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PRACTICE GUIDELINES

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

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Abstract

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

Methods: Certainty of evidence and strength of recommendations were rated by experts according to the Grading of Recommendation Assessment, Development, and Evaluation approach. PICO (patient population, intervention, comparator, and outcome) questions were developed and voted on by the group. Recommendations were formulated using the Evidence to Decision framework.

Results: The current literature supports many of the previous recommendations and several new recommendations. Invasive testing with strain antimicrobial susceptibility analysis is recommended for the diagnosis and selection of eradication therapy for *H. pylori* infection. Molecular methods are acceptable for detection of infection and of antibiotic resistance 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. When investigating causes of chronic immune thrombocytopenic purpura, testing for *H. pylori* is no longer recommended. When investigating other diseases such as inflammatory bowel disease, celiac disease, or eosinophilic

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Matjaž Homan and Nicola L. Jones shared cofirst authorship.

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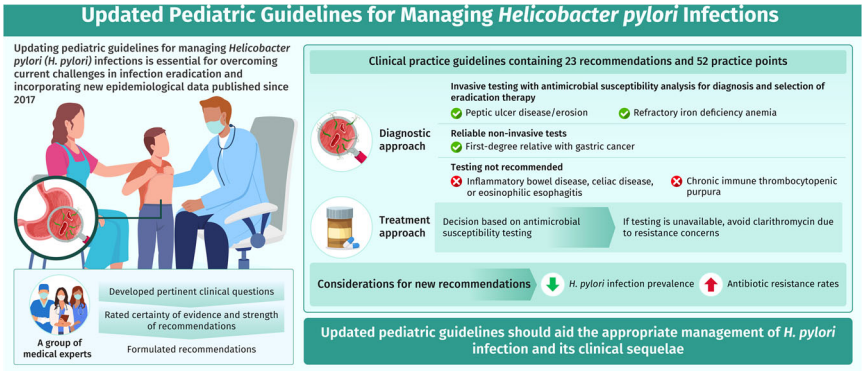
esophagitis, specific diagnostic biopsies for *H. pylori* infection are not indicated. However, if *H. pylori* is an incidental finding, treatment may be considered after discussing the risks and benefits. Treatment should be based on antibiotic antimicrobial susceptibility testing and, if unavailable, regimens containing clarithromycin should be avoided.

Conclusions: Due to decreasing prevalence of infection, increasing challenges with antibiotic resistance, and emerging evidence regarding complications of infection, clinicians must be aware of these recommended changes to appropriately manage *H. pylori* infection and its clinical sequelae in children.



KEYWORDS

antibiotic resistance, child, clinical guidelines, eradication therapy, Helicobacter pylori

1 | INTRODUCTION

Helicobacter 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.[1] 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.[2,3]

The last European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) guidelines on *H. pylori* were developed over 5 years ago and as the clinical epidemiology of infection evolves and research knowledge advances, the development of revised guidelines is needed to appropriately manage the diagnosis and treatment of *H. pylori* infection in children and adolescents.[4] Moreover, updated adult guidelines (Maastricht VI) were recently published.[5] 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. Variations, based on clinical judgment considering individual (i.e., the patient/family-healthcare provider relationship) and national circumstances, may be appropriate. Evidence-based guidelines should not curtail patient-centered practice aimed at improving health outcomes of individual patients by taking into account patients' values, preferences, goals, and circumstances.

What is Known

- The prior recommendations for managing *Helicobacter pylori* infection in children and adolescents are summarized in Table 1.
- Recommendations that remain unchanged (what is known) are highlighted in the table.

What is New

- The relevant literature was reviewed to develop the current recommendations for management of *Helicobacter pylori* infection in children and adolescents (Table 2).
- New recommendations (what is new) are highlighted in Table 1.

2 | METHODS

With approval from ESPGHAN and NASPGHAN, the grading of recommendations assessment, development, and evaluation (GRADE) process[6–9] was used to update the previous guidelines for the management of *H. pylori* infection in children developed in 2016 and published in 2017.[4] A systematic literature review was performed using PubMed, MEDLINE, EMBASE, Cochrane library, and Scopus databases between 2016 and 2021 using the following subject headings and keywords ([helicobacter pylori or helicobacter infections] and [adolescent or child or infant or newborn or minor or pediatrics]), limited to research on humans in journal articles published in English. Where relevant, literature published after 2021 was also included in the discussion but was not a part of the GRADE review process.

The consensus group consisted of experts in clinical epidemiology, pediatric gastroenterology, microbiology, pathology, and the GRADE process. The consensus group was divided into five working groups, specifically (a) who to test, (b) how to test, (c) who to treat, (d) how to treat, and (e) miscellaneous clinical issues. Each group developed PICO (patient population, intervention, comparator, and outcome) questions relevant to their topic and presented these to the larger working group for approval through a series of iterative discussions and voting using a modified Delphi process. Critical outcomes were established a priori to include *H. pylori* eradication rates and serious adverse events.

Each group performed duplicate screening of the literature search results with data extraction and risk of bias assessment for their topic (Supporting Information). Using the GRADE approach, each group then assessed the certainty of evidence (CoE) for each PICO question (very low, low, moderate, or high)[6] (Supporting Information S1: Table 1), or denoted as no new evidence if there was a lack of additional data in the literature since the previous guidelines. The five groups developed evidence summaries for each PICO question, along with the supporting evidence, for the consensus group to review and using the GRADE Evidence-to-Decision approach, recommendations for each topic were developed based on the CoE, feasibility, acceptability, resource availability, and cost–benefit analysis and presented at several virtual consensus meetings.[7,8,10] Consensus members provided feedback, suggested modifications, and subsequently voted on the direction of each recommendation (Yes or No). A second vote was then taken on the strength of each recommendation (strong ["we recommend"] or conditional ["we suggest"]) (Supporting Information S1: Table 2) taking into consideration paradigms where a strong recommendation may be warranted despite low quality of evidence. For each vote, consensus was defined as at least 80% agreement among voting members.

Each of the working groups provided a written summary of their recommendations, which was subsequently used to draft the final manuscript by the ESPGHAN and NASPGHAN cochairs, respectively (M. H. and N. L. J.). The final version was circulated to the consensus group for revisions as well as the members from both societies for final approval before submission for peer-reviewed publication.

3 | RECOMMENDATIONS

Summarized in Table 2 are the recommendations prepared according to the relevant PICO questions for each of the topics (Supporting Information S1: Table 3) with the results of voting for the grading of quality of evidence and strength of recommendations. Practical points are added after the recommendations to help the physician in collaborative decision-making with patients for common problems regarding treating children infected with *H. pylori*. Moreover, the supporting evidence for each recommendation is summarized and provided in the discussion section below each recommendation. Differences in the current and previous guidelines are outlined in Table 1.

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 *H. pylori*. *(Unchanged from previous 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. (Similar to previous 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 (DGBI), is not indicated. *(Similar to previous guidelines)*

GRADE: strong recommendation. Quality of evidence: no new evidence (Prior guidelines rated as high). Agreement: 100%

Practice points:

1. Current evidence indicates that *H. pylori* infection does not cause symptoms in children in the absence

TABLE 1 Changes in updated guidelines in comparison with previous guidelines published in 2017.[4]

No.	Current guideline recommendation	U/M/ N/NI	No.	Previous guideline
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.*	U		
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.	M	3	We recommend that testing for *H. pylori* be performed in children with gastric or duodenal ulcers. If *H. pylori* infection is identified, then treatment should be advised and eradication be confirmed.
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.	M	4	We recommend against diagnostic testing for *H. pylori* infection in children with functional abdominal pain.
4a	We suggest that when investigating other diseases such as IBD, CD, or EoE, specific diagnostic biopsies for *H. pylori* infection are not indicated.	N		
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	N		
5a	We recommend against noninvasive testing for *H. pylori* in the initial investigation or management of IDA.	M	5a	We recommend against diagnostic testing for *H. pylori* infection as part of the initial investigation in children with IDA.
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	M	5b	We suggest that in children with refractory IDA in which other causes have been ruled out, testing for *H. pylori* during upper endoscopy may be considered.
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.	N		
6a	We recommend against testing for *H. pylori* infection when investigating causes of short stature.	M	7	We recommend against diagnostic testing for *H. pylori* infection when investigating causes of short stature.
6b	We do not recommend routine *H. pylori* treatment in growth failure before exclusion of other plausible causes of growth failure.	N		
7a	We suggest against testing (invasive or noninvasive) for *H. pylori* infection when investigating causes of cITP in children.	M	6	We suggest that noninvasive diagnostic testing for *H. pylori* infection may be considered when investigating causes of chronic ITP.
7b	We suggest against treating *H. pylori* infection to improve the platelet count in cITP.	N		
8	We suggest that children with history of GC in a first-degree relative have a noninvasive test for *H. pylori.*	N		
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	N		
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.	M	9a	We recommend that the diagnosis of *H. pylori* infection should be based on either (a) histopathology (*H. pylori*-positive gastritis) plus at least one other positive biopsy-based test or (b) positive culture.

