Updated joint ESPGHAN/NASPGHAN guidelines for management of *Helicobacter pylori* infection in children and adolescents (2023)

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JPGN Sep;79(3):758-785. doi: 10.1002/jpn3.12314. Epub 2024 Aug 15. PMID: 39148213

Short Version – Summary of Recommendations

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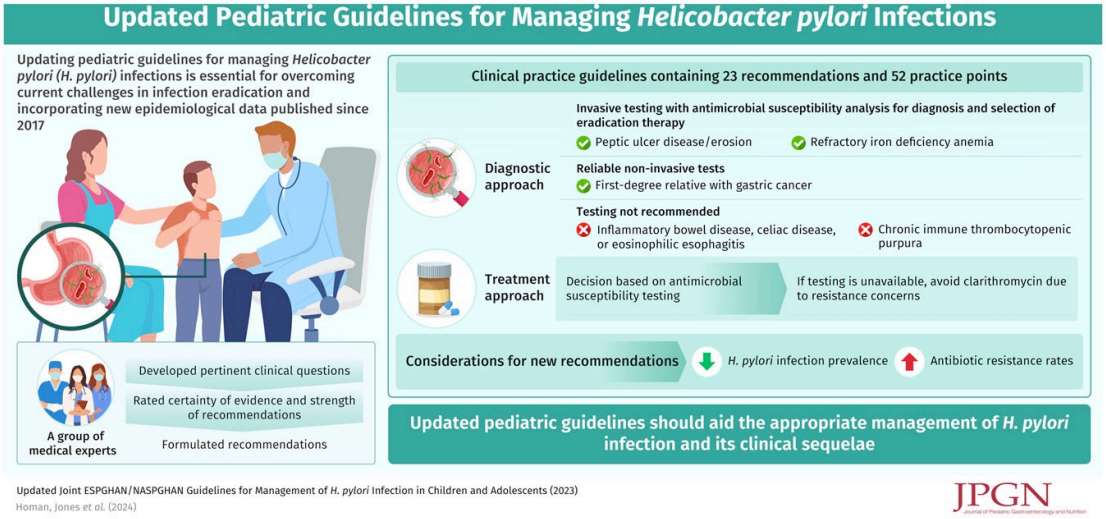

Summary

Evolving epidemiological data and increasing antibiotic resistance mandate an update of the European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition guidelines.

Invasive testing with antimicrobial susceptibility analysis is recommended for the diagnosis and selection of eradication therapy for *Helicobacter pylori* (*H. pylori*) infection. Molecular methods are acceptable for detection of infection and of antibiotic resistance to clarithromycin in gastric biopsy specimens. Reliable, noninvasive tests can be used as a screening method for children with history of gastric cancer in a first degree relative. Testing for *H. pylori* in children with chronic immune thrombocytopenic purpura, is no longer recommended. When investigating other gastrointestinal diseases such as inflammatory bowel disease, celiac disease, or eosinophilic esophagitis, specific diagnostic biopsies for *H. pylori* infection are not indicated. However, if *H. pylori* is an incidental finding, treatment may be considered after discussing the risks and benefits. Treatment should be based on antibiotic antimicrobial susceptibility testing and, if unavailable, regimens containing clarithromycin should be avoided.

Introduction

H. pylori infection is acquired in childhood and generally persists for life unless specific eradication therapy is administered. *H. pylori* infection causes chronic gastritis and may progress to peptic ulcer disease (PUD) and gastric cancer (GC). However, in comparison to adults, these complications are rare in children. Furthermore, the prevalence of infection in children is decreasing in developed countries. In addition, antibiotic resistance rates are increasing worldwide leading the World Health Organization to put *H. pylori* infection on its priority pathogen list due to clarithromycin (CLA) resistance, which necessitates appropriate antibiotic stewardship for treatment. Recommendations in this current document are focused on children and adolescents and serve as general guidelines for use in North America (NA) and Europe, and do not serve as an exclusive protocol for all patients.

