especially diarrhea and bloating. Regarding the duration of probiotic supplementation, it seems logic to opt for at least 14 days of treatment, similar to the recommended duration of eradication therapy.

However, the evidence of the role of probiotics in *H. pylori*-infected children remains scarce and further studies are needed to better understanding which probiotic strains and which dosage in standardize manner are useful. The main pediatric international guidelines do not recommend the

routine addition of either single or combination probiotics to eradication therapy neither to reduce side effects nor to improve eradication rates.[32,33] Symbiotics, instead, have been less studied than probiotics and their effects on eradication are still inconsistent, especially in children.[20]

Phytotherapy

Plants products and their active extracts and bioactive compounds have renowned health benefits and they largely used over centuries. As is well known the active molecules used in pharmaceutical industry are formerly derived from bioactive molecules extracted from plants and other living organisms.[34]

Since many years, there is an increasing use of natural products in both health and disease. Botanical compounds contain active molecules with pharmacological activities in relieving symptoms or curing diseases. Several studies analyzed the anti-*H. pylori* activity of plant extracts.[28,35] Some natural compounds showed discordant results in *H. pylori* infection. *Citrus bergamia* resulted in antimicrobial properties, but blueberry and grape seed extracts combined with TT did not show significant differences in eradication rate in adults.[28]

Although *in vitro* study proved an activity against *H. pylori* of mastic gum, it did not increase the eradication in infected humans, while ginger and curcumin improved eradication rate in *H. pylori*-infected adult patients. Cinnamon extract as adjuvant of *H. pylori* eradication therapy in adults resulted in higher eradication rates ($p = 0.036$) and fewer side effects ($p < 0.05$) than control group.[28]

Also, flavonoids have several properties as antioxidant, hepatoprotective, anti-inflammatory, anticancer, antiviral, and antibacterial effects, but they are studied only *in vitro* in *H. pylori* infection, so far.[36]

In conclusion, some authors have been studied natural compounds in *H. pylori*-infected patients, but only in adults; we did not find pediatric studies in this regards. Furthermore, most of the phytotherapic products have been analyzed only *in vitro* or in animal models; therefore, their efficacy in humans needs to be better elucidated.[34]

Therapeutic regimen combinations

Unlike adults, in which a wider variety of treatment choices can be used, in *H. pylori*-infected children gastroenterologist must choose between a limited number of antibiotics.[2,8]

For obtaining a higher successful eradication rate, it would be necessary to evaluate three strategic points:

1) The eradication rate by geographic area
2) The systematic use of susceptibility testing
3) Treatment compliance greater than 90%.[37]

Usually, in clinical practice in children, the antimicrobial susceptibility testing for *H. pylori* infection is performed using gastric biopsy-based methods during gastroscopy (at least one biopsy from the antrum and one from the corpus).[8]

Since its discovery, various combinations of PPIs and antimicrobial agents have been used to treat *H. pylori* infection. In children, the most used therapeutic regimen is the TT. Alternatively, one can use ST, bismuth-containing quadruple therapy (BQT), and concomitant therapy (CT also called non-BQT). However, the eradication rate does not often achieve the targeted 90% in children. Lower eradication rates in children than in adults using the same regimen could be explained through some conjecture, such as different antibiotic susceptibility or compliance to therapy between children and adults.[38]

Quadruple therapies (either BQT or CT) were also suggested as empirical first-line treatments for adults and children.[2,8–10,39]

Tetracyclines (TETs) are relatively contraindicated in children aged less than 8 years due to their side effects of permanent tooth discoloration and retardation of bone growth. Fluoroquinolones too are relatively contraindicated in children due to the negative effects of growth. Hence, as the flexibility of antibiotic choice in children is limited, to avoid the use of these off-labeled second-line antibiotics, the efficacy of first-line therapy is of vital importance.[8]

For this reason, it is really essential to improve the successful rate that, before starting an eradication

treatment, doctors emphasize the importance of a strict adherence to therapy.[8]