(Continues)

TABLE 1 (Continued)

No.	Current guideline recommendation	U/M/N/NI	No.	Previous guideline
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.	M	9b	We recommend that for the diagnosis of *H. pylori* infection at upper gastrointestinal endoscopy, at least six gastric biopsies be obtained.
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.	M	8	We recommend that before testing for *H. pylori*, waiting at least 2 weeks after stopping PPI and 4 weeks after stopping antibiotics.
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.	M	11	We recommend that antimicrobial sensitivity be obtained for the infecting *H. pylori* strain (s), and eradication therapy tailored accordingly.
13	We suggest against the use of stool for molecular tests or culture for *H. pylori* infection detection or for susceptibility testing.	N		
14	We recommend that one of the following tests be used to determine whether *H. pylori* treatment was successful: (a) ^{13}C-UBT and (b) a two-step monoclonal SAT.	M	15	We recommend that the outcome of anti-*H. pylori* therapy be assessed at least 4 weeks after completion of therapy using one of the following tests: (a) the ^{13}C-UBT or (b) a two-step monoclonal SAT.
15	We recommend against antibody-based tests for *H. pylori* in serum, whole blood, urine, and saliva, in the clinical setting.	M	10	We recommend against using antibody-based tests (IgG, IgA) for *H. pylori* in serum, whole blood, urine, and saliva in the clinical setting.
16	We recommend against molecular tests for *H. pylori* in serum, whole blood, urine, saliva, dental plaques, and periodontal pockets in the clinical setting.	N		
17	We recommend that the outcome of anti-*H. pylori* therapy be assessed 6–8 weeks after completion of therapy.	M	15	We recommend that the outcome of anti-*H. pylori* therapy be assessed at least 4 weeks after completion of therapy using one of the following tests: (a) The ^{13}C-UBT or (b) a two-step monoclonal SAT.
18a	We recommend using CLA-AST to guide eradication therapy to maximize eradication rates.	N		
18b	We recommend against using CLA when CLA-AST is not performed.	N		
19	We recommend against using MET-AST to guide eradication therapy since results are unreliable and do not improve the eradication rate.	N		
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.	N		
21	We suggest AST-guided triple therapy over sequential-quadruple therapy.	N		
22	We suggest a bismuth-based quadruple therapy (bismuth, PPI, AMO, MET) as an empiric first-line eradication therapy in the absence of AST.	N		
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.	M	14	We recommend first-line therapy for *H. pylori* infection as listed in tab. 2 of Jones et al.[4]

TABLE 1 (Continued)

No.	Current guideline recommendation	U/M/ N/NI	No.	Previous guideline
23b	We suggest using Bismuth quadruple therapy with tetracycline in adolescents if the strain is resistant to CLA and allergy to penicillin is confirmed	M	14	We recommend first-line therapy for *H. pylori* infection as listed in tab. 2 of Jones et al.[4]
		NI	2a	We recommend that during endoscopy additional biopsies for RUT and culture should only be taken if treatment is likely to be offered if infections are confirmed.
		NI	2b	We suggest that if *H. pylori* infection is an incidental finding at endoscopy, treatment may be considered after careful discussion of the risks and benefits of *H. pylori* treatment with the patient/parents.
		NI	2c	We recommend against a "test and treat" strategy for *H. pylori* infection in children.
		NI	12	We recommend that the effectiveness of first-line therapy be evaluated in national/ regional centers.
		NI	13	We recommend that the physician explain to the patient/family the importance of adherence to the anti-*H. pylori* therapy to enhance successful eradication.
		NI	16	We recommend that when *H. pylori* treatment fails, rescue therapy should be individualized considering antibiotic susceptibility, the age of the child, and available antimicrobial options.

Abbreviations: ^{13}C-UBT, urea breath test ^{13}C; AMO, amoxicillin; AST, antimicrobial susceptibility testing; CD, celiac disease; cITP, chronic immune thrombocytopenic purpura; CLA, clarithromycin; EoE, eosinophilic esophagitis; GC, gastric cancer; GI, gastrointestinal; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; IgA, immunoglobulin A; IgG, immunoglobulin G; ITP, immune thrombocytopenic purpura; M, modified; MET, metronidazole; N, new; NA, North America; NI, not included; PCR, polymerase chain reaction; PPIs, proton pump inhibitors; RUT, rapid urease test; SAT, stool antigen test; U, unchanged.

TABLE 2 Synopsis of recommendations.

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*. ***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. ***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 DGBI, is not indicated. ***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, celiac disease, or EoE, specific diagnostic biopsies for *H. pylori* infection are not indicated. ***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, celiac disease, EoE), treatment may be considered after discussion of the risks and benefits of treatment with the patient/family. ***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. ***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. ***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. ***GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%***
6a	We recommend against testing for *H. pylori* infection when investigating causes of short stature. ***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. ***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. ***GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%***
7b	We suggest against treating *H. pylori* infection to improve the platelet count in cITP. ***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*. ***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 North America/Europe. ***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. ***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. ***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. ***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 polymerase chain reaction for CLA resistance, and eradication treatment tailored accordingly. ***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. ***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) ^{13}C-UBT and (b) a two-step monoclonal SAT. ***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. ***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. ***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. ***GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%***
18a	We recommend using CLA-AST to guide eradication therapy to maximize eradication rates. ***GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%***
18b	We recommend against using CLA when CLA-AST is not performed. ***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. ***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. ***GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%***
21	We suggest AST-guided triple therapy over sequential-quadruple therapy. ***GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%***
22	We suggest a bismuth-based quadruple therapy (bismuth, PPIs, AMO, MET) as an empiric first-line eradication therapy in the absence of AST. ***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. ***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 the allergy to penicillin is confirmed. ***GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%***

Abbreviations: ^{13}C-UBT, urea breath test ^{13}C; AMO, amoxicillin; AST, antimicrobial susceptibility testing; cITP, chronic immune thrombocytopenic purpura; CLA, clarithromycin; DGBI, disorder of gut–brain interaction; EoE, eosinophilic esophagitis; GC, gastric cancer; GI, gastrointestinal; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; MET, metronidazole; PPIs, proton pump inhibitors; SAT, stool antigen test.

of PUD and/or erosions. Therefore, performing a noninvasive test to detect infection is not indicated. There is no evidence to support a "test and treat" strategy in children.

2. Children with recurrent abdominal pain without any alarm signs or symptoms (described in Rome criteria[11]) most likely have a DGBI, independent of *H. pylori* status.
3. In recurrent abdominal pain when no ulcers or erosions are seen on endoscopy, *H. pylori* eradication has not been proven to improve symptoms. Therefore, treatment is not recommended over standard of care.
4. Noninvasive *H. pylori* testing in children with a DGBI, should not be undertaken because a positive test may induce anxiety and possible referral for unnecessary endoscopy.
5. If erosions, ulcers, or scarring are visualized during upper endoscopy, biopsies should be taken to identify the presence of *H. pylori* infection.
6. Although *H. pylori* infection is only one of several causes of gastric or duodenal erosions/ulceration in children, it is a treatable condition. Eradication of *H. pylori* infection prevents ulcer recurrence.
7. During endoscopy, additional biopsies for diagnosis of *H. pylori* infection should only be taken if treatment is likely to be offered if infection is confirmed.

Discussion: PUD remains a clear and definite indication for *H. pylori* eradication. Retrospective analysis of data for more than two decades indicates that children with duodenal ulcer disease, gastric or duodenal erosions usually had *H. pylori* infection.[12]

We reviewed new literature after the previous guidelines for studies where the primary objective was to examine if there was a causal relationship between *H. pylori* and abdominal symptoms in children. In most studies, participants were assessed because of abdominal symptoms and therefore assessing differences in

symptoms or severity of symptoms between *H. pylori*-infected and uninfected participants is challenging. While epidemiological studies report no difference in the prevalence of abdominal symptoms between those who are infected with *H. pylori* and those who are not infected, they do not address the question of causation.[13,14] Similarly, a clinical endoscopy study from Brazil found no difference in abdominal pain or combination of abdominal symptoms between those who were infected and those who were not infected.[15] While one study from Turkey examined the impact of *H. pylori* eradication therapy on functional abdominal pain, a DGBI, in children, the failure to conceal treatment allocation or to blind investigators as to the *H. pylori* status of participants post-treatment, and an incorrect approach to post-treatment data analysis led to the exclusion of this study from review. However, the authors did report that there was no difference in symptoms scores between *H. pylori*-infected children and noninfected children pre-endoscopy.[16]

In conclusion, there is no new relevant evidence to modify the previous recommendations regarding the investigation of children with abdominal pain. The presence of upper gastrointestinal (GI) symptoms consistent with functional abdominal pain, a DGBI, does not indicate the need for *H. pylori* investigations in children. If invasive testing for *H. pylori* has been performed in this scenario and is positive, there is no indication that treatment *for H. pylori* will improve symptoms. Therefore, *H. pylori*-specific treatment to improve the DGBI is not indicated. A discussion of the risks and benefits of treatment with the parents should be undertaken. The DGBI should be managed according to the current standard of care even with proven *H. pylori* infection.

