

Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children

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ABSTRACT

Objective: As the clinical implications of *Helicobacter pylori* infection in children and adolescents continue to evolve, ESPGHAN and NASPGHAN jointly renewed clinical guidelines using a standardized evidence-based approach to develop updated recommendations for children and adolescents in North America and Europe.

Methods: An international panel of 11 pediatric gastroenterologists, 2 epidemiologists, 1 microbiologist, and 1 pathologist was selected by societies that developed evidence-based guidelines based on the Delphi process with anonymous voting in a final face-to-face meeting. A systematic literature search was performed on 8 databases of relevance including publications from January 2000 to December 2009. After excluding nonrelevant publications, tables of evidence were constructed for different focus areas according to the Oxford classification. Statements and recommendations were formulated in the following areas: whom to test, how to test, whom to treat, and how to treat. Grades of evidence were assigned to each recommendation based on the GRADE system.

Results: A total of 2290 publications were identified, from which 738 were finally reviewed. A total of 21 recommendations were generated, and an algorithm was proposed by the joint committee providing evidence-based guidelines on the diagnostic workup and treatment of children with *H pylori* infection.

Conclusions: These clinical practice guidelines represent updated, best-available evidence and are meant for children and adolescents living in Europe and North America, but they may not apply to those living on other continents, particularly in developing countries with a high *H pylori* infection rate and limited health care resources.

Key Words: antibiotic resistance, children and adolescents, diagnostic tests, *Helicobacter pylori*, treatment

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SYNOPSIS

The current recommendations for managing *Helicobacter pylori* infection in children are as follows:

1. The primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *H pylori* infection.
2. Diagnostic testing for *H pylori* infection is not recommended in children with functional abdominal pain.
3. In children with first-degree relatives with gastric cancer, testing for *H pylori* may be considered.
4. In children with refractory iron-deficiency anemia, in which other causes have been ruled out, testing for *H pylori* infection may be considered.
5. There is insufficient evidence that *H pylori* infection is causally related to otitis media, upper respiratory tract infections, periodontal disease, food allergy, sudden infant death syndrome (SIDS), idiopathic thrombocytopenic purpura, and short stature.
6. For the diagnosis of *H pylori* infection during esophagogastroduodenoscopy (EGD), it is recommended that gastric biopsies (antrum and corpus) for histopathology be obtained.
7. It is recommended that the initial diagnosis of *H pylori* infection be based on either a positive histopathology plus a positive rapid urease test or a positive culture.
8. The ¹³C-urea breath test (UBT) is a reliable noninvasive test to determine whether *H pylori* has been eradicated.
9. A validated enzyme-linked immunosorbent assay (ELISA) test for detection of *H pylori* antigen in stool is a reliable

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- noninvasive test to determine whether *H pylori* has been eradicated.
10. Tests based on the detection of antibodies (IgG, IgA) against *H pylori* in serum, whole blood, urine, and saliva are not reliable for use in the clinical setting.
 11. It is recommended that clinicians wait at least 2 weeks after stopping proton pump inhibitor (PPI) therapy and 4 weeks after stopping antibiotics to perform biopsy-based and noninvasive tests (UBT, stool test) for *H pylori*.
 12. In the presence of *H pylori*-positive peptic ulcer disease (PUD), eradication of the organism is recommended.
 13. When *H pylori* infection is detected by biopsy-based methods in the absence of PUD, *H pylori* treatment may be considered.
 14. A "test and treat" strategy is not recommended in children.
 15. In children who are infected with *H pylori* and whose first-degree relative has gastric cancer, treatment may be offered.
 16. Surveillance of antibiotic resistance rates of *H pylori* strains in children and adolescents is recommended in the different countries and geographic areas.
 17. First-line eradication regimens are the following: triple therapy with a PPI + amoxicillin + clarithromycin or an imidazole

- or bismuth salts + amoxicillin + an imidazole or sequential therapy.
18. Antibiotic susceptibility testing for clarithromycin is recommended before initial clarithromycin-based triple therapy in areas/populations with a known high resistance rate (>20%) of *H pylori* to clarithromycin (Fig. 1).
19. It is recommended that the duration of triple therapy be 7 to 14 days. Costs, compliance, and adverse effects should be taken into account.
20. A reliable noninvasive test for eradication is recommended at least 4 to 8 weeks following completion of therapy.
21. If treatment has failed, 3 options are recommended: EGD, with culture and susceptibility testing including alternative antibiotics, if not performed before guide therapy; fluorescence in situ hybridization (FISH) on previous paraffin-embedded biopsies if clarithromycin susceptibility testing has not been performed before guide therapy; modification of therapy by adding an antibiotic, using different antibiotics, adding bismuth, and/or increasing the dose and/or duration of therapy.