Since current evidence indicates that *H. pylori* infection does not cause symptoms in the absence of peptic ulcer disease and no substantial evidence has been documented regarding the health benefits of treatment in eliminating the infection in children, ESPGHAN/NASPGHAN, LASPGHAN, and JSPHGAN guidelines do not recommend *'test and treat'* strategy.[8–10]

Overall, the following treatment regimens are shared by ESPGHAN/NASPGHAN, LASPGHAN, JSPGHAN, and Korean guidelines.[8–11]

In Japan, neither BQT nor ST are therapeutic regimens approved in children.[10]

Known antimicrobial susceptibility

The most recent pediatric international guidelines recommend setting up the eradication therapy based on susceptibility testing.[8] The treatment regimen tailored to antimicrobial susceptibility beyond increasing the successful rate, it is more cost-effective than the empiric therapy.[40]

The main culture method of *H. pylori* is made by gastric biopsies, usually one specimen from the antrum and one from the corpus, but *H. pylori* is difficult to culture, and this method, beyond its high costs, is not widely available in all medical institutions.[8,41]

Culture by biopsies or polymerase chain reaction (PCR) or fluorescence *in situ* hybridization on previously obtained paraffin-embedded biopsies should be performed to guide the subsequent therapy.[8] In addition, recently other noninvasive antimicrobial susceptibility methods have been developed.[42,43]

First-line treatment

a) Either fully antibiotic susceptibility of CLA, MET, and AMO is known, or patient has MET resistance alone, the TT (PPI-CLA-AMO) at standard dose for 14 days is recommended.[8,43]
b) Whether patient has AMO and MET susceptibility and CLA resistance, the TT based on PPI-AMO-MET at standard dose for 14 days is recommended.
c) Whether you have CLA and MET resistance, the TT with PPI-AMO at high-dose MET at high dose for 14 days, is recommended*.
d) Whether AMO resistance (or allergy to penicillin) is present and CLA and MET are susceptible, the TT with PPI-CLA-MET at standard dose for 14 days is recommended.
e) ST for 10–14 days remains a valid alternative option mainly in patients with fully antibiotic susceptibility (see below) (Tables 1 and 2).

In each regimen above (except in ST), all drugs are administered twice a day.

Standard doses are so composed: PPI ranging from 1 to 2 mg/kg/die, AMO ranging from 50 to 70 mg/kg/die, CLA from 20 to 30 mg/kg/die, and MET from 20 to 30 mg/kg/die. All these drugs divided in two equal daily doses.

High dose of AMO instead means 75 mg/kg/die, maximum 3 g/die, divided in two daily doses.

Alternatively, in all cases in which either one or two antibiotic resistance is present, clinicians can choose BQT for 14 days including bismuth salts and MET with AMO or TET based on the age of children (<8 years or >8 years, respectively).[8,9]

Table 1. First-line treatment with known antimicrobial susceptibility.

Therapeutic choice	All susceptible antibiotics or MET-R	CLA-R	CLA-R and MET-R	AMO-R**
TT 14 days	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d
	AMO 50–70 mg/kg/d	AMO 50–70 mg/kg/d	AMO 75 mg/kg/d	CLA 20–30 mg/kg/d
	CLA 20–30 mg/kg/d	MET 20–30 mg/kg/d	MET 30–40 mg/kg/d*	MET 20–30 mg/kg/d

All drugs are administered in two equal daily doses. ST for 10–14 days is a valid option in patients with fully antibiotic susceptibility: (a) PPIs 1–2 mg/kg/d + AMO 50–75 mg/kg/d for the first 5–7 days. (b) PPIs 1–2 mg/kg/d + CLA 20–30 mg/kg/d + MET 20–30 mg/kg/d for the second 5–7 days.
*The *in vitro* MET resistance may be overcome *in vivo* by longer treatment (14 days) and/or higher doses (30–40 mg/kg/die).[8,44]
**This regimen is also valid whether patients have allergy to penicillin (and both CLA and MET susceptibility).
AMO, amoxicillin; CLA, clarithromycin; MET, metronidazole; PPIs, proton pump inhibitors; ST, sequential therapy; TT, triple therapy.