4a. We suggest that when investigating other diseases such as inflammatory bowel disease (IBD), celiac disease, or eosinophilic esophagitis (EoE), specific diagnostic biopsies for *H. pylori* infection are not indicated. *(New)*

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, celiac disease, EoE), treatment may be considered after discussion of the risks and benefits of treatment with the patient/family. *(New)*

GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

Practice points:

1. *H. pylori*-associated gastritis may be an incidental histopathologic finding during upper endoscopy performed for other GI diseases such as IBD, celiac disease, or EoE, especially in areas with a high prevalence of infection.

Discussion: Endoscopy with biopsies remains the gold standard for the diagnosis of *H. pylori*, but with the continued decline in the prevalence of *H. pylori* in Europe and NA, the question of whether all children undergoing endoscopy should have *H. pylori*-specific biopsies arises.[1] Since the last guidelines, there have been several studies that evaluated the diagnostic yield of upper GI endoscopy in children, defined as the proportion of endoscopies in which there was a new diagnosis or a change in management following endoscopy. Consistent with prior reports that assess the diagnostic yield of upper endoscopy in children with abdominal pain without known underlying GI disease,[17–19] more recent studies in the UK,[20] Germany,[21] USA,[22] and in Israel,[23] all observed that most endoscopies have neither macroscopic nor histological abnormalities present, when conditions such as IBD, celiac disease are excluded or when follow-up endoscopies are excluded. Given the very low prevalence of *H. pylori* at endoscopy in NA and Europe, no studies to date have examined the clinical indications for *H. pylori*-specific biopsies at endoscopy. In addition, the accuracy of invasive tests is also questioned due to the low prevalence of infection in developed countries.

Other GI diseases: There are several lines of evidence to suggest that *H. pylori* may be protective against GI diseases including IBD, celiac disease, and EoE in children.[24] However, most such evidence is limited to inverse associations with no data on the sequence of events and insufficient control of confounding variables such as socioeconomic status indicators. Prospective epidemiological studies that can demonstrate a true protective role for *H. pylori* in GI diseases are lacking, with few studies examining the incidence of new-onset disease (IBD, celiac disease, or EoE) in children with and without *H. pylori* infection while controlling for confounding factors. Much of the evidence is based on adult retrospective and cross-sectional research data, or administrative pathology databases which have a significant risk of bias. Furthermore, results specific to children and the number of children included in these studies is limited. In case-control studies examining the relationship between *H. pylori* and other GI diseases, assessing the prevalence of *H. pylori* using patients undergoing endoscopy without the GI disease of interest (e.g., IBD) as controls does not provide an optimal control group because the prevalence of *H. pylori* in such patients cannot be assumed to provide an accurate estimate of the prevalence of *H. pylori* in the general population, given that most children or adults with *H. pylori* infection do not have indications for endoscopy. In contrast, the diagnosis of serious GI diseases such as IBD relies on endoscopic confirmation of disease at the

time that symptoms manifest, which provides accurate estimates of IBD incidence (new onsets) in the population/community. Because the time of *H. pylori* infection onset is generally unknown, evaluating the role of *H. pylori* as a protective factor for developing other GI diseases is a challenge. Even using a study design that observes *H. pylori* status before the development of other GI disease, careful measurement and consideration of confounding factors would be required to infer a protective effect of *H. pylori*. Given that *H. pylori* prevalence is largely determined by poor sociodemographic factors, such factors are likely to confound its associations with diseases that have different sociodemographic profiles.

IBD: Recently, numerous epidemiological and basic experimental studies suggested a possible association of chronic *H. pylori* infection in protecting against IBD by inducing systemic immune tolerance and suppressing inflammatory responses through *H. pylori*-induced tolerogenic dendritic cells and immunosuppressive regulatory T cells. A systematic review of the relationship between *H. pylori* and IBD reported that the protective (inverse) relationship between *H. pylori* and IBD was independent of the classification of IBD (ulcerative colitis, Crohn's disease, or IBD unclassified), the methods used to diagnose *H. pylori*, previous treatment with aminosalicylates or corticosteroids, or ethnicity.[25] When stratified by age, a stronger inverse relationship in younger compared to older participants was identified from which the authors inferred that infection with *H. pylori* induces immune tolerance from a very young age. Of note, in this systematic review, there were two pediatric-focused studies and three studies that included both adults and children. The protective role of *H. pylori* in IBD was also suggested in another meta-analysis published by Shirzad-Aski et al.[26]

In summary, there is evidence that *H. pylori* infection is inversely associated with IBD. However, there is no human evidence for a causal or protective relationship between *H. pylori* and IBD. Furthermore, it remains unknown how *H. pylori* eradication may modify microbiota in children with IBD or the clinical course of IBD.

Celiac disease: There is debate as to whether the incidence of celiac disease is increasing, or if the apparent increase in prevalence can be attributed to an increased awareness and change in diagnostic approach for the detection of celiac disease.[27–29] In addition, the introduction of gluten into the diet and different baby feeding practices may give rise to differences in the prevalence of celiac disease in different populations.[29] A systematic review and meta-analysis suggested an inverse association between celiac disease and *H. pylori* colonization (26 studies including nine pediatric studies, with a total of 6001 participants with celiac disease and 135,512 controls).[30] However, there are concerns with the approach taken for study inclusion. Most of the studies compared infection in children with celiac disease with healthy children undergoing endoscopy which, as noted above, does not provide an accurate evaluation of the prevalence of *H. pylori* in the general population. In addition, of the pediatric studies reviewed, five reported no difference in *H. pylori* prevalence between participants with celiac disease and controls at endoscopy, with all five studies having a moderate to high risk of bias. In addition, there is no evidence that *H. pylori* eradication has any impact on the natural history of celiac disease. Furthermore, there are no well-conducted cohort studies to support a causal/protective relationship between *H. pylori* infection and celiac disease in children.

EoE: A systematic review suggests that *H. pylori* infection protects against EoE (pooled odds ratio [OR]: 0.63; 95% confidence interval [CI]: 0.51–0.78).[31] However, this systematic review highlights the many issues with case definitions for EoE, evaluation of *H. pylori* status, the changing practices for *H. pylori* diagnosis over time, the lack of appropriate a priori publication of protocols for the conduct of systematic reviews, and even the lack of *H. pylori* data in one of the included studies.[32] Pathology databases have been used to examine the relationship between EoE and *H. pylori*. Allowing for the inherent risk of selection bias and confounding when using such databases, Sonnenberg et al. reported that *H. pylori* was protective for EoE in adults (OR: 0.45; 95% CI: 0.38–0.55).[33] A recent multicenter Spanish case-control study in 23 centers of 404 cases and 404 controls of whom 170 were children, found minimal difference in the prevalence of *H. pylori* between participants with EoE and controls (37% vs. 40%, $p = 0.3$; OR: 0.97; 95% CI: 0.73–1.30) neither in children (42% vs. 46%, $p = 0.1$) nor in adults (36% vs. 38%, $p = 0.4$).[34] In summary, although there is a lack of good-quality pediatric studies in this area, current evidence does not indicate that *H. pylori* eradication can influence EoE.

Allergy/atopy: There is epidemiologic evidence that *H. pylori* infection, especially in young children, may be associated with a reduced prevalence of atopic and allergic disease. However, the higher prevalence of *H. pylori* infection may be a surrogate marker of poor hygiene that could confer protection against autoimmunity and allergy.[35,36]

Incidental finding of *H. pylori*-associated gastritis in children with other GI diseases: According to current evidence, the finding of *H. pylori*-associated gastritis (including nodular gastritis) in children with other GI diseases without duodenal or gastric mucosal lesions poses a dilemma for the pediatric gastroenterologist about whether to recommend eradication treatment. In this clinical setting, treatment may be considered after discussing with the family the benefits and risks of eradication.

The potential benefits of *H. pylori* eradication include:

1. The prevention of future gastric complications including, PUD, atrophy/intestinal metaplasia, gastric MALT lymphoma, and GC. However, there are currently no good biomarkers to identify the small number of individuals that will go on to develop more severe sequelae of infection later in life. The risk of peptic disease is low in children, and the risk of severe complications is extremely low in Europe and NA.
2. Reduce parental anxiety due to "nontreatment."

The risks of *H. pylori* eradication include:

1. Rise in antibiotic resistance, side effects of antibiotics, and negative influences on microbiota.[37]
2. Treatment failure and the need for retreatment.
3. Reinfection which may reach up to 10% in high-prevalence areas.[38]
4. Possible protective effect of *H. pylori* from specific chronic diseases in children (unproven).

In conclusion, we recommend that when endoscopy is undertaken to confirm a diagnosis of IBD celiac disease or EoE, specific *H. pylori* biopsies according to the upgraded Sydney classification are not indicated.

5a. We recommend *against* noninvasive testing for *H. pylori* in the initial investigation or management of iron deficiency anemia (IDA). *(Similar to previous 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 from previous 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 whom other causes of IDA have been ruled out. *(New)*

GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

Practice points:

1. Children with IDA should be managed according to current guidelines for the treatment of IDA considering the clinical history and age of the child.
2. Noninvasive testing for *H. pylori* is not recommended as part of the initial investigation of IDA in children.
3. If upper endoscopy is clinically indicated to identify the underlying cause of IDA refractory to iron therapy, *H. pylori* testing may be considered, and, if the infection is found, then eradication therapy be initiated.