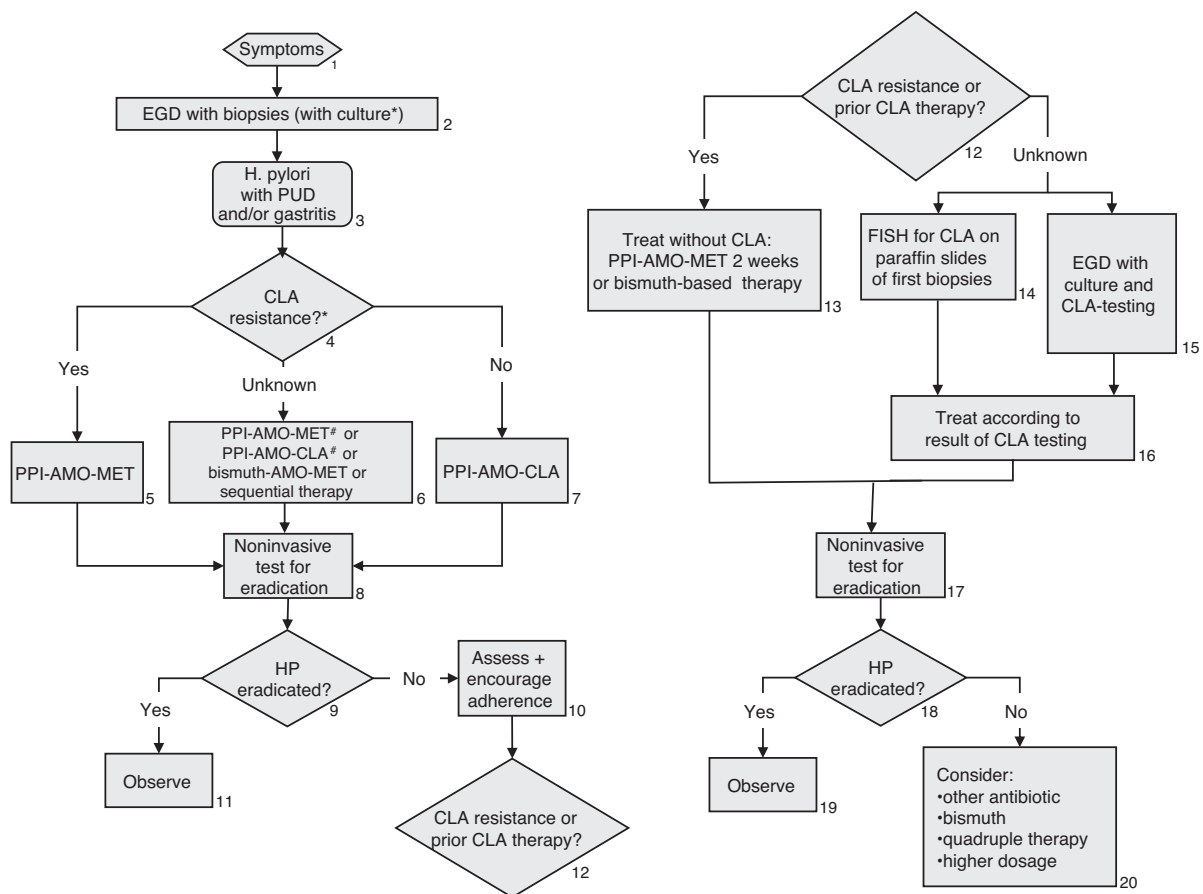


FIGURE 1. Proposed algorithm of how to treat *Helicobacter pylori* infection in pediatric patients. AMO = amoxicillin; CLA = clarithromycin; EGD = esophagogastroduodenoscopy; FISH = fluorescence in situ hybridization; HP = *H pylori*; MET = metronidazole; PPI = proton pump inhibitor; PUD = peptic ulcer disease. *In areas or populations with a primary clarithromycin-resistance rate of >20% or unknown background antibiotic resistance rates, culture and susceptibility testing should be performed and the treatment should be chosen accordingly. #If susceptibility testing has not been performed or has failed, antibiotics should be chosen according to the background of the child (1).

1. SCOPE AND PURPOSE

1.1. Introduction and Aims

Children differ from adults with respect to *H pylori* infection in terms of the prevalence of the infection, the complication rate, the near-absence of gastric malignancies, age-specific problems with diagnostic tests and drugs, and a higher rate of antibiotic resistance. Compared with adults, PUD is found less often in infected children undergoing upper endoscopy. In a large European multicenter study including 1233 symptomatic children with *H pylori* infection, PUD was diagnosed in <5% of children younger than 12 years of age and ~10% of teenagers (1). Gastric malignancies associated with *H pylori* infection typically occur in adulthood, with only a few case reports of lymphomas in the pediatric age group (2,3). The differential diagnosis for abdominal pain and dyspeptic symptoms is different. Children are often unable to provide precise descriptions of the location and the character of the pain (4,5). Some disorders such as idiopathic thrombocytopenic purpura, which have been associated with *H pylori* infection in adults, do not show a relation in children, probably because of a different pathogenesis in the pediatric population. The level of evidence for most disease outcomes is lower. Few randomized placebo-controlled treatment trials are available for the different outcomes, often with only small numbers of cases included (6,7). These and other differences explain why some of the recommendations for adults (8) may not apply in children.