Table 2. Alternative first-line treatment when one antibiotic resistance is present.

BQT 14 days, aged <8 years	PPIs 1–2 mg/kg/d
	AMO 50–70 mg/kg/d
	MET 20–30 mg/kg/d
	Bismuth 8 mg/kg/d
BQT 14 days, aged >8 years	PPIs 1–2 mg/kg/d
	MET 20–30 mg/kg/d
	TET 50 mg/kg/d
	Bismuth 8 mg/kg/d

PPIs, AMO, and MET are administered in two equal daily doses, TET and bismuth in four equal daily doses.
AMO, amoxicillin; BQT, bismuth-containing quadruple therapy; MET, metronidazole; PPIs, proton pump inhibitors; TET, tetracycline.

Second-line treatment. In known antimicrobial susceptibility, and unsuccessful of first-line treatment, we should choose an alternatively combination of antibiotic, not used before, possible based on susceptibility as reported above, or BQT, if available (Table 3).

CT represents another possible choice, either whether fully antibiotic susceptibility or antibiotic resistance is present (PPI-AMO-CLA-MET at standard dose for 14 days).[8]

Otherwise, the therapeutic choice is TT with AMO at high dose combined with CLA or MET, based on their susceptibility.[8]

Rescue treatment. In the same way, as rescue therapy, a different regimen compared to other two previously used, always possibly based on antimicrobial susceptibility should be selected. Usually, as rescue therapy, either BQT or TT with higher dose of AMO is a good option.[8]

Korean guidelines recommend that when treating *H. pylori* infection in pediatric as well as adult patients, anti-*H. pylori* eradication therapy should be determined without the knowledge of antibiotic susceptibility. For this reason in Korea, BQT is the preferred first-line regimen.[11]

Not-known antimicrobial susceptibility

Whether antibiotic susceptibility has not known, the treatment should be rely on clinical experience, regional antimicrobial susceptibility profiles, and recent antibiotic courses of the patient. Since forever, pediatricians and pediatric gastroenterologists tried to move therapeutic choices used in adult patients, adapting them to pediatric age (Table 4).

Alternatively, TT for 14 days, BQT for 14 days, CT for 10–14 days, or ST for 10–14 days represent valid options.[2,8]

TETs and quinolones are contraindicated under a certain age; TET can be used starting from 8 years old and quinolones from adolescence.[8]

High-dose dual therapy (HDDT) maybe represent a not so new regimen, widely used in adult population, but it has not yet been employed in children so far.[45]

Furthermore, an eradication therapy with vonoprazan, a new potassium-competitive acid blocker (P-CAB), showed good successful rates, both in children and adults.[7,46]

Sequential therapy. The main international guidelines recommend ST for 10–14 days as first- or second-line treatment in case of fully susceptibility of antibiotics (Table 1).[8,9,11]

However, several authors showed a good eradication rate both in children and adults by using ST even in the presence of antibiotic resistances.[47–49]

Our group showed in 2018 that ST could overcome the antibiotic resistance in children with *H. pylori* infection, with an acceptable eradication rate (88.7%).[47]

However, antibiotic-resistant strains of *H. pylori* remain a challenge for a successful eradication and a tailored therapy should be always encouraged.

Da-Jyun Su *et al.* evaluated the differences in eradication efficacy between 14-day ST and 14-day and 7-day TT as first-line treatment in children. Their results showed how 14-day ST is significantly superior to 7-day TT (97.4% *versus* 80%, $p=0.032$), and tend to be better than 14-day TT (97.4% *versus* 83.3%, $p=0.07$) in an

Table 3. Second-line treatment.