Discussion: Iron deficiency (ID) and IDA are the most common nutritional disorders worldwide, particularly in developing countries. Previous data suggest that *H. pylori* eradication results in improved iron status of children and adults with ID/IDA compared with iron therapy alone. The literature assessing a potential relationship between *H. pylori* and IDA in children was reviewed. Studies which examined ID markers were excluded unless evidence of anemia was also studied. Studies in adults, mixed studies or studies using serology to diagnose *H. pylori* were excluded. An updated systematic review suggests that there is an increased likelihood of an association between depleted iron stores and *H. pylori*.[39] However, this systematic review included adult and pediatric studies, with no restrictions for the appropriate diagnosis of *H. pylori* in children. Furthermore, most studies did not adjust for confounders of socioeconomic status or poor diet. In a population-based study examining risk factors for nutritional deficiencies in Nepal based on data from the national micronutrient status survey, Ford et al. demonstrated in a populational-based cohort that there was no difference in the prevalence of *H. pylori* between those with and without IDA.[40] Two small hospital-based studies in Iran[41] and Turkey[42] similarly reported no difference in IDA parameters between those with and without *H. pylori* infection. Taken together, the relevant evidence does not indicate an association between *H. pylori* infection and a high risk of developing IDA in children. However, *H. pylori* eradication therapy, added to iron therapy, might be beneficial in increasing ferritin and hemoglobin level in children with refractory IDA.[43]

6a. We recommend against testing for *H. pylori* infection when investigating causes of short stature. (*Similar to previous 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)*

GRADE: weak recommendation. Quality of evidence: low. Agreement: 100%

Practice points:

1. Short stature should be screened and treated according to local standard of care policies, which differ for countries with distinct socioeconomic profiles.

2. In an *H. pylori*-positive child with growth delay, exclusion of other causes of growth delay should be the priority. If *H. pylori* is identified on gastric biopsies, discussion with parents about the significance of infection will guide management as there is no evidence that eradication treatment is expected to improve growth delay.

Discussion: The published literature has unclear messages regarding *H. pylori* infection and growth. In a meta-analysis of 15 studies, *H. pylori* infection had no relationship with short stature when the prevalence of *H. pylori* was greater than 50%, highlighting that poor socioeconomic conditions are a confounder for the relationship between *H. pylori* and short stature.[44] Across studies, the evaluation of growth used heterogeneous variables with nearly all using static measures of height, instead of longitudinal dynamic follow-up to determine growth velocity. The only published longitudinal study analyzed growth velocity over a 3-year period in Colombian children and showed slower growth velocity in *H. pylori*-infected children (−0.0264 cm/month [95% CI: −0.047, −0.005] [$p = 0.014$]), after adjusting for baseline height and age[45] although the difference might be considered modest. No data regarding catch-up growth after *H. pylori* treatment were published. In conclusion, there is no clear evidence that *H. pylori* infection causes growth delay in European and North American countries, nor is there evidence that eradication treatment is expected to improve growth delay. However, strong evidence to the contrary is lacking, so further research is needed, especially in the developed world.

7a. We suggest *against* testing (invasive or noninvasive) for *H. pylori* infection when investigating causes of chronic immune thrombocytopenic purpura (cITP) in children. *(Opposite to previous 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)*

GRADE: conditional recommendation. Quality of evidence: very low to low. Agreement: 100%

Practice points:

None.

Discussion: Immune thrombocytopenic purpura (ITP) is a rare autoimmune-mediated disorder in children and adults characterized by low platelet count due to platelet destruction or impaired platelet production. Up to 2/3 of children with ITP experience a preceding viral illness. Approximately 50%–70% of children with ITP experience remission within 6–12 months regardless of intervention. The American Society for Hematology (ASH) guidelines recommend observation in children with no or mild bleeding regardless of the platelet count.[46] There is no consideration given to treatment of secondary causes of ITP in children and no recommendation for the eradication of *H. pylori* in adults. Children who develop cITP are usually older, which suggests that acute infection with *H. pylori* is unlikely to be the cause of cITP.

Since the first report of an association between *H. pylori* and cITP in 1998, there have been numerous studies that examined the effect of eradication of *H. pylori* on the natural history of cITP.[47] Additionally, there is an important geographic difference as most studies were conducted in Asia.[48] However, because cITP is a rare disorder, well-designed studies to examine the hypothesis are challenging and most of the data to date in either adults or in children is based on small retrospective studies. In a recent meta-analysis of randomized controlled trials to examine the effect of *H. pylori* eradication on the natural history of cITP, six studies met the inclusion criteria —four of which were in children with 103 children in the *H. pylori* eradication group and 96 in the control group.[49] Only two studies provided post-treatment platelet counts, and one provided data on relapse rates at 1 year. In the meta-analysis of studies in children, there was no statistically significant difference in platelet counts between the group receiving *H. pylori* eradication therapy and the comparison group. Since this review was published there have been two further studies in children which do not add further to the body of evidence because they are not randomized controlled trials (RCTs).

There are significant differences in children compared to adults regarding cITP and *H. pylori* infection. The Maastricht VI (Statement 13) guideline recommends *H. pylori* eradication for adult patients with ITP.[5] Table 3 highlights differences in the Maastricht VI and the updated pediatric guidelines. The American College of Gastroenterology guidelines make a conditional recommendation based on very low-quality evidence that adult patients with cITP should be tested for *H. pylori* and those infected treated.[50] They note that the evidence for *H. pylori* testing in children with cITP is less compelling. In contrast, as noted above, the ASH recommended against testing children with cITP for *H. pylori* infection.[46] Taking all the data together, we changed the recommendation from our previous guidelines. In the evaluation of a child with cITP, noninvasive testing for *H. pylori* is not recommended. However, in a child with cITP who undergoes an upper GI endoscopy for GI bleeding, *H. pylori* testing and treatment if found, may be considered.

8. We suggest that children with a history of GC in a first-degree relative have a noninvasive test for *H. pylori. (new)*

TABLE 3 Comparison of updated pediatric with the Maastricht VI adult guidelines.[5]

No.	Pediatric guidelines	No.	Adult guidelines	Comments
		1/3	Test and treat is an appropriate strategy for uninvestigated dyspepsia.	No evidence for test and treat strategy.
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.
		2/1	In young dyspeptic patients (age below 50) with no specific risk and no alarm symptoms, noninvasive testing for *H. pylori* infection is recommended.	Noninvasive testing is recommended only in children with first-degree relative with a history of gastric cancer.
		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.	

TABLE 3 (Continued)

No.	Pediatric guidelines	No.	Adult guidelines	Comments
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.

GRADE: conditional recommendation. Quality of evidence: low to moderate. Agreement: 80%

Practice points:

1. Either urea breath test (UBT) or monoclonal two-step stool antigen test (SAT) is appropriate in this clinical situation.

Discussion: Chronic infection with *H. pylori* is recognized as the most important infectious cause of cancer worldwide.[51,52] Despite the decline in the prevalence of *H. pylori* worldwide, the impact of *H. pylori*-associated GC remains substantial with over 1,000,000 new cases worldwide and 800,000 deaths in 2020.[51] The rate of GC differs among populations with countries in East Asia, Eastern and Southern Europe, and South America having a much higher incidence of noncardia GC than North and West European countries. Almost half of all GC deaths in 2020 occurred in people under 65 years of age and thus GC is not simply a disease of old age.[51]

In regions with a high prevalence of GC, there have been several important randomized controlled clinical trials that examined the impact of *H. pylori* eradication on the incidence of GC. An updated systematic review with meta-analysis[53] provides good evidence that the number needed to treat *H. pylori* infection to prevent one GC onset was 45 (95% CI: 35–74) while the number needed to treat to prevent one death from GC was 92.5 (95% CI: 58–629). Consistent with those findings, *H. pylori* eradication may be associated with decreased risk for GC in healthy asymptomatic Japanese adults. Furthermore, the risk of developing metachronous GC was also reduced in Japanese adults who were treated for *H. pylori* infection.[54] While the data from countries with a low prevalence of GC is very limited, Kumar et al. also demonstrated the benefits of *H. pylori* eradication therapy for the prevention of GC in the United States. However, due to the retrospective nature of the data, there is a substantial risk of bias in this study.[55]

Because only a small fraction of people with *H. pylori* will develop GC, cost-effective prevention measures require identifying in whom and at which ages treatment to eliminate *H. pylori* is most beneficial for GC prevention. The prevalence of atrophy in children with *H. pylori* is low[56] and at present, there is no evidence that a biomarker can identify children at increased risk of developing GC. Furthermore, we know that *H. pylori* is clustered in families and strains are shared among family members. A family history of GC in a first-degree relative is associated with a two- to threefold increased risk of GC.[57] While there is evidence that eradication of *H. pylori* slows the progression of premalignant changes and reduces the risk of GC, how to manage family members when a patient is diagnosed with GC is a clinical challenge. To

date, only one study has examined the effect of *H. pylori* eradication on GC incidence in individuals with a family history of GC.[58] While there was a reduction in GC incidence in those who received eradication therapy there was no reduction in mortality from GC, though longer follow-up may be required to show an effect on GC mortality. The adult guidelines recommend endoscopy with biopsy in asymptomatic family members over 45 years. While a noninvasive test for *H. pylori* in children with a family history of GC in first-degree relatives would suffice in most clinical scenarios, some cases in which *H. pylori* is detected may warrant endoscopic examination with susceptibility testing. Invasive testing should be limited to *H. pylori*-positive children who reside in a household with first-degree relatives in whom GC has been diagnosed. Following treatment of infection, successful eradication of *H. pylori* should be confirmed.