H pylori infection is usually acquired during the first years of life in both developing and industrialized countries (9,10). In Europe and North America, the epidemiology of *H pylori* infection in children has changed in recent decades. Low incidence rates are found in the northern and western European countries, resulting in prevalence far below 10% in children and adolescents. In contrast, the infection is still common in certain geographic areas such as southern or eastern Europe, Mexico, and certain immigrant populations from South America, Africa, and most Asian countries, and aboriginal people in North America (11–13). The different prevalence of infection and the corresponding effect on health care resources in industrialized compared with developing countries require different recommendations with respect to testing and treating children. These guidelines apply only to children living in Europe and North America, but not to those living in other continents, particularly in developing countries with a high *H pylori* infection rate in children and adolescents and with limited resources for health care. The guidelines may need to be adapted to national health care systems because certain tests or treatment regimens may not be available and/or reimbursed by health insurance programs.

2. DEVELOPMENT OF GUIDELINES

2.1. Selection of Topics and Patients

In 2000, the Pediatric Task Force of the *H pylori* Study Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published consensus statements on *H pylori* infection in children (14). Shortly thereafter, a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) published a Medical Position Paper on the same topic, including recommendations for treatment (15). In 2004, the Canadian *Helicobacter* Study Group initiated a consensus conference including patients from Canada, the United States, and Europe. Recommendations covered how to approach *H pylori* infection in children (6). In 2005, ESPGHAN and NASPGHAN decided independently to renew their guidelines, this time with a joint evidence-based methodology. The councils of both

societies decided in 2006 that the process should be combined to have the same recommendations for North America and Europe.

The following 4 areas were identified and covered by 4 subgroups, which formulated the critical questions for each area:

1. Who should be tested? (differentiating among screening, surveillance, and clinically based testing)
2. What tests should be used?
3. Who should be treated?
4. What treatment regimens are most appropriate?

Each society assigned 1 chair (Benjamin Gold for NASPGHAN and Sibylle Koletzko for ESPGHAN). At least 2 members from each society were assigned to the subgroups for the 4 areas of interest. Members were mostly pediatric gastroenterologists, but experts in epidemiology, microbiology, and pathology were also selected based on their peer-reviewed publications, research activities in the field, and participation in national or international activities. The European patients were recruited from the Pediatric Task Force on *H pylori* Infection (ESPGHAN Working Group on *H pylori*) and also included a representative from the European *Helicobacter* Study Group (Francis Mégraud).

2.2. Literature Search and Grading the Articles for Quality of Evidence

A systematic literature search was designed by Karen Goodman, an epidemiologist, using accessible databases of relevance: PubMed, MEDLINE, EMBASE, Cochrane Library, Biosis Previews, EBM Reviews, ISI Web of Science, and Scopus. The search included publications from 2000 to August 2007. The search included publications of all types presenting or reviewing data on *H pylori* in patients younger than 20 years old, selecting on Medical Subjects Headings (MeSH) terms as listed below, with no language restrictions:

Search Strategy

- 1 *Helicobacter pylori*
- 2 *Helicobacter* infection
- 3 *pylori*
- 4 or/1–3
- 5 Newborn
- 6 Infant
- 7 Child
- 8 Adolescent
- 9 Pediatrics
- 10 or/5–9
- 11 4 and 10
- 12 11 and py = 2005:2006
- 13 Limit 12 to human

The search identified 1979 unique publications and an additional 63 publications were generated from the citations of relevant reviews. Of these 2042 papers, the following were excluded: 800 that did not present evidence on relevant topics; 635 that did not present evidence for pediatric groups; 40 letters, commentaries, or case reports; 33 abstracts; 25 non-English-language publications that did not present relevant data in an English-language abstract; and 19 nonsystematic reviews. The total number of selected papers was 490, including 80 reviews. The papers were grouped according to the review focus areas. Summaries of review papers were prepared and tables were constructed

to organize key data regarding study, quality, and findings from the original research reports.

In addition, within each subgroup, the members were asked to search the literature with respect to their topics to add evidence that may have been missed by the search criteria. In particular, this increased inclusion of publications from less widely circulated journals and from non-English-language sources. Grading of the quality of evidence was performed by epidemiologists and individual group members, according to the classification system of the Oxford Centre for Evidence-Based Medicine (<http://www.cebm.net/index.asp>), because this is the only grading system in which studies of diagnostic tests can be scored accordingly. The lists of rated articles and synthesis tables were circulated to the subgroups, and the information was expanded or revised upon closer inspection as appropriate.

2.3. Voting on Consensus Statements and Grading the Statements for Quality of Evidence

In preparation for a meeting in December 2007 in Munich, Germany, each subgroup had formulated the statements circulated to each member of the subgroups. In addition, the European members of the 4 subgroups presented the statements during the annual meeting of the ESPGHAN Pediatric Task Force in October 2007 in Istanbul, Turkey, where they were extensively discussed and adapted according to the comments of the attendees.