What is New

- **The relevant literature was reviewed to develop the current recommendations for management of *Helicobacter pylori* infection in children and adolescents in 2023.**
- **15 New, 15 Modified & 1 Unchanged recommendations versus last guidelines are highlighted in the synopsis of recommendations section.**

The new guidelines included 6 tables and 1 figure

Table 1- Summarizes the differences in the current and previous guidelines.
Table 2- Summarizes the recommendations prepared according to the relevant PICO questions for each of the topics.
Table 3- Comparison of the updated pediatric guidelines with the Maastricht VI adult guidelines.
Table 4- Treatment regimens for *Helicobacter pylori* infection in children based on CLA-AST.
Table 5- Drugs fixed dose according to subject body weight.
Table 6- Rescue treatment.
Table 7- Summary of recommendations of when to test.
Figure 1 - Algorithm for *Helicobacter pylori* eradication therapy, based on availability of antimicrobial susceptibility testing for CLA.

Synopsis of recommendations (Table 2)

1 **We recommend that the primary goal of clinical investigation of gastrointestinal symptoms should be to determine the underlying cause of the symptoms and not solely the diagnosis of *Helicobacter pylori.*** *(Unchanged vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: no new evidence (Prior guidelines philosophy of care therefore did not provide GRADE evaluation). Agreement: 100%

2 **We recommend that testing for *H. pylori* be performed in children with gastric or duodenal ulcers and/or erosions. If *H. pylori* infection is identified, then treatment should be administered, and eradication confirmed.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: no new evidence (Prior guidelines rated as high). Agreement: 100%

3 **We recommend that diagnostic testing (invasive or noninvasive) for *H. pylori* infection in children with functional abdominal pain, a disorder of gut–brain interaction is not indicated.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: no new evidence (Prior guidelines rated as high). Agreement: 100%

4a **We suggest that when investigating other diseases such as IBD, CD, or EoE, specific diagnostic biopsies for *H. pylori* infection are not indicated.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: very low to low. Agreement: 100%

4b **We suggest that if *H. pylori* is an incidental finding during endoscopy performed for other GI diseases (IBD, CD, EoE), treatment may be considered after discussion of the risks and benefits of treatment with the patient/family.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

5a **We recommend against noninvasive testing for *H. pylori* in the initial investigation or management of IDA.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: very low to low. Agreement: 100%

5b **We suggest that if endoscopy is indicated after failure of therapy for IDA, testing for *H. pylori* may be considered and treated if found.** *(Modified vs last guidelines)*
GRADE: conditional recommendation. Quality of evidence: very low to low. Agreement: 100%

5c **We suggest treating *H. pylori* infection identified during upper endoscopy in children with IDA after failed iron supplementation in which other causes of IDA have been ruled out.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

6a **We recommend against testing for *H. pylori* infection when investigating causes of short stature.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: low. Agreement: 100%

6b **We do not recommend routine *H. pylori* treatment in growth failure before exclusion of other plausible causes of growth failure.** *(New recommendation)*
GRADE: weak recommendation. Quality of evidence: low. Agreement: 100%

7a **We suggest against testing (invasive or noninvasive) for *H. pylori* infection when investigating causes of cITP in children.** *(Modified vs last guidelines)*
GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

7b **We suggest against treating *H. pylori* infection to improve the platelet count in cITP.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: very low to low. Agreement: 100%

8 **We suggest that children with history of GC in a first‐degree relative have a noninvasive test for *H. pylori*.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: low to moderate. Agreement: 80%
9 **We recommend against screening for *H. pylori* in children belonging to racial/ethnic groups at increased risk for GC that are living in NA/Europe.** *(New recommendation)*
GRADE: strong recommendation. Quality of evidence: low. Agreement: 100%
10a **We recommend that the diagnosis of *H. pylori* infection should be gastric biopsy based using the following tests: (a) culture or molecular tests and (b) histopathology according to Sydney system.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: high. Agreement: 90%
10b **We recommend that at least six gastric biopsies (three from corpus and three from antrum) should be obtained for the diagnosis of *H. pylori* infection during upper endoscopy.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%
11 **We recommend that before invasive testing for diagnosis and noninvasive testing confirmation of *H. pylori* eradication, to wait at least 2 weeks after stopping PPIs and 4 weeks after stopping antibiotics and bismuth salts.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%
12 **We recommend that antimicrobial susceptibility be obtained by culture for the infecting *H. pylori* strain(s) according to a standardized methodology and/or by real-time PCR for CLA resistance, and the eradication treatment tailored accordingly.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: high. Agreement: 80%
13 **We suggest against the use of stool for molecular tests or culture for *H. pylori* infection detection or for susceptibility testing.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%
14 **We recommend that one of the following tests be used to determine whether *H. pylori* treatment was successful: (a) 13C‐UBT and (b) a two‐step monoclonal SAT.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: high. Agreement: 100%
15 **We recommend against antibody‐based tests for *H. pylori* in serum, whole blood, urine, and saliva, in the clinical setting.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: low to moderate. Agreement: 100%
16 **We recommend against molecular tests for *H. pylori* in serum, whole blood, urine, saliva, dental plaques, and periodontal pockets in the clinical setting.** *(New recommendation)*
GRADE: strong recommendation. Quality of evidence: low to moderate. Agreement: 100%
17 **We recommend that the outcome of anti‐*H. pylori* therapy be assessed 6–8 weeks after completion of therapy.** *(Modified vs last guidelines)*
GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%