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*)

   GRADE: strong recommendation. Quality of evidence: low. Agreement: 100%

   Practice points:

   None.

Discussion: Despite good evidence that eradication of *H. pylori* reduces the risk of GC in high-risk populations, no consensus statement to date has advocated for a population-based screening for *H. pylori* in asymptomatic adults or children. The Japanese guidelines recommend against a "test and treat" strategy for *H. pylori* infection to protect against GC development for asymptomatic children. However, they recommend consideration of eradication therapy for children who have a family history of GC in their first- or second-degree relatives and in whom active *H. pylori* infection has been found.[59]

The recent Maastricht guidelines for adults state that *H. pylori* eradication offers the chance for GC prevention at any age in adulthood and is most effective for GC prevention before the development of severe chronic atrophic gastritis. They suggest further that population-based *H. pylori* "test and treat" programs should be integrated into healthcare priorities in regions with intermediate to high incidence of GC.[5] While this appears reasonable and noncontroversial, the Maastricht guidelines do not address the implications, particularly benefits, and harms, of a national screening strategy for the prevention of GC in a low prevalence population. Moreover, screening for *H. pylori* to prevent GC does not meet the World Health Organization guidelines for screening programs.[60] Given the lack of a test with a high positive predictive value for GC in those who are infected with *H. pylori* is not available, implementation of a screening strategy for GC prevention among children in Europe or NA is not warranted. Therefore, we do not recommend noninvasive opportunistic screening for *H. pylori* in children belonging to demographic groups (African Americans, Alaska Natives, American Indians, Asian Americans, Hispanic Americans, Indigenous Canadians, and residents of Europe and NA who immigrated from countries with high GC incidence) at increased risk of GC.

10a. **Recommendation:** We recommend that the diagnosis of *H. pylori* infection should be gastric biopsy-based using the following tests:
   1. culture or molecular tests and
   2. histopathology assessed according to the Sydney system. (*Modified from previous 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. (*Unchanged from previous guidelines*)

   GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%

   Practice points:

   1. At least six gastric biopsies should be taken for the initial diagnosis of *H. pylori* infection and labeled by specific site for histopathological evaluation, culture and antibiogram, molecular tests, and rapid urease test (RUT).
   2. We recommend one biopsy from the antrum and one biopsy from the corpus for culture and molecular tests or other tests, that is, RUT.
   3. We recommend two biopsies from the antrum (one from posterior and one from anterior wall) and two biopsies from the corpus (one from posterior and one from anterior wall) for the histopathological evaluation applying the updated Sydney system.
   4. Confirmation of *H. pylori* infection is based either on positive culture and/or molecular tests or positive *H. pylori* gastritis on histopathology and positive RUT.
   5. Active bleeding decreases the sensitivity of biopsy-based tests for *H. pylori* infection detection.

11. **Recommendation:** We recommend that before invasive testing for diagnosis of *H. pylori* infection or noninvasive testing for confirmation of eradication, to wait at least 2 weeks after stopping proton pump inhibitors (PPIs) and 4 weeks after stopping antibiotics and bismuth salts. (*Similar to previous guidelines)*

GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%

Practice points:

1. Parents or guardians should be asked about drug intake, that is, antibiotics and PPIs and bismuth salts during the 4 weeks before testing.
2. Antibiotics and bismuth salts may suppress bacterial growth and may result in false-negative test results in all applied diagnostic methods.
3. If acid suppressive therapy cannot be discontinued for 2 weeks because of recurrence of symptoms, changing to an H_2-receptor antagonist with discontinuation of the drug 2 days before testing may improve the sensitivity of the diagnostic test.
4. Antacids do not affect UBT and SAT performances.

Discussion: These recommendations remain largely unchanged from the previous guidelines. Given Recommendation 1, that, the primary goal of clinical investigation of GI symptoms in children should be to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection, the initial diagnosis of *H. pylori* infection should be based on upper GI endoscopy with biopsy-based methods rather than noninvasive tests such as the UBT or SAT. In addition, endoscopy allows the detection of mucosal erosions, ulceration, and scars. Although there are other morphologic features associated with *H. pylori* infection in children, most notably nodular antral gastritis which represents the most common endoscopic finding during *H. pylori* infection in children, these features are not specific and therefore biopsies must be taken to accurately diagnose infection. As noted in the previous guidelines, none of the methods have near-perfect accuracy. All tests can result in false negatives when bacterial density is low and there are mechanisms by which all tests can result in false positives.[4] For example, in a validation study of diagnostic methods for detecting *H. pylori* infection, RUT had sensitivity of 87% (95% CI: 0.79–0.95) but low specificity of 65% (95% CI: 0.58–0.71) compared to other diagnostic methods.[61] Therefore, it is recommended to perform at least two tests to confirm infection.

Since the last guidelines, a variety of studies have described histopathologic features associated with infection. Classification of gastritis using the updated Sydney system allows consistency in defining the histopathology associated with infection. In a recent pediatric systematic review and meta-analysis of histological gastric biopsies assesse according to the Updated Sydney System in children carried out in 5990 *H. pylori*-infected and 17,782 uninfected children, showed that *H. pylori* infection was associated with higher risk of chronic antral and corpus gastritis and follicular gastritis.[56] In comparison to adults, gastric atrophy and intestinal metaplasia are rarely detected.[62,63] Children more commonly lack active inflammation and are more likely to have chronic inflammation.[62,63]

If false-negative results of invasive biopsy-based tests are suspected due to active bleeding, or drug intake, noninvasive tests (^{13}C urea breath test [^{13}C-UBT] and/or SAT) may be helpful to determine whether the clinical findings may be related to *H. pylori* infection.[61,64] In such cases, a positive noninvasive test supports the diagnosis when positive histology is the only invasive test available.

12. **Recommendation:** 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 polymerase chain reaction (PCR) for CLA resistance, and eradication treatment tailored accordingly. (*Modified from previous guidelines*)

GRADE: strong recommendation. Quality of evidence: high. Agreement: 80%

Practice points:

1. Optimal methods must be used for collection, preservation, and transport of gastric biopsy specimens to enhance culture of the organism.
2. Adequate sampling of gastric mucosa biopsy samples from antrum and corpus allows maximum recovery of organisms and improves the detection of antimicrobial resistance.
3. Molecular methods are acceptable for detection of infection and of resistance markers in gastric biopsy specimens.

Discussion: Antimicrobial susceptibility testing has not routinely been included in current laboratory practice because of limitations in the ability to cultivate the organism. The laboratory method is time-consuming, and it should be performed according to appropriate methodology guidelines (e.g., European Committee for Antimicrobial Susceptibility Testing, Clinical and Laboratory Standards Institute (https://www.eucast.org https://clsi.org/standards/products/microbiology/documents/m45)). However, susceptibility testing when available can direct appropriate therapy and, in this sense, treat *H. pylori* infection like an infectious disease. It is well documented that antimicrobial resistance patterns differ by geographic regions and treatment failure leads to additional and often unnecessary procedures for patients and increases healthcare costs.[65,66] Antimicrobial stewardship requires detailed knowledge of susceptibility patterns for effective therapeutic decisions and to obviate development of resistance.

While determining susceptibility from cultured organism is recommended, it is acknowledged that culture,

is typically the most specific diagnostic method for detection, has inferior sensitivity compared to molecular test detection mainly due to transport conditions.[67–70] However, culture has the advantage of facilitating antimicrobial susceptibility testing for all recommended antibiotics. Culturing the organism may be challenging especially in cases of low bacterial load and there may not be an isolate for in vitro susceptibility testing.[65,67] To optimize culture, the transport of gastric biopsies should be transported in special transport media rather than normal saline, and a temperature of 4°C is highly recommended to enhance the success rate for culture. Given that some patients may be infected by more than one strain, it is recommended to take gastric biopsy samples from both antrum and corpus to increase the sensitivity for detecting different strains that may have multiple resistance profiles or varying pathogenicity markers.

The current evidence supports the use of molecular techniques for detection of resistance markers directly from biopsied material. Studies detail the accurate detection of CLA resistance markers by real-time PCR in *H. pylori* from DNA extracted from gastric biopsies with confirmation by sequencing or in vitro testing.[65,68] Gastric biopsy-based molecular tests showed estimated sensitivities from 94.3% to 100% and estimated specificities varied from 74% to 99.3%.[67,69,70] The use of in house[68] and commercially available assays have also proven reliable in detection of CLA[67,69] as well as fluoroquinolone resistance. Gene chip technology is an emerging molecular technology that has the capacity to detect additional resistance markers for other antimicrobials.[70] A compelling reason for the use of molecular technology is its sensitivity compared to culture in detection of both the organism and resistance markers, particularly in the early stage of the infection when the bacterial load is very low.[71]

Next-generation sequencing can provide susceptibility results for the six antibiotics of potential use in the treatment of *H. pylori* infection and can be performed on gastric biopsies even after fixation, and on stool. However, at present, this method is not widely available and quite expensive. Furthermore, in most cases, knowledge of CLA susceptibility is most important. Therefore currently, next-generation sequencing remains a research tool to better understand at the molecular level, the frequent metronidazole resistance and the rare amoxicillin resistance.