At the meeting in Munich, the group voted on 2 iterations of each of the consensus statements. Statements were revised based on feedback provided from the patients and further critical review of the available literature. Some of the statements were deleted by voting and the content of these was condensed into comments pertaining to relevant statements that remained. Additional statements were added on matters that had not been addressed previously.

All of the votes were anonymous. A 6-point scale was used: 1, agree strongly (A+); 2, agree moderately (A); 3, just agree (A-); 4, just disagree (D-); 5, disagree moderately (D); and 6, disagree strongly (D+). Agreement with the statement (the sum of voting for A+, A, or A-) by three-quarters (ie, $\geq 75\%$) of the voting members was defined a priori as consensus. The level of agreement in the final vote is provided for each statement, expressed as a percentage.

2.4. Grades of Evidence

Grades of evidence for each statement were based on the grading of the literature and were finally assigned using the GRADE system of 2004 (16) as follows:

1. High: further research is unlikely to change our confidence in the estimate of effect.
2. Moderate: further research is likely to have an important influence on our confidence in the estimate of effect and may change the estimate.
3. Low: further research is very likely to have an important influence on our confidence in the estimate of effect and may change the estimate.
4. Very low: any estimate of effect is uncertain.

The designation "not applicable" was used for situations in which these grades of evidence were not relevant for a particular statement.

2.5. Consensus Meeting and Funding Sources

The Munich meeting was organized by Sibylle Koletzko and supported financially by NASPGHAN and ESPGHAN. There was

no financial support from industry. Seven North American members (4 from the United States, 2 from Canada, 1 from Mexico) and 8 European members attended the final meeting. One attendee, who was not eligible to vote, observed and documented the voting process, which was later compared with the recorded electronic voting slides. The statements were presented at the World Congress of Pediatric Gastroenterology in Iguassu Falls, Brazil, on August 19, 2008 to the scientific community and feedback was requested. The first-draft manuscript was prepared by the chair of the European group, Sibylle Koletzko, in collaboration with Nicola Jones of the North American group, and the 2 epidemiologists Karen Goodman and Marion Rowland. Because of a change in the NASPGHAN chair, the manuscript was on hold for 18 months. In December 2009, an updated systematic literature search was performed including articles published from September 2007 to 2009. A total of 248 new publications were retrieved and reviewed for new evidence, which may have influence on the recommendations, the evidence, or the strength of recommendations compared with the version presented in August 2008 at the World Congress. The new literature was implemented in the final draft, which then was circulated to all members of the consensus group and their input was worked into the manuscript.

3. RESULTS

3.1. Statements and Comments

For the first round of voting, 43 statements were presented and agreement was reached for 22 of them. Several statements were omitted, some combined into 1, and others reworded after discussion. There were 21 statements in the final round of voting, and consensus was reached for all of them. The result of the final voting is provided for every statement.

3.2. Who Should Be Tested?

Recommendation 1 The primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *H pylori* infection.

Agree: 100% (A+ 92%, A 8%). Grade of evidence: not applicable.

Recommendation 2 Diagnostic testing for *H pylori* infection is not recommended in children with functional abdominal pain.

Agree: 92% (A+ 54%, A 23%, A- 15%, D- 8%). Grade of evidence: high.

Comment on Recommendations 1 and 2:

Abdominal complaints such as pain, nausea, or other dyspeptic symptoms are nonspecific and can be caused by different organic diseases within and outside the digestive tract. These diseases may be missed or their diagnosis and treatment delayed, if a noninvasive test for *H pylori* infection is positive and treatment initiated. For example, Levine et al (17) performed endoscopy in children with epigastric pain and symptoms suggestive of gastroesophageal reflux disease. After treatment, improvement of epigastric pain correlated with improvement of reflux disease, but was not related to *H pylori* eradication. Abdominal complaints may also be part of a functional gastrointestinal disorder (18). Children younger than 8 years old, or even as old as 12 years, may not be able to provide accurate descriptions of the degree, character, and location of pain (4). Whether *H pylori* gastritis causes abdominal pain in the absence of PUD is still debatable. Several studies from the 1990s applied different noninvasive tests for *H pylori*

infection and compared the prevalence of positive results in children with recurrent abdominal pain and controls and found no significant difference in infection rates between cases and controls (19,20). A meta-analysis of 45 studies concluded that *H pylori* infection is not associated with abdominal pain (21). Epidemiological studies on the prevalence of chronic or recurrent abdominal pain in pediatric age groups in different European countries yielded estimated frequencies ranging from 0.3% to 19%; however, the frequencies in different countries were not related to the background of *H pylori* prevalence in the respective countries (4). More recent case-control studies confirmed the lack of evidence for a causal relation between *H pylori* infection and abdominal pain. In a study of 1221 children from Germany, Bode et al (22) identified in a multivariable logistic regression analysis that social and familial factors (single-parent household, family history of PUD, or functional pain) were significantly associated with abdominal pain, but not with the *H pylori* status of the child, as assessed by the ¹³C-UBT. Tindberg et al (23) reported no significant association of recurrent abdominal pain with *H pylori* infection in 695 schoolchildren between 10 and 12 years old. In fact, an inverse relation was noted for *H pylori* positivity and the occurrence of any abdominal pain after adjustment for selected possible confounders (odds ratio [OR] 0.5; 95% confidence interval [CI] 0.3–0.8).