Therapeutic choices	Fully antibiotic susceptibility	CLA-R, MET-S	MET-R, CLA-S	MET-R, CLA-R	AMO-R
TT 14 days as reported in Table 1, not used before	√	√	√	√	
BQT 14 days as reported in Table 2	√	√	√	√	√
					Second part of Table 2
CT 14 days	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d
	AMO 50–70 mg/kg/d	AMO 50–70 mg/kg/d	AMO 50–70 mg/kg/d	AMO 50–70 mg/kg/d	AMO 50–70 mg/kg/d
	MET 20–30 mg/kg/d	MET 20–30 mg/kg/d	MET 20–30 mg/kg/d	MET 20–30 mg/kg/d	MET 20–30 mg/kg/d
	CLA 20–30 mg/kg/d	CLA 20–30 mg/kg/d	CLA 20–30 mg/kg/d	CLA 20–30 mg/kg/d	CLA 20–30 mg/kg/d
TT 14 days		PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	PPIs 1–2 mg/kg/d	
		AMO 75 mg/kg/d	AMO 75 mg/kg/d	AMO 75 mg/kg/d	
		MET 20–30 mg/kg/d	CLA 20–30 mg/kg/d	MET 30–40 mg/kg/d*	

PPIs, AMO, MET, and CLA are administered in two equal daily doses.
*The *in vitro* MET resistance may be overcome *in vivo* by longer treatment (14 days) and/or higher doses (30–40 mg/kg/die).[8,44]
AMO, amoxicillin; BQT, bismuth-containing quadruple therapy; CLA, clarithromycin; CT, concomitant therapy; MET, metronidazole; PPIs, proton pump inhibitors; TT, triple therapy.

Table 4. Eradication therapies in not-known antimicrobial susceptibility.

Therapeutic choices in children with not-known antimicrobial susceptibility
TT for 14 days
BQT for 14 days
CT for 14 days
ST for 10–14 days
HDDT for 14 days*
Vonoprazan-AMO 7 days

The treatment should be rely on clinical experience, regional antimicrobial susceptibility profiles, and recent antibiotic courses of the patient.
*HDDT has never been used so far in children.
BQT, bismuth-containing quadruple therapy; HDDT, high-dose dual therapy; CT, concomitant therapy; ST, sequential therapy; TT, triple therapy.

area of high CLA resistance.[48] This could be explained considering that ST could impair the efflux pump on the bacterial wall through the ability of AMO, and increase the intracellular concentration of macrolides afterwards. Among these treatment regimens, only 14-day ST achieved an above 90% eradication rate, which is recommended by ESPGHAN/NASPGHAN and LASPGHAN guideline.[8,9]

ST regimen efficacy was previously investigated by Horvath *et al.* and Huang *et al.* in meta-analyses.[50,51] They considered the eradication rate of 10-day ST, ranging from 63.2% to 86.1% and not better than that of 14-day TT in the pediatric population.

The most recent adult guidelines recommend against the use of ST, as first- or second-line therapy.[2,52]

ST is not approved as eradication treatment in Japanese children.[10]

Bismuth quadruple therapy. Another therapeutic regimen option is represented by BQT. It

classically involves a combination of PPI, bismuth salts, MET, and TET. BQT for 10–14 days is recommended by the Maastricht VI/Florence Consensus Report (Europe), Toronto Consensus, and American College of Gastroenterology Clinical Guideline (North America) as the first-line treatment for adult patients in areas with high *H. pylori* CLA resistance, as it eradicates *H. pylori* better than TT.[2,39,52–54]

Interest in this therapy rises with the advent of the three-in-one single-capsule BQT (marketed as Pylera), containing bismuth, MET, and TET, and achieving an effective eradication rate of approximately 90% both in first- and second-line therapy, as recently reported in a meta-analysis.[55]

In children, ESPGHAN/NASPGHAN and LASPGHAN guidelines recommend BQT as second-line or rescue therapy. In children aged less than 8 years, the BQT should contain PPI-AMO-MET (at standard doses) plus bismuth salts at a dose of 8 mg/kg/die. Otherwise, in children aged more than 8 years, the BQT should contain PPI-MET-TET (at standard doses) and bismuth salts, always for 10–14 days.[8,9]