13. **Recommendation**: We suggest *against* the use of stool for molecular tests or culture for *H. pylori* infection detection or for susceptibility testing. (*New*)

    GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

    Practice points:

    None.

Discussion: There is progress on the use of stool as a specimen for detecting *H. pylori* and resistance markers using molecular techniques.[72–74] Stool contains known inhibitors to molecular amplification techniques. Although extraction methods designed specifically for stool have been valuable in decreasing these inhibitors, several studies still describe performance issues for *H. pylori* detection in stool by molecular techniques in comparison with the monoclonal SAT.[73] Similarly, detection of infection by stool culture is less sensitive in comparison with SAT.

We conclude that stool molecular detection of *H. pylori* infection and antimicrobial resistance markers in stool may be a good alternative when optimal samples are not available, but the test performance is not sufficiently accurate to recommend the use of this method. Optimal methods and controls must be used when performing molecular assays on stool samples to reduce the effects of inhibitors to amplification techniques. In addition, stool for culture has lower sensitivity than antigen detection.

14. **Recommendation:** We recommend that one of the following tests be used to determine whether *H. pylori* treatment was successful:
    (a) ^{13}C-UBT and
    (b) a two-step monoclonal SAT. (*Unchanged from previous guidelines*)

    GRADE: strong recommendation. Quality of evidence: high. Agreement: 100%

    Practice points:

    1. The relief of symptoms is not an indicator for successful treatment. Therefore, all children treated for *H. pylori* should be assessed for treatment success with a reliable test.
    2. ^{13}C-UBT and/or monoclonal SAT are the most reliable tests to be used to assess *H. pylori* eradication treatment.
    3. In case of complicated PUD, endoscopy, and biopsy-based tests to confirm eradication are recommended in pediatric patients.
    4. The ^{13}C-UBT may give false-positive results in children younger than 6 years of age.
    5. A two-step monoclonal SAT has better performance than the polyclonal SAT test or one-step immune-chromatographic stool test for *H. pylori* detection.
    6. Rapid office-based stool tests should not be used due to lower performance than laboratory-based tests.
    7. Use of the ^{14}C-UBT[75] or breath ammonia test is not recommended in children.[76]

Discussion: The use of ^{13}C-UBT and monoclonal SAT is the best direct noninvasive diagnostic methods to detect active *H. pylori* infection and to monitor eradication success. A systematic review of

the Cochrane database was performed for validation studies of the detection of *H. pylori* using the ^{13}C-UBT in children and adults.[75] The ^{13}C-UBT showed excellent test performance; with estimated sensitivity of 97.7%, specificity of 96.1%, positive predictive value of 90.4%, and negative predictive value of 99.2%.[75] The delta over baseline (DOB) value positivity cut-off is normally >4%, but for children, some studies favored a cutoff of 2.4% due to reduced bacterial loads. Citric acid may be more favorable than the other test meals because it helps slow gastric emptying, enhances gastric distribution of the substrate, and increases the contact time with *H. pylori* urease. Of note, the ^{13}C-UBT may give false-positive results in children younger than 6 years of age because of the lower distribution volume and different CO_2 production rates. False-positive results may also be due to technical difficulties in performing ^{13}C-UBT in young children because they often have challenges swallowing the substrate and oral urease–producing organisms can then split the substrate. However, this has little relevance in clinical practice in which eradication therapy is rarely indicated in children younger than 6 years. A systematic review of the Cochrane database for validation studies of the detection of *H. pylori* using the SAT in children and adults evaluated SAT in 29 studies (2988 participants). The sensitivity estimated at a fixed specificity of 0.90 (the median from studies across four comparison tests) was 0.83 (95% CI: 0.73–0.90) for the SAT.[75]

The use of the monoclonal SAT is also recommended for assessing the success of treatment and demonstrates excellent sensitivities of 100% and specificities of 92.3% in this setting.[64,77] The polyclonal SAT has a lower accuracy compared to the ^{13}C-UBT and the monoclonal SAT but may be an option in situations when neither of the other two tests are available.[61,64,75]

15. **Recommendation:** We recommend *against* antibody-based tests for *H. pylori* in serum, whole blood, urine, and saliva, in the clinical setting. (*Similar to previous guidelines*)

    GRADE: strong recommendation. Quality of evidence: moderate to low. Agreement: 100%

    Practice points:

    1. Whole blood, urine, or saliva testing are not recommended either for *H. pylori* detection or for assessing successful treatment.[78,79]

Discussion: Systematic review of the current literature continues to reaffirm the limited role of serology in the clinical setting.[80,81] Serology lacks the ability to indicate active infection as antibodies often persist over time. Tests may remain positive for months after appropriate therapy and eradication of organisms.

16. **Recommendation:** We recommend *against* molecular tests for *H. pylori* in serum, whole blood, urine, saliva, dental plaques, and periodontal pockets in the clinical setting. (*New*)

    GRADE: strong recommendation. Quality of evidence: low to moderate. Agreement: 100%

    Practice points:

    None.

Discussion: Evidence for a role of the oral cavity as a reservoir for *H. pylori* is scarce and conflicting. Thus, molecular tests for *H. pylori* in dental plaques, periodontal pockets, or saliva are not recommended for *H. pylori* detection or for assessing successful treatment.[82,83]

17. **Recommendation:** We recommend that the outcome of anti-*H. pylori* therapy be assessed 6–8 weeks after completion of therapy. (*Similar to previous guidelines*)

    GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%

    Practice points:

    1. ^{13}C-UBT and/or monoclonal SAT are the preferred methods for confirmation of *H. pylori* eradication.
    2. Testing for *H. pylori* eradication should be performed 6–8 weeks after completion of therapy to avoid false-negative results before 6 weeks, and to avoid a positive result that may be due to reinfection rather than treatment failure if performed later than 8 weeks after treatment.

Discussion: When monitoring the outcome of therapy, it is important to employ the most accurate test for the detection of active infection. The 13C-UBT and monoclonal SAT are the best direct, noninvasive diagnostic methods for monitoring eradication success.[75] Endoscopy and biopsy-based tests to confirm eradication are rarely needed in pediatric patients with uncomplicated PUD. PUD and or erosions have a low risk for relapse with clearance of the infection.

For both 13C-UBT and monoclonal SAT, false-negative results can occur when medications are taken that decrease the bacterial load or suppress gastric acid.[64,84] Therefore, testing to assess the success of eradication therapy should be performed at least 6–8 weeks after completion of treatment. This drug-free period is necessary to allow any recrudescence of the bacteria to become detectable and reduce the chance of false-negative results. The frequency of reinfection in children varies according to local prevalence; one study estimated reinfection at 5.4%–6% per patient-year with increased risk in those who had close contact with young children, especially siblings younger than 5 years of age.[85] Therefore, a positive noninvasive test for infection that was obtained much later than the

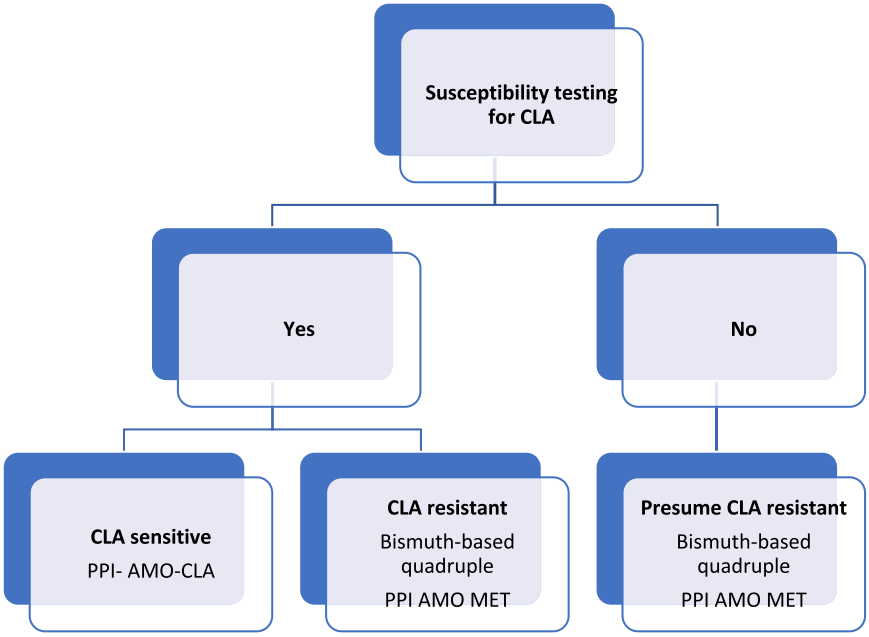


FIGURE 1 Algorithm for *Helicobacter pylori* eradication therapy, based on availability of antimicrobial susceptibility testing for CLA employing drug dosages recommended in Table 5. AMO, amoxicillin; CLA, clarithromycin; MET, metronidazole; PPI, proton pump inhibitor.