Several uncontrolled intervention studies showed improvement of symptoms after treatment; however, in some of the studies, treatment success was not monitored and eradication of the bacteria was assumed in cases with symptomatic improvement (12,24–26). Other studies had a short follow-up period of a few weeks only (27). These uncontrolled intervention studies provide weak evidence of a causal relation between *H pylori* infection and abdominal pain, particularly because functional abdominal pain resolves in 30% to 70% of patients by 2 to 8 weeks after diagnosis accompanied by reassurance of the child and the parents (28,29).

Only 1 double-blind randomized placebo-controlled trial was performed in a population of symptomatic children with *H pylori* infection, excluding cases of PUD (30). In this small trial with 20 children studied for 12 months, a relation between symptom relief and *H pylori* eradication or histological healing was not observed.

In summary, at present, there is inadequate evidence supporting a causal relation between *H pylori* gastritis and abdominal symptoms in the absence of ulcer disease. Therefore, cases of abdominal pain consistent with the diagnostic criteria of functional pain (18) should not be investigated for *H pylori*, unless upper endoscopy is performed during the diagnostic workup in search for organic disease.

Recommendation 3 In children with first-degree relatives with gastric cancer, testing for *H pylori* may be considered.

Agree: 93% (A+ 29%, A 50%, A– 14%, D 7%). Grade of evidence: low.

Comment on Recommendation 3:

A causal relation between *H pylori* infection and the risk of gastric malignancies, including cancer and gastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, has been shown in animal models and is supported by several epidemiological and intervention studies (31–34). Both of these cancer types are extremely rare during the first 2 decades of life. Although *H pylori*-associated gastric cancer has not been reported in children, MALT lymphomas have been described in a few *H pylori*-infected pediatric patients (2,3).

In 1994, the World Health Organization declared *H pylori* a class I carcinogen. A meta-analysis estimated that the risk for gastric cancer is increased by a factor of 2 to 3 in *H pylori*-infected individuals. The risk is further increased if only noncardia

carcinomas are considered; however, the risk of gastric cancer not only depends on the infection itself but also is strongly modified by the presence of bacterial virulence factors (35) and other factors such as the genetic makeup of the host and environmental influences, including diet (36). The eradication of *H pylori* may have the potential to decrease the risk of gastric cancer (37–39). In a large interventional trial in adults, subgroup analysis suggested that eradication may be beneficial in people without precancerous lesions (39). The time point for an effective intervention, and therefore screening strategy, however, is not yet clear (40). In previous studies of patients younger than 45 years old with gastric cancer, *H pylori* had been identified as a risk factor (41).

Individuals with a positive family history for gastric cancer are considered a high-risk group. The risk may be particularly high in *H pylori*-infected children in whom the father or the mother is affected by gastric cancer. This child not only shares genetic and environmental factors with the affected parent but may also have the same bacterial strain with pathogenic properties (42,43). Therefore, the risk of gastric cancer may be much higher for individual children with such histories than what has been estimated from epidemiological studies that lack information on relevant factors.

Although there is little evidence that addresses whether this approach is beneficial, there was strong agreement within the panel that testing for *H pylori* infection be considered in children with a first-degree relative with gastric cancer. There was also agreement that if *H pylori* infection is confirmed in these children either with a reliable noninvasive test or with biopsy-based methods, treatment should be offered and the success of therapy evaluated to ensure successful eradication.

Approximately 70% of gastric MALT lymphomas can be successfully treated with *H pylori* eradication. In the rare cases of *H pylori*-infected children with established MALT lymphoma, eradication therapy needs to be performed regardless of the staging of the lymphoma. The translocation t(11;18)(q21;q21) characteristic of MALT lymphoma is recognized to be a marker of *H pylori* independence, but this marker is found in only half of the MALT lymphomas that are resistant to *H pylori* eradication (44). In patients with the translocation t(11;18)(q21;q21), conventional chemotherapy can be considered in addition to eradication of *H pylori*.

Screening for *H pylori* infection in the general population is not recommended. In populations with a high prevalence of *H pylori* infection, the benefit of screening can be assessed by considering the risk of *H pylori*-associated gastric cancer in particular populations, along with the health care priorities of those populations. In populations with a high incidence of gastric cancer and in which gastric cancer-screening programs are in place, children can be included in screening programs for *H pylori* infection, and close surveillance in those who develop atrophy or intestinal metaplasia is indicated.

Recommendation 4 In children with refractory iron-deficiency anemia in which other causes have been ruled out, testing for *H pylori* infection may be considered.

Agree: 100% (A+ 36%, A 36%, A– 28%). Grade of evidence: low.