Bismuth performs its anti-*H. pylori* effects in four different manners. It forms complexes in the bacterial wall and periplasmic space; it inhibits several enzymes of *H. pylori* such as urease, fumarase, alcohol dehydrogenase, and phospholipase; inhibits ATP synthesis of bacteria; and inhibits adherence of *H. pylori* to the gastric mucosa. Moreover, inhibition of acid gastric secretion is described. In addition, it showed that colloidal bismuth sub-citrate impedes proton entry into *H. pylori*, increasing the efficacy of growth-dependent antibiotics. Again, bismuth salts have a synergistic effect with antibiotics and may help to overcome the resistance to MET and to CLA.[56,57]

A recent study in Turkish children evaluated the effectiveness of a novel sequential treatment regimen containing bismuth for 14 days. Patients were treated with a novel combination of PPI + AMO at standard doses for 7 days followed by PPI-MET, at standard doses plus TET (50 mg/kg/die, divided into four equal doses, maximum 4×500 mg), and bismuth subsalicylate (at different doses according to age of patients for the second 7 days. This novel scheme achieved an eradication rate of 92%.[58]

Bismuth quadruple therapy, as well as ST, is not approved as eradication treatment in Japanese children.[10]

As in Korean children, eradication therapy should be usually selected empirically, BQT is the preferred choice as first-line treatment regimen.[11]

Concomitant therapy. Currently, there are not many studies assessing CT in pediatrics. In 2011, a pilot study compared a 10-day ST with 5-day CT (PPI-AMO-CLA-tinidazole) in children with similar eradication rates.[59]

CT regimen is usually based on the combination of PPI-AMO-CLA-MET for 14 days. Its eradication rate, accordingly to a prospective, comparative, cross-sectional study, was 84.6% in Chinese children.[60]

However, this study showed a superiority of BQT compared to TT, ST, and CT. Antibiotic resistance could decrease the efficacy of CT. The eradication rate is 100% in sensitive strains and only 59% in resistant strains.[60]

ESPGHAN/NASPGHAN guidelines stated that CT for 14 days might be a better option compared to TT with high dose of AMO, in children with primary double resistance to CLA and MET. Another disadvantage of CT is represented by the low compliance because of multiple drugs and subsequent side effects.[8]

Hybrid and reverse hybrid therapy. In 2011, Hsu *et al.* first used a novel 14-day therapeutic regimen composed by PPI and AMO for the first 7 days, following by PPI-AMO-CLA-MET for the second 7 days, in adults with very good results.[61]

The same authors, a few years later, reversed the hybrid therapy with higher results compared to TT, always in adult patients.[62]

These two regimens showed good compliance and acceptable side effects.

To our knowledge, neither hybrid nor reverse hybrid therapy has been never used so far in children.

High-dose dual therapy. The resistances of *H. pylori* to CLA and MET are increasing

worldwide, although with different rate among regions and countries.

On the contrary, despite AMO is widely used in common therapeutic regimens worldwide, its primary and secondary resistance of *H. pylori* remains generally low or very low, worldwide.[2,8,15]

Universally, dual therapy, including both AMO and PPI for 14 days, was first reported in the 1990s as a first-line *H. pylori* eradication treatment with good successful.[63,64] This combination resulted in a better eradication rate than PPI alone (0%) ore AMO alone (14.2%).[65]

HDDT, including OME 40 mg and AMO 750 mg, three times daily was first proposed in 1995 and gave an eradication rate greater than 90% in adults.[64]

In contrast to regular dual therapy, in HDDT the PPI and AMO are given three or four times daily. This scheme seems ameliorate the impact of CYP2C19 genotype.[66]