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[a]
	PPI AMO MET
In the presence of confirmed penicillin allergy	
+	PPI MET CLA
– or unknown	Bismuth PPI MET TET (>8 years)[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 rates.

recommended 6–8 weeks following eradication treatment has a greater chance of being due to reinfection rather than treatment failure.

18a. **Recommendation:** We recommend using CLA-Antimicrobial susceptibility testing (AST) to guide eradication therapy to maximize eradication rates. (*New*)

GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%

18b. **Recommendation:** We recommend *against* using CLA when CLA-AST is not performed. (*New*)

GRADE: strong recommendation. Quality of evidence: moderate. Agreement: 100%

Practice points:

1. If CLA resistance is detected, CLA should not be used as part of eradication therapy (see algorithm for treatment in Figure 1).
2. If the *H. pylori* strain is susceptible to CLA, CLA can be used in tailored triple therapy (Table 4) using the weight-based dosage indicated in Table 5.
3. CLA-AST can be performed by culture-based methods or by PCR.
4. PCR-based methods are preferable as they are more sensitive and provide more rapid results.
5. The effectiveness of first-line therapy should be evaluated in national/regional centers.

Discussion: Since the mid-90s, CLA has been widely used in regimens employed for *H. pylori* eradication. Triple therapy combining PPIs with amoxicillin (AMO) and CLA is the most widely utilized standard regimen in adults and in children. It has been clearly shown in the adult consensus guidelines[5] and the latest pediatric consensus guidelines[4] that the success of this regimen is best when given for 14 days. Although *H. pylori* strain resistance to macrolides (MAC) was very low in 1995, the frequency of resistance has been increasing worldwide ever since. Empirical use of CLA has been suggested if the resistance rate in a region is lower than 15% but this threshold is exceeded now in most regions where resistance testing has been performed.[86,87] Therefore, empiric use of CLA cannot be recommended in the absence of CLA-AST. CLA binds to 23S rRNA, a

TABLE 5 Drugs fixed dose according to subject body weight.

	Body weight (kg)	Morning (mg)	Noon (mg)	Evening (mg)
Colloidal bismuth subcitrate[a]	15–24	60	60	60
	25–34	120	60	60
	35–49	120	120	120
	>50	180	120	120
PPI[b]	15–24	20	—	20
	25–34	30	—	30
	35–49	40	—	40
	>50	40	—	40
Amoxicillin	15–24	500	500	500
	25–34	750	750	750
	35–49	1000	1000	1000
	>50	1000	1000	1000
Metronidazole	15–24	250	—	250
	25–34	500	—	250
	35–49	500	—	500
	>50	750	—	750
Clarithromycin	15–24	250	—	250
	25–34	500	—	250
	35–49	500	—	500
	>50	500	—	500
Tetracycline[c]				

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

[a]The dosing of bismuth subsalicylate is <10 years 262 mg QID; >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.

component of the 50S subunit of the bacterial ribosome, thereby inhibiting peptide translation. Mutations in this 23S rRNA decrease the affinity of CLA for the bacterial ribosome, which leads to a significant increase in the mean inhibitory concentration (MIC) of this antibiotic, making its overall effectiveness in *H. pylori* eradication regimens very low.

More recent studies have demonstrated that some patients are infected with a mixture of susceptible and resistant *H. pylori* strains. This phenomenon of mixed strains colonizing the host gastric mucosa is called heteroresistance.[88–90] Therefore, taking several gastric biopsy samples to perform CLA-AST is advisable.

Several studies evaluating the effectiveness of eradication therapy containing CLA have been published since the last consensus guidelines. Studies using a variety of treatment regimens including triple therapy or sequential therapy show unacceptably low eradication rates in the presence of CLA-resistant strains.[91–95] The meta-analysis of Wen et al. shows an eradication rate of 71% (647/911) with empirical triple therapy containing either CLA or metronidazole (MET).[96] Studies with CLA-AST and tailored treatment show eradication rates of 71% (duration 10 days),[97] 98% (duration 14 days),[98] and 100% (although duration was only 7 days).[91] These studies demonstrate that in comparison to empirical treatment using CLA, tailored treatment based on the susceptibility profiles of the infecting strain results in improved eradication rates. Of note, the efficacy of empirical treatment containing CLA is significantly lower than the 90% target rate. In a recently published multicenter study, an eradication rate of 88% was obtained using a tailored triple therapy containing CLA. Some of this effect may have been due to the addition of probiotics.

19. **Recommendation:** We recommend *against* using MET-AST to guide eradication therapy since results are unreliable and do not improve the eradication rate. (*New*)

    GRADE: strong recommendation. Quality of evidence: low. Agreement: 100%

    Practice points:

    1. The reproducibility of culture-based methods for detection of MET resistance is low, particularly using the E-test. Therefore, the results are not reliable.
    2. Currently, there is no reliable molecular diagnostic method for MET-AST.
    3. If MET-AST is routinely performed as part of a panel, it should be noted that antibiotic susceptibility data has not been shown to increase overall eradication rates and, therefore, does not help when choosing an eradication regimen.
    4. The eradication rate is influenced by longer duration (minimum 14 days) and increased dosage (up to 30 mg/kg up to 1500 mg daily) when prescribing triple therapy containing MET.
    5. If MET is used in an eradication scheme, the weight-based dosage indicated in Table 5 is recommended.

Discussion: MET resistance is complex and molecular-based methods for detecting MET resistance are lacking. There is a poor predictability and lack of reproducibility in culture-based methods that assess MET susceptibility,[99] and thus in vitro MET resistance does not correlate with in vivo resistance.[100] Therefore, MET-AST has limited clinical utility and should be used with caution to tailor eradication therapy. Additionally,

eradication is possible using a 14-day triple therapy containing MET even when in-vitro resistance has been shown.[91,97] In the most recent European multicenter study, eradication rates of 100% were achieved in patients infected with a MET-resistant strain who were treated with a MET-containing regimen.[3]

20. **Recommendation:** 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*)

    GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%

    Practice points:

    1. Drug dosages based on weight are indicated in Table 5.
    2. To enhance successful eradication the importance of adherence to the eradication treatment protocol should be explained to the patient/family.

Discussion: Unfortunately, there are no head-to-head comparisons of these treatment regimes in pediatric populations. Therefore, it is necessary to rely on adult data, which have been reviewed in the Maastricht VI consensus report.[5] The first statement concerning treatment indicates that it is reasonable to recommend AST with respect to antibiotic stewardship. In addition, a pediatric study from Slovenia provided strong evidence that in countries with a high prevalence of resistant *H. pylori* strains, AST and tailored therapy was essential.[101] Concerning the length of treatment, a report of an analysis of data from 21,000 patients included in the *H. pylori* European Register (Hp-EuReg) indicates that a 14-day duration is superior to 7 and 10 days.[102] The use of high-dose PPIs twice daily increases the efficacy of the triple therapy,[103] considering the presence of rapid metabolizers.[104] The dosage of AMO was not discussed but the pharmacodynamics of this antibiotic justifies a dose given three times a day (TID).[105] Adherence to therapy is critical to optimize eradication and reduce the risk of inducing antibiotic resistance.[97,106] Therefore, the physician should explain the importance of adherence to the eradication treatment protocol and consider providing additional written or other supports to the patient/family to enhance successful eradication.

21. **Recommendation:** We suggest AST-guided triple therapy over sequential-quadruple therapy. (*New*)

    GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

    Practice points:

    1. Sequential quadruple therapy comes with a higher risk of inducing antibiotic resistance, perturbation of microbiota, adverse events, and lower adherence.

Discussion: A 2016 study demonstrated sequential therapy had a lower eradication rate in infected children than triple therapy (CAO) in CLA-susceptible strains (90% vs. 100%).[91] However, in a Taiwanese study in the pediatric population, 14-day sequential therapy (omeprazole and AMO for 5 days followed by 5 days of treatment with omeprazole, CLA, and MET) was superior to 7-day triple therapy (97% vs. 80% eradication). CLA resistance was inversely associated with eradication success ($OR = 0.017$, $p < 0.001$)[107] highlighting the importance of an antimicrobial susceptibility approach to select targeted therapy. Zhou et al. compared four 14-day regimens of eradication therapy in children: standard triple therapy, sequential therapy, bismuth-based quadruple therapy containing AMO, and concomitant therapy.[108] Bismuth-based quadruple therapy was superior to triple therapy, while sequential therapy and concomitant therapy were not superior to triple therapy. However, adherence to prescribed therapy has been shown to be an important factor in the optimization of *H. pylori* eradication rates and quadruple sequential therapy increases the complexity of the treatment regimen.[97] A triple therapy, tailored to susceptibility to CLA, seems therefore a superior option over sequential or concomitant quadruple regimens without bismuth for the *H. pylori*-infected child. In the era of increasing antibiotic resistance, using treatments based on more than two different antibiotics (e.g., sequential, concomitant therapy) for eradicating *H. pylori* in children should be avoided.