Comment on Recommendation 4:

Iron-deficiency anemia in children and adolescents may have different causes. If noninvasive diagnostic tests are not able to find the cause and/or if the iron deficiency is refractory to oral iron therapy, then diagnostic upper endoscopy is indicated. In these situations, mucosal biopsies are taken to rule out pathologic conditions such as celiac disease. In addition, gastric biopsies are taken for evaluation of *H pylori* by histology and culture because *H pylori* infection may be the cause of iron-deficiency anemia, even in the

absence of erosions or ulceration (45,46) or gastrointestinal symptoms (47).

Several studies have shown an association between low iron status and *H pylori* infection (48–50). Because both *H pylori* infection and iron deficiency are associated with poor socioeconomic and hygienic conditions, and cross-sectional studies cannot determine whether the purported cause preceded the effect, only randomized intervention studies can provide strong evidence of a causal relation. The first randomized placebo-controlled study included only 22 *H pylori*-infected pediatric patients randomized into 3 treatment arms: iron only, eradication therapy only, or both (48). Eradication therapy increased hemoglobin levels even without iron substitution, whereas iron therapy alone did not. In a study of 140 children between 6 and 16 years old from Turkey, it was reported that eradication therapy in the absence of iron supplementation was sufficient to improve iron deficiency and anemia (49); however, this beneficial effect of *H pylori* therapy on iron status could not be confirmed in recent intervention trials in children living in Alaska and Bangladesh (50,50a). Further placebo-controlled studies are needed to show whether *H pylori* infection can cause iron deficiency even in the absence of mucosal breaks because low iron status can have harmful effects on both mental and physical development.

Recommendation 5 There is insufficient evidence that *H pylori* infection is causally related to otitis media, upper respiratory tract infections, periodontal disease, food allergy, SIDS, idiopathic thrombocytopenic purpura, and short stature.

Agree: 100% (A+ 36%, A 28%, A–, 36%). Grade of evidence: low.

Comment on Recommendation 5:

A wide variety of extraintestinal manifestations are suggested to be associated with *H pylori* infection; however, current evidence for a causal relation for these associations in children is not compelling (51–62).

3.3. Which Diagnostic Test Should Be Applied in Which Situation?

Numerous tests that detect *H pylori* are available. They are divided into noninvasive and invasive tests. Invasive tests require gastric tissue for detecting the organism and include culture, rapid urease test, histopathology, polymerase chain reaction, and FISH. (63). Noninvasive tests include different methods for the detection of *H pylori* antigens in stool, detection of antibodies against *H pylori* in serum, urine, and oral samples, and the ¹³C-UBT. The sensitivities and specificities obtained in different pediatric studies have been reviewed by the 4 members of the guideline subgroup and recently published (63).

All diagnostic tests are generally feasible in children; however, tests requiring patient cooperation, such as the UBT, are more difficult to perform in infants, toddlers, or physically challenged children. A crucial question for all tests performed in a pediatric population is whether the accuracy of the applied method is influenced by the age of the tested child. It is necessary to consider different age groups: infants, toddlers, preschool-age and school-age children, and adolescents (64). Most of the validation studies in children included only a few *H pylori*-infected infants and toddlers. Therefore, the information with respect to sensitivity is limited in these age groups.

It is necessary to compare a test to a reference standard; however, no single test for detection of *H pylori* infection can be used as a fully reliable reference method. Culture is the only method

that is considered to be 100% specific, a positive culture being sufficient to prove *H pylori* infection, but its sensitivity is lower (65,66). For that reason, concordant results of at least 2 tests are needed to define the *H pylori* infection status. For noninvasive tests, biopsy-based tests should be the reference. If culture was not successful or not performed, concordant positive results for histology and rapid urease test indicate a positive *H pylori* status. The definition of a negative *H pylori* status is that all of 2 or 3 invasive tests performed are negative. For the validation of an invasive test, such as histopathology, other biopsy-based tests, with or without the combination of reliable noninvasive tests, should be the reference. All of the tests are suitable for the detection of infection before and after treatment, with the exception of serology, which may remain positive for some time after successful eradication.

For the interpretation of test results, factors that can lead to false-positive or false-negative results must be known and considered. Antibiotics, including penicillin and cephalosporines, and acid-suppressive drugs, particularly PPIs, should be discontinued before testing for at least 4 and 2 weeks, respectively. This recommendation is extrapolated from adult studies (67–69).

Recommendation 6 For the diagnosis of *H pylori* infection during EGD, it is recommended that gastric biopsies (antrum and corpus) for histopathology are obtained.

Agree: 93% (A+ 33%, A 40%, A– 20%, D– 7%). Grade of evidence: moderate.

Recommendation 7 It is recommended that the initial diagnosis of *H pylori* infection be based on either positive histopathology + positive rapid urease test or a positive culture.

Agree: 100% (A+ 36%, A 50%, A– 14%). Grade of evidence: moderate.