The presence of gastric acid environment is essential to maintain *H. pylori* strains in a sleeping, not-replicative state. It is now well recognized that improving the efficacy of gastric antisecretory therapy, by increasing the dose and/or the frequency of administration of PPI, a higher eradication rate is facilitated.[67]

The concept to use HDDT with PPI and AMO is to modify the gastric acid environment. Drastically increasing the gastric pH with high dose of PPI, the sleeping strains of *H. pylori* reactivates, getting them into replicative state, thus more susceptible to the action of AMO.[67,68]

AMO is a pH-dependent drug (it is stable at $pH > 5.5$) and it is time dependent. In fact, it is absorbed more rapidly into the plasma and it is excreted within 6–8 h after the administration. For this reason, it is more efficacy if administered 3–4 times daily, to maintain stable its plasmatic concentration and to have its bactericidal effect.[69]

Here because it is essential to maintain an intragastric $pH \geq 5.5$, with high doses and frequent administrations of PPI. Moreover, high dose of PPIs allows a higher bactericidal direct effect against *H. pylori*.[70]

Again, the high dose and frequency of PPIs consent to overcome their metabolization in subject with 'rapid' and 'ultra-rapid metabolizers' genotype, which represent about the 56%–81% of Caucasic people.[8,68]

However, side effects and poor patient compliance due to the high dose, high frequency of administration, and long treatment duration are the main downsides of HDDT. For these reasons, many authors reserved the HDDT as rescue treatment. More recent studies reconsidered HDDT for the treatment of *H. pylori* infection, especially in adult population.[71,72] A RCT conducted in Taiwan by Yang *et al.*, comparing the efficacy of HDDT with standard therapies in treatment-naïve or treatment-experienced patients with *H pylori* infection, demonstrated the superiority of HDDT to standard regimens as empiric first-line or rescue therapy, with similar safety profiles and tolerability.[68] In 2020, a Turkish study investigated the efficacy of HDDT as first-line treatment in adult population. The authors administrated to all patients 14-day HDDT involving rabeprazole (20 mg tid) and AMO (1 g tid). They demonstrated highly effective as a first-line therapy for *H. pylori* eradication. This regimen was also well tolerated and easily available.[72]

To our best knowledge, at this time, HDDT has never been used in children so far.

Moving the dosage from adult patients, we think that the appropriate combination of HDDT in children could be constituted from omeprazole (OME) or esomeprazole (ESO), the unique PPIs recommended in children (at least in Italy), with AMO at the dosage of 75 mg/kg/die, as recommended by the international guidelines.[8] The usually recommended dosage of OME or ESO is around 0.5–1 mg/kg/die divided into two equal doses. Therefore, a HDDT in children could be constituted by PPI at dose of 3 mg/kg/die, divided into three equal doses (maximum dose 40 mg tid) plus AMO at 75 mg/kg/die, divided into four equal doses (maximum dose 750 mg qid): everything for 14 days. Studies in this regard are encouraged.

Eradication therapy with vonoprazan. Nowadays, we could consider the shift from conventional PPIs to vonoprazan in dual therapies. Vonoprazan is a P-CAB with stronger and longer-lasting

reduction in gastric acid secretion than PPIs. Higher acid suppression has been shown to be associated with successful eradication of *H. pylori* with TT. Nevertheless, the acid-inhibitory effect of PPIs is slow and cumulative, and many doses are required to inhibit newly synthesized proton pumps and carry out maximum acid inhibition.[73] Some trials conducted in Asia showed how vonoprazan combined with AMO and CLA (VAC) achieves better results than PAC (PPI-AMO-CLA) in eradication rates.[74]

Moreover, vonoprazan and AMO dual therapy could be an alternative treatment for *H. pylori* eradication. Several studies demonstrated that 7-day vonoprazan (20 mg/die) and AMO (750 mg bid) achieve *H. pylori* eradication rates of 85–93%, similar to the results of 7-day vonoprazan TT in regions with high CLA resistance.[75,76]

A prospective study, conducted in junior school students in Japan between 2015 and 2017, investigated the efficacy of the first-line TT with vonoprazan for *H. pylori* eradication. These authors demonstrated an eradication rate of this first-line TT of 85.7% in PP analysis, which was better than the historical results using a PPI in children; however, it was still below 90%.[77,78]

In addition, the vonoprazan-AMO dual therapy has less impact on gut microbiota compared with the vonoprazan TT.[79]

These trials suggest that more potent acid suppression increases eradication of CLA-resistant strains by improving AMO effectiveness.