18a **We recommend using CLA‐AST to guide eradication therapy to maximize eradication rates.** *(New recommendation)*
GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%
18b **We recommend against using CLA when CLA‐AST is not performed**. *(New recommendation)*
GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%
19 **We recommend against using MET‐AST to guide eradication therapy since results are unreliable and do not improve the eradication rate.** *(New recommendation)*
GRADE: strong recommendation. Quality of evidence: low. Agreement: 100%
20 **We suggest AST‐guided triple therapy using a high dosage of PPIs, a high dosage of AMO, and 14 days duration to maximize the eradication rate.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%
21 **We suggest AST‐guided triple therapy over sequential‐quadruple therapy.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%
22 **We suggest a bismuth‐based quadruple therapy (bismuth, PPI, AMO, MET) as an empiric first‐line eradication therapy in the absence of AST.** *(New recommendation)*
GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%
23a **We suggest using triple therapy containing CLA (if the strain is susceptible to CLA) and MET for 14 days if allergy to penicillin is confirmed.** *(Modified vs last guidelines)*
GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%
23b **We suggest using Bismuth quadruple therapy with tetracycline in adolescents if the strain is resistant to CLA and allergy to penicillin is confirmed.** *(Modified vs last guidelines)*
GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%

Conclusions

Based on rigorous review of the current literature, specific recommendations for diagnosing, managing, and treating *H. pylori* infection in children were developed using the GRADE method to aid decision making for practitioners when encountering children and adolescents with clinical symptoms concerning for complications associated with *H. pylori* infection Importantly, in the context of the current literature, the decreasing prevalence of infection, lack of complications in children, and increasing rates of antibiotic resistance were taken into consideration to inform these recommendations.

Futures directions

Due to increasing antibiotic resistance, eradication of infection is met with increasing challenges and thus development of novel therapies is required. In adults, PCABs have shown efficacy in eradication trials, particularly in Japan, and we await trials assessing their efficacy in eradication regimens in children.

Although there was great excitement from the initial studies identifying a potentially successful vaccine in children, there were no further studies on primary prevention in children during this review period.

H. pylori infection significantly affects gastric and intestinal microbiota in adults, but the importance of this change in microbiota has yet to be characterized. However, there was insufficient evidence to draw any specific conclusions regarding the effect of *H. pylori* infection on the gastric microbiota in children.

In adults, it is accepted that *H. pylori* gastritis is an infectious disease, and that infection must be treated irrespective of symptoms due to possible serious consequences such as GC. Mass screening in areas with high GC burden have been implemented or considered. However, the advent of more sophisticated techniques for assessing the proteome as well as machine learning algorithms may lead to the identification of biomarkers that determine which infected children need eradication therapy because of higher risk of complications such as GC later in life.

Figure 1 Algorithm for *Helicobacter pylori* eradication therapy, based on availability of antimicrobial susceptibility