Comment on Recommendations 6 and 7:

For histology, 2 biopsies should be obtained from both the antrum and the corpus, and the findings should be reported according to the updated Sydney classification (70). Because the density of *H pylori* may be patchy, the sensitivity increases with the number of biopsies taken. Normally, the highest bacterial count is found in the antrum; however, in cases of low gastric acidity, the bacteria may be present only in the corpus. In a small single-center study of children undergoing endoscopy for symptoms of acid peptic disease in Italy, in 22 children in whom *H pylori* infection was identified, biopsies of the cardia were more sensitive for the detection of *H pylori* than biopsies of the antrum or corpus (71); however, these findings need to be confirmed in additional centers. Special staining (Giemsa or silver stain) and immunohistochemistry may improve the detection of *H pylori*. Biopsies should be stained with hematoxylin and eosin for histopathology because this is the best method to detect atrophy and intestinal metaplasia. Atrophy can be assessed only in biopsy material that is oriented correctly, and diagnostic concordance between pathologists can be difficult to achieve. Histopathology also allows the recognition of the rare *Helicobacter heilmannii* infection (72).

In children with suspected *H pylori* infection, it is highly recommended to take not only biopsies for histopathology but also 1 biopsy each for a rapid urease test and, if available, culture. The suspicion of an infection is often based on the macroscopic findings of a nodular mucosa in the antrum or bulbus and/or gastric or duodenal erosions or ulcerations. The rationale for the recommendation to perform more than 1 diagnostic test is based on the sensitivity results of invasive tests, which range from 66% to 100% for histology and from 75% to 100% for rapid urease tests in published series from children (63). With decreasing prevalence

of the infection in pediatric populations in many areas of Europe and North America, the predictive values of the diagnostic test results fall. For example, a test with a sensitivity of 90% has a positive predictive value of only 50%, if the prevalence of the infection in the population is 10%. Therefore, concordant positive results on 2 different tests are recommended to confirm the diagnosis and justify the costs and adverse effects of treatment. If the results of histology and rapid urease test are discordant, then a noninvasive test (UBT or stool test) should be applied. One exception from the rule of 2 concordant test results is a positive culture, which is 100% specific and therefore in itself sufficient to diagnose *H pylori* infection. Another exception is the presence of a bleeding peptic ulcer, in which case 1 positive biopsy-based test is considered to be sufficient to initiate anti-*H pylori* therapy. A recent meta-analysis on the accuracy of diagnostic tests in adults with PUD clearly indicated that active bleeding decreases the sensitivity of invasive diagnostic tests, but the specificity is high (73).

Recommendation 8 The ¹³C-UBT is a reliable noninvasive test to determine whether *H pylori* has been eradicated.

Agree: 94% (A+ 67%, A 20%, A- 7%, D- 6%). Grade of evidence: high.

Comment on Recommendation 8:

The UBT has been evaluated in a large number of pediatric studies of high quality against a reference standard, both before and after therapy (74–78). In spite of a high variability of tracer dose and tracer application, the type of test meal, the duration of the fasting period before the meal, the time point of breath sampling, the type of analysis, and the cutoff levels, this test has a high accuracy, sensitivity, and specificity (63,64). When the UBT is performed, the patient should have an empty stomach before receiving an acid drink (apple or orange juice, citric acid solution) because the urease activity of the bacteria decreases rapidly with increasing pH (79). After ingestion of the tracer, the drink without tracer should be provided to the child to avoid degradation of the tracer by oral flora. This is a particular problem in infants and toddlers and may at least in part explain the lower specificity reported in children younger than 6 years old compared with older children (74,76,80–84). False-positive results can also occur in young children because of the lower distribution volume and a different CO₂ production rate, which can be adjusted for (85).

Recommendation 9 A validated ELISA for detection of *H pylori* antigen in stool is a reliable noninvasive test to determine whether *H pylori* has been eradicated.

Agree: 86% (A+ 21%, A 29%, A- 36%, D 7%, D+ 7%). Grade of evidence: moderate.

Comment on Recommendation 9:

Detection of *H pylori* antigen in stool is an attractive noninvasive method that seems suitable for both clinical use and epidemiological studies. Several methods are available for the detection of *H pylori* antigen in stool, such as enzyme immunoassay (EIA) based on polyclonal or monoclonal antibodies, and immunochromatographic tests (so-called rapid or quick tests). Stool tests are generally more convenient in pediatric patients than the UBT. Stool samples can be obtained from children without their active collaboration and are transportable by mail for analysis. Neither keeping the samples at room temperature for up to 5 days nor freezing for months or even years seems to influence the accuracy of the stool tests (86–89). In most countries, an EIA would be less costly than the UBT. In addition, the EIA stool test is the only

diagnostic noninvasive test that has not shown an age dependence on the accuracy of the test results (64,87). Therefore, validation studies in adults may be extrapolated to children.

The first commercial EIA test to detect *H pylori* antigen in stool was the Premier Platinum HpSA (Meridian Diagnostics, Cincinnati, OH). This test is based on polyclonal antibodies. There is a wide range for sensitivity and specificity of the test in children, both pretreatment (86,90–98) and posttreatment (89,91,92,95). Testing the same stool samples with different production lots of the polyclonal test indicated interassay variation (99). This may explain the wider range reported for the sensitivity and specificity of the polyclonal stool tests. A different polyclonal EIA (Equipar Diagnostici, Saronno, Italy) was recently evaluated against invasive methods, but the present study included only 33 children with a biopsy-proven *H pylori* status (100).