Furthermore, it has been shown how neglecting CLA from this combination (VA) provides similar results to VAC, hinting that CLA was an unnecessary antibiotic in CLA-resistant infections.[78] For this reason, the earlier referenced guidelines recommend CLA-containing TT only in areas with low CLA resistance and only in patients who have not received macrolide antibiotics, previously.[80] In this randomized trial of 1046 patients, VA and VAC were both compared with PAC.[7] The vonoprazan regimens achieve similar results as PAC, with eradication success in 78.5% and 84.7% *versus* 78.8%, respectively, in patients with CLA- and AMO-susceptible strains. In patients with CLA-resistant organisms, they demonstrated the superiority of both VA and VAC *versus* PAC (69.6% and 65.8% *versus* 31.9%; $p < 0.001$). Another study showed higher eradication rate of the VA in smaller patient body size, including lower body mass index and lower body surface area.[81]

However, poor data were collected in pediatric population.[77]

Most of them were collected in Asian children, where vonoprazan is approved and used nowadays.

Discussion

On the basis of this review of the literature, it emerges that an ideal treatment regimen of *H. pylori* infection does not exist in children as well as in adults. This occurs because of differences in drugs availability and antimicrobial resistance of *H. pylori* in different regions. In addition, we know that a successful eradication depends on two main factors: the knowledge of antimicrobial susceptibility and the adherence to treatment.[1]

Thus, as recommended by the main pediatric international guidelines (ESPGHAN/NASPGHAN, LASPGHAN, and JSPGHAN), the first-line treatment should be guided by antibiotic susceptibility testing, even if the culture method of *H. pylori* is often difficult to perform, and not available in every medical institution and moreover almost always this exam needs upper endoscopy, an invasive procedure.[8,10,41]

The eradication rates for pediatric *H. pylori* infection, compared to adult populations, are not satisfactory, and in most studies, the currently used regimens could not achieve the target of 90% or above.[8]

It is already accepted that nowadays, the best approach warranting the higher eradication rate in children is the susceptible-based TT for 14 days.[8–10] This treatment allows to minimize the antibiotic resistances and the risk of additional therapeutic attempts. Alternatively, ST (better for 14 days) is considered a good option in first-line treatment, in case of fully susceptibility (except for Japanese guidelines). Some authors showed a good eradication rate of ST even in patients with antibiotic resistances.[48,49]

Otherwise or as second-line therapy, we can select either BQT, if bismuth salts are available or CT.

Instead, when there is one antibiotic resistance perhaps the more effective eradication therapy including TT with MET and high dose of AMO, always for 14 days.[8]

The advantage of BQT is that its efficacy is not affected by antibiotic resistance, while dual resistance to CLA and MET impaired the efficacy of all non-BQTs.[41]

For this reason, BQT should not be used as first-line therapy, but reserved as second-line or rescue therapy, mainly in children.[8]

Susceptibility testing should be carried out mainly in regions with high CLA resistance or in patients who are not suitable for upper endoscopy or have refractory infections, as susceptibility testing can avoid the hazards associated with the abuse of antibiotics and prevent increases in the development of secondary or multiple antibiotics resistance.[2,82]

Recently, the possibility to test the antibiotic susceptibility with noninvasive methods, by stools, so providing the opportunity to start a tailored therapy, with higher probability to obtain an eradication success. Sometimes, 'test and treat' strategy may be indicated in children; for example, if there is lack of access to endoscopy, if the child has complex comorbidities that make the procedure risky, or if family refuses it.[71,83]