22. **Recommendation:** We suggest a bismuth-based quadruple therapy (bismuth, PPIs, AMO, MET) as an empiric first-line eradication therapy in the absence of AST. (*New*)

    GRADE: conditional recommendation. Quality of evidence: low. Agreement: 100%

    Practice points:

    1. A combination of bismuth with PPI, AMO, and MET is an effective treatment and with similar side effects when compared to triple therapies (except dark stools).
    2. Drug dosages indicated in Table 5 are recommended.
    3. Duration of treatment should be 10–14 days (both showing similar results in the literature).

Discussion: Few data are available from pediatric studies regarding bismuth-based eradication protocols. Before 2012, when only case series were published, the overall percentages of children with successful eradication for bismuth-containing schemes were 82% and 86% according to ITT and per protocol (PP) analysis, respectively.[109] Similarly, a retrospective study in Korean children showed significantly higher (84%) eradication rates with bismuth-based quadruple therapy, including PPIs, AMO, and MET for 7 days than

with standard triple therapy consisting of PPIs, AMO, and CLA for 14 days (68%).[110] The more recent nonblinded, nonrandomized study of the effects of four different regimens in 288 Chinese children showed that bismuth-based therapy (bismuth, PPIs, AMO, and MET) had an effectiveness of 89.8%, which was superior to standard triple therapy (74%).[108] Another recently published study proposed a sequential 7-day PPIs plus AMO followed by 7-day PPIs, TET, MET, and bismuth subsalicylate scheme for *H. pylori* eradication in Turkish adolescents (mean age 15.1 ± 2.4 years) with a high eradication rate (92%).[111] In a prospective single-arm trial of 36 children from Belgium, a 10-day PPI, AMO, MET, and bismuth subcitrate regimen also showed a very high eradication rate (97%).[112] Finally, in Vietnam, in a prospective trial involving 237 children treated with different tailored regimens, 43 children infected with multidrug-resistant *H. pylori* strains received 14 days of bismuth-based quadruple therapy (PPIs, MET, and AMO or TET according to age and bismuth) with an overall eradication rate of 88%.[113]

When properly recorded, adverse events are frequent in most *H. pylori* eradication regimens. Zhou et al.[108] showed the rate of adverse events in Chinese children was similar among the four treatment regimens (bismuth, standard triple, concomitant, sequential), with 15.3% of patients reporting adverse events for the bismuth group. In a study of Belgian children,[112] 64% of patients reported at least one adverse event of mild or moderate intensity. Still, treatment adherence was excellent, with 83% of patients taking >90% of the treatment prescribed and only 2.8% taking <80%. In a large multicenter trial in adults of 10-day concomitant, 10-day bismuth quadruple with TET, and 14-triple therapy, adverse events were higher for the bismuth group (67%), and 10% discontinued their treatment.[114] However, AMO-containing bismuth therapies seem to be better tolerated than TET-containing bismuth therapies, as shown in another study in adults comparing TET versus AMO-containing bismuth-based schemes where adverse events were reported by 43% of the patients in the AMO group and 65% of the patients in the TET group.[115]

The addition of probiotics to eradication regimens has been suggested to improve adherence and reduce side effects. In adults, a number of published meta-analyses and systematic reviews of RCTs focused on the efficacy of probiotics in decreasing adverse events during *H. pylori* treatment indicated mainly positive findings.[116–118] However, data specific to children remain scarce. Since the last pediatric guidelines were published, two meta-analyses with pediatric data on probiotic use during treatment were published.[119,120] However, due to heterogeneity in the probiotics administered and differing dosing regimens it is not possible to make specific recommendations regarding probiotic therapy. Therefore, additional prospective pediatric data pertaining to specific probiotic strains is necessary to be able to draw valid conclusions before probiotics can be recommended as adjunct therapy.

23a. **Recommendation:** 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. (*Similar to previous guidelines*)

GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%

23b. **Recommendation:** We suggest using Bismuth quadruple therapy with tetracycline (TET) in adolescents if the strain is resistant to CLA and the allergy to penicillin is confirmed. (*Similar to previous guidelines*)

GRADE: conditional recommendation. Quality of evidence: very low. Agreement: 100%

Discussion: Allergy to penicillin is commonly reported; however, the presence of actual penicillin allergy is much lower. Therefore, it is reasonable to first consider formal allergy testing to confirm true AMO allergy. If allergy to AMO is confirmed and if the strain is susceptible to CLA, then therapy with CLA and MET should be used with a PPI. In a clinical trial of 82 patients aged 1–15, with three dropping out due to adverse effects, *H. pylori* eradication was achieved in 34 of 39 (87%, 95% CI: 74%–96%) on 14-day CLA, AMO, and omeprazole (CAO), and 37 of 40 (93%, 95% CI: 80%–98%) on CLA, MET, and omeprazole (CMO),[121] while the results for the two regimens were similar, the lack of statistical precision arising from the small study size does not rule out superiority of either one over the other.

When the infecting *H. pylori* strains have CLA resistance, bismuth-based quadruple therapy containing TET may be considered but should only be used in children (≥8 years old) with proven ulcer disease and after adequate documentation of allergy to AMO due to the risks of TET use in younger children. At present, there are no data showing the efficacy nor safety of the combined preparation of bismuth subcitrate, MET, and TET under the age of 18 years. In children under the age of 8 with confirmed penicillin allergy and CLA resistance, treatment options are very limited. Use of fluoroquinolone-containing regimens can be considered if they have not previously been taken and are in an area where resistance is low.

4 | EXPERT OPINION FOR RESCUE THERAPY

There was insufficient evidence to generate specific recommendations for rescue therapy in the pediatric population, therefore the following section consists of

suggestions based on expert opinion. Children who have persistent *H. pylori* infection after completing initial therapy should be treated again with an alternative regimen. Evaluating the reason for previous failure can be useful (inadequate adherence, early cessation of the treatment due to adverse events, treatment not tailored to CLA-AST, or inadequate dosing). If there is a history of any prior treatment with MAC or fluoroquinolones then CLA- or levofloxacin-based regimens, respectively, should be avoided given the high likelihood of resistance. Resistance to AMO is rare, and regimens containing these medications can be considered for subsequent therapies after eradication failure. However, AMO should be given in three divided doses. In addition, resistance to MET can be overcome with a longer duration and higher dosage. Because inadequate acid suppression is associated with eradication failure, high doses, and more potent PPIs, if available, should be considered in cases of refractory *H. pylori* infection. Recommended rescue therapies based on expert opinion can be found in Table 6.

In general, shared decision-making with patients/families regarding ongoing attempts to eradicate *H. pylori* is worthwhile. The potential benefits of *H. pylori* eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated exposure to antibiotics and high-dose acid suppression, particularly in vulnerable populations. After two failed therapies with confirmed patient adherence, *H. pylori* susceptibility testing should be reconsidered to guide the selection of subsequent regimens.[122]

Finally, as an alternative to PPIs-based therapies, recent randomized controlled clinical trials in adults show promise for the newer antisecretory drugs, potassium-competitive acid blockers (PCABs), which are currently approved for the treatment of adults in several countries, including Japan and the United States. PCABs increase intragastric pH rapidly and potently and maintain it to a greater degree than PPIs; in adults, this property has been associated with higher *H. pylori* eradication rates. Moreover, studies also demonstrate in adolescents and preteens that PCABs, that is, Vonoprazan have minimal effect on the upper GI tract microbiota, particularly the gastric microbiome.[123] A recent randomized clinical trial in over 1000 US and European adults demonstrated that PCAB-based triple therapy could be a suitable alternative to first-line CLA-based triple therapy or bismuth-based quadruple therapy.[124] Well-designed studies of PCABs as part of *H. pylori* eradication therapy in children are awaited.

5 | SUMMARY

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 (Table 7 outlines the summary of recommendations of whom to test for 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.

6 | FUTURE 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.[125] Thus, the development of a protective vaccine against

TABLE 6 Rescue treatment.

CLA susceptibility	Prior treatment regimen	Rescue therapy
+	PPI AMO CLA	PPI AMO MET
+	PPI AMO MET	PPI AMO CLA
– or unknown	PPI AMO MET	Bismuth PPI AMO MET[a]
		Consider performing an endoscopy to assess 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; IDA, iron deficiency anemia; N, no; NA, North America; Y, yes.

H. pylori infection should be a priority. In the era of new mRNA vaccines, the development of an effective vaccine to protect children against *H. pylori* infection appears closer to reality.

H. pylori infection significantly affects gastric and intestinal microbiota in adults, but the importance of this change in microbiota has yet to be characterized. During the current review period, there was insufficient evidence to draw any specific conclusions regarding the effect of *H. pylori* infection on the gastric microbiota in children. However, with enhanced knowledge concerning gastric microbiota a tailored approach to manipulating the microbiome to decrease complications of infection, and perhaps enhancing eradication and decreasing side effects may be feasible.

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, in childhood *H. pylori* infection rarely causes complications. Moreover, there is growing evidence for a role of *H. pylori* infection in reducing the risk of some chronic conditions like asthma and allergies. 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.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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