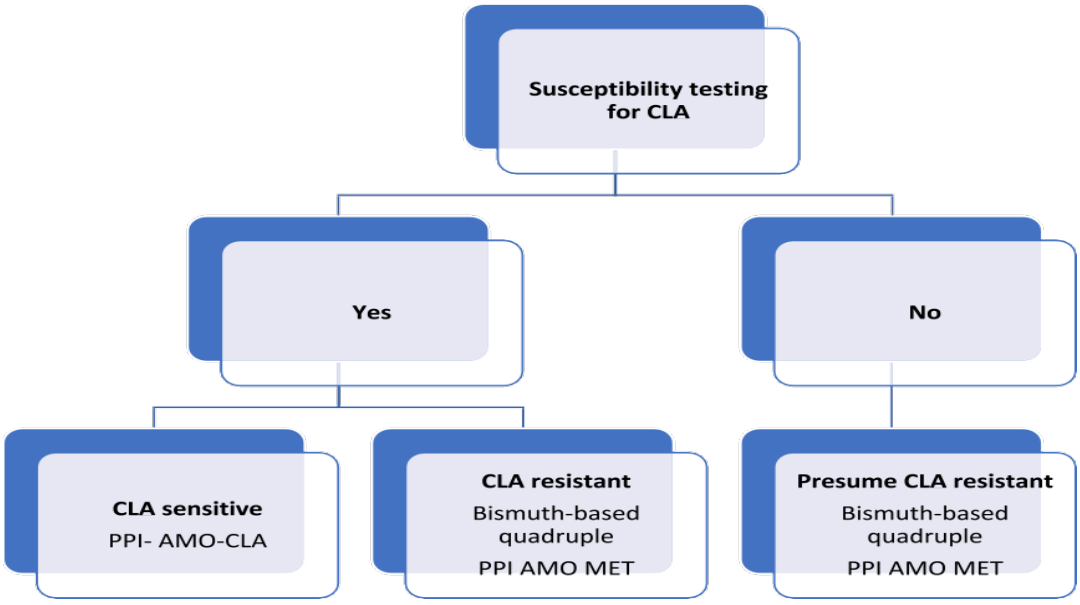

TABLE 3 Comparison of updated pediatric with the Maastricht VI adult guidelines.

	No. Pediatric guidelines		No. Adult guidelines	Comments
		1/3	Test and treat is an appropriate strategy for uninvestigated dyspepsia.	
3	We recommend that diagnostic testing (invasive or noninvasive) for *Helicobacter pylori* infection in children with functional abdominal pain, a disorder of gut–brain interaction, is not indicated.	1/7	*H. pylori* gastritis has to be excluded before a reliable diagnosis of FD can be made.	
5c	We suggest treating *H. pylori* infection identified during upper endoscopy in children with IDA after failed iron supplementation in which other causes of IDA have been ruled out.	1/13	*H. pylori* eradication is recommended for patients with unexplained IDA, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency.	
7b	We suggest against treating *H. pylori* infection to improve the platelet count in cITP.			
		1/14	*H. pylori* eradication is the first-line treatment for localized low-grade gastric MALT lymphoma. *H. pylori* eradication therapy is also recommended for cases without evidence of *H. pylori* infection and may provide benefit even for more advanced staged disease.	No new evidence from last pediatric guidelines regarding gastric MALT lymphoma and *H. pylori* infection in children.
		3/9	P-CAB—antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first-line and second-line treatment, and superior in patients with evidence of antimicrobial-resistant infections.	Data regarding the use of P-CAB's in eradication protocols in children are scarce.
		2/12	Gastric mucosal atrophy is defined as "loss of native glands." Atrophy is the major determinant of nonhereditary GC risk assessed by endoscopy and histology, and it may be complementarily assessed by gastric functional serology.	The development of atrophic gastritis in children is a rare condition.
		3/9	P-CAB—antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first-line and second-line treatment, and superior in patients with evidence of antimicrobial-resistant infections.	Data regarding the use of P-CAB's in eradication protocols in children are scarce.
		3/11	After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics or rifabutin may be an option.	It is not recommended for children to be treated for *H. pylori* eradication with antibiotics such as quinolone, tetracycline (under the age of 8) or rifabutin.
9	We recommend against screening for *H. pylori* in children belonging to racial/ethnic groups at increased risk for GC that are living in NA/Europe.	4/19	A population-based *H. pylori* test-and-treat program is cost- effective in populations with intermediate or high incidence of GC.	
15	We recommend against antibody-based tests for *H. pylori* in serum, whole blood, urine, and saliva, in the clinical setting.	4/12	If a serological method is used for *H. pylori* detection a further test (UBT, SAT) confirming current infection is required before initiating therapy	
		5/6	Certain probiotics have been shown to be effective in reducing GI side effects caused by *H. pylori* eradication therapies.	Relevant pediatric studies with specific probiotic strains in sufficient amounts are lacking to recommend certain probiotic strain as part of eradication therapy protocol.
		5/7	Certain probiotics may have a beneficial effect on *H. pylori* eradication therapy through reduction of antibiotic-related side effects.	