Thus, developing simple and noninvasive means to diagnose antibiotic susceptibility will greatly facilitate antibiotic therapy.[84]

Next-generation sequencing of stools for six antibiotics (AMO, CLA, MET, TET, rifabutin, and levofloxacin) is already available in the United States. Therefore, clinicians should encourage the local hospital to perform a noninvasive PCR-based susceptibility testing at least for CLA.[42]

In this way, we could greatly reduce the risk of unsuccessful eradication rate; furthermore, mainly in adults with no alarm signs, we could treat infected patients with tailored therapy without being forced to perform gastroscopy.

Vonoprazan-based dual or triple therapy seems to represent the unique eradication regimen allowing higher successful rates than other combination therapies. However, at this moment, the availability of vonoprazan is still limited; therefore, we need more studies to evaluate this therapy worldwide.[7,75,78]

Failure of eradication is usually due to antibiotic resistance or poor compliance to treatment, which is more common in children (also because some antibiotics as MET are available in tablets and not in syrup). In addition, the efficacy data of second-line therapy are exiguous. Otherwise, retreatment using TT with high dose of AMO plus MET, BQT, or CT for 14 days are the actual recommended treatments by the current pediatric international guidelines.[8–10]

Overall, if the antimicrobial susceptibility testing is difficult to perform and vonoprazan is not available, we should use a 14-day TT based on local antimicrobial sensitivity, even considering the recent antibiotics used by patients.[8] Alternatively, BQT is accepted with the exception of Japanese guidelines.[10]

Although we do not have yet studies on HDDT in children, we think it could represent a good therapeutic option even in pediatric age, considering the optimal results achieved in adults. In addition, vonoprazan-AMO dual therapy has less impact on gut microbiota compared with vonoprazan-TT.[78] Even if adding probiotics to the eradication therapy could not improve the successful rate, they might alleviate dysbiosis secondary to antibiotics, though there is no univocal consensus regarding which strains and what doses must be used.[8]

The dual therapy including PPI (or vonoprazan) would permit to use only one antibiotic (AMO) and save the others for the second or third attempt.[68,71–73]

The main international guidelines agree in evaluating successful of eradication using either urea breath test (in children aged >6 years) or stool antigen test (by a two-step monoclonal test), at least 4 weeks after the end of the therapy with the recommendation to stop PPI and antibiotics at least 2 or 4 weeks earlier, respectively. Invasive methods are not recommended in the current situation where accurate noninvasive test can be performed.[8,85]

Conclusion

H. pylori, the most common infection of childhood, remains a vital pathogen that results in life-threatening complications during adulthood if left untreated. In all patients, but particularly in children, it is important to improve the success rate of first-line treatment due to the limited number of antibiotics that are appropriate to use for rescue therapy. In addition, the empiric use of CLA and MET may promote further increases in *H. pylori* antimicrobial resistance and further, the therapeutic regimens may induce intestinal dysbiosis with potential digestive and metabolism disorders.

For these reasons, the best strategy for eradicating *H. pylori* infection in children remains the tailored therapy based on antimicrobial susceptibility test. Alternatively, empirical treatment according to either local susceptibility or personal antibiotic history is acceptable.

Maybe HDDT or vonoprazan-AMO dual therapy may represent the most promising therapeutic choice. Although adding selective probiotics to eradication treatment seems ameliorate both the successful rate and poly-antibiotic-related side effects, the efficacy of probiotics in improving the eradication rate of *H. pylori* infection remains controversial both in adults and children therefore, they are not still recommended in clinical practice because of the low certainty of evidence of the studies.

Declarations

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Not applicable.

Consent for publication

Not applicable.

Author contributions

Marco Manfredi: Conceptualization; Data curation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Giancarlo Gargano: Data curation.

Pierpacifico Gismondi: Data curation; Writing – review & editing.

Bernardino Ferrari: Data curation.

Silvia Iuliano: Data curation; Methodology; Writing – original draft.

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