Abbreviations: cITP, chronic immune thrombocytopenic purpura; FD, functional dyspepsia; GC, gastric cancer; IDA, iron deficiency anemia; MALT, mucosa-associated lymphoid tissue; NA, North America; P-CAB, potassium-competitive acid blockers; PPIs, proton pump inhibitors; SAT, stool antigen test; UBT, urea breath test

TABLE 4 Treatment regimens for *Helicobacter pylori* infection in children based on CLA-AST.

CLA susceptible	Suggested regimen
+	PPI AMO CLA
- or unknown	Bismuth PPI AMO MET PPI AMO MET[a]
In the presence of confirmed penicillin allergy	
+	PPI MET CLA
- or unknown	Bismuth PPI MET TET (>8 years old)[a]

Note: If a child is >8 years TET can replace AMO; however, pediatric data is lacking.

Abbreviations: AMO, amoxicillin; AST, antimicrobial susceptibility testing; CLA, clarithromycin; MET, metronidazole; PPI, proton pump inhibitor; TET, tetracycline.

[a] Where available bismuth quadruple regimens are preferred due to higher eradication

TABLE 5 Drugs fixed dose according to subject body weight.

	Body weight	Morning	Noon	Evening
Colloidal Bismut Subcitrate*	15-24 kg	60 mg	60 mg	60 mg
	25-34 kg	120 mg	60 mg	60 mg
	35-49 kg	120 mg	120 mg	120 mg
	>50 kg	180 mg	120 mg	120 mg
PPI**	15-24 kg	20 mg	-	20 mg
	25-34 kg	30 mg	-	30 mg
	35-49 kg	40 mg	-	40 mg
	>50 kg	40 mg	-	40 mg
Amoxicillin	15-24 kg	500 mg	500 mg	500 mg
	25-34 kg	750 mg	750 mg	750 mg
	35-49 kg	1000 mg	1000 mg	1000 mg
	>50 kg	1000 mg	1000 mg	1000 mg
Metronidazole	15-24 kg	250 mg	-	250 mg
	25-34 kg	500 mg	-	250 mg
	35-49 kg	500 mg	-	500 mg
	>50 kg	750 mg	-	750 mg
Clarithromycin	15-24 kg	250 mg	-	250 mg
	25-34 kg	500 mg	-	250 mg
	35-49 kg	500 mg	-	500 mg
	>50 kg	500 mg	-	500 mg
Tetracycline***				

Abbreviations: PPI, proton pump inhibitor; QID, four times a day.

[a] The dosing of bismuth subsalicylate is 10 years 524 mg QID.

[b] The doses of PPI are not equivalent. Esomoprazole is less susceptible to degradation by rapid metabolizers with relevant cytochrome polymorphisms and therefore, may be preferred when available.

[c] Tetracycline dosing >8 years of age 25–50 mg/kg/day (maximum 3 g/day) divided q6h

TABLE 6 Rescue treatment.

CLA susceptibility	Prior treatment regimen	Rescue therapy
+	PPI AMO CLA	PPI AMO MET
+	PPI AMO MET	PPI AMO CLA
- or known	PPI AMO MET	Bismuth PPI AMO MET [a]
		Consider performing endoscopy to asssess for resistance

Abbreviations: AMO, amoxicillin; CLA, clarithromycin; MET, metronidazole; PPI, proton pump inhibitor; TET, tetracycline.
[a] Where available bismuth quadruple regimens are preferred over triple therapy due to higher eradication rates. If a child is >8 years TET can replace AMO; however, pediatric data are lacking.

TABLE 7 Summary of recommendations of when to test.

Clinical scenario	Test (Y/N)	Recommendation
DGBI	N	Strong
Children with other GI diseases (e.g., celiac, IBD, EoE	N	Conditional
Ulcer disease/erosions	Y	Strong
First degree relative with GC	Y	Conditional
Screening children belonging to groups at increased risk of GC living in NA/Europe	N	Strong
IDA	N	Strong
Unexplained refractory IDA	Y	Conditional
cITP	N	Conditional
Short stature	N	Strong

Abbreviations: cITP, chronic immune thrombocytopenic purpura; DGBI, disorder of gut–brain interaction; EoE, eosinophilic esophagitis; GC, gastric cancer; GI, gastrointestinal; IBD, inflammatory bowel disease; N, no; NA, North America; Y, yes