So far, only the EIA based on monoclonal antibodies has achieved the accuracy of the UBT, which is considered the reference standard of the noninvasive tests (87,99,101–103). A systematic review and meta-analysis of the 8 studies directly comparing the polyclonal with the monoclonal EIA, including pediatric and adult patients, confirmed the significantly better performance with respect to sensitivity of the monoclonal test, both before and after therapy (104). No difference in accuracy has been observed between studies in adults and children, and within the pediatric studies, young age did not influence the performance of the tests (87,99,101–103).

So-called rapid or office-based fecal tests based on an immunochromatography using monoclonal antibodies have been evaluated in children (102,105). The accuracy was lower compared with EIA, even though the tests were based on the same antigens. Although these tests have improved over time, the problem of interobserver variability in weakly positive tests remains unresolved (102,106).

Additional ELISA tests for the detection of *H pylori* antigen in stool will be developed and evaluated in the near future. Therefore, this statement applies only to the tests that have been evaluated in pediatric populations and have shown an equal or better performance as the UBT or validated stool tests (87,104).

Recommendation 10 Tests based on the detection of antibodies (IgG, IgA) against *H pylori* in serum, whole blood, urine, and saliva are not reliable for use in the clinical setting.

Agree: 87% (A+53%, A 20%, A- 13%, D- 7%, D 7%). Grade of evidence: high.

Comment on Recommendation 10:

H pylori infection induces an early increase of specific IgM and a later and persistent increase of specific IgA and IgG antibodies. These antibodies can be detected in whole blood, serum, urine, and saliva (63). In general, serologic assays cannot be used on their own to perform the diagnosis of *H pylori* infection or to monitor the success of therapy because the sensitivity and specificity for detection of antibodies (IgG or IgA) against *H pylori* in children vary widely. Specific IgG may remain positive for several months or even years after the infection resolves. Thus, the tests cannot be used reliably for treatment outcomes.

Many tests based on the detection of antibodies are commercially available, easy to perform, and inexpensive. In spite of these advantages, they have not been recommended for clinical practice in pediatric patients by previous American, Canadian, or European consensus statements (6,14,15).

The main problems are age dependence, particularly with respect to sensitivity in younger children, and test-to-test variability. IgA-based tests detect only 20% to 50% of *H pylori*-infected children, and are not suitable for diagnosis. IgG-based tests offer a

better sensitivity than IgA-based tests, but the sensitivity of most tests is much lower when used in children compared with adults from the same geographic region. The use of cutoff values obtained in validation studies in adults results in a failure to detect a large proportion of infected children, especially in children younger than 6 to 8 years. Oliveira et al (107) used a second-generation EIA in comparison with biopsy-based methods and found a low sensitivity of 44% in children ages 2 to 6 years. Sensitivity increased to 77% in children ages 7 to 11 years and to 93% in adolescents, which is comparable with results in adults. When 2 IgG-based EIAs were applied to sera of 175 children with biopsy-proven *H pylori* status, a remarkable difference of sensitivity was observed, mainly in the younger age groups (108). Immunoblotting was found to be superior to serology for diagnosis of *H pylori* infection in children (109). In a European multicenter study, however, a more recent third-generation EIA seems to perform better, with sensitivity just less than the UBT (76). Tests based on the detection of *H pylori* antibodies in saliva or office-based tests on whole blood or serum display even worse performance characteristics than laboratory-based serologic EIAs. Therefore, these tests cannot be recommended in children of any age group (63).

Recommendation 11 It is recommended that clinicians wait at least 2 weeks after stopping PPI therapy and 4 weeks after stopping antibiotics to perform biopsy-based and noninvasive tests (UBT, stool test) for *H pylori*.

Agree: 100% (A+ 47%, A 40%, A- 13%). Grade of evidence: high.

Comment on Recommendation 11:

Studies in adults suggest that antibiotic or PPI therapy can cause false-negative test results because of a reduction in bacterial load without eradication of the bacterium (69,110,111). Therefore, it is recommended that testing be performed at least 4 weeks after completion of antibiotic treatment and 2 weeks following cessation of PPI therapy.

3.4. Who Should Be Treated?

Recommendation 12 In the presence of *H pylori*-positive PUD, eradication of the organism is recommended.

Agree: 100% (A+ 79%, A, 13%, A- 7%). Grade of evidence: high.

Comment on Recommendation 12:

Several meta-analyses in adults consistently demonstrate that eradication of *H pylori* in patients with PUD significantly reduces the relapse rate for ulcer disease and for recurrent bleeding ulcers (112,113). Previous pediatric studies in children with PUD indicated that the relapse rate is high without treatment of *H pylori* infection (114). Only 1 randomized controlled pediatric trial in *H pylori*-infected children with PUD (n = 106) has been published. This trial compared the eradication rate of *H pylori* and the cure rate of PUD with 3 different treatment regimens, but did not report the recurrence of ulcer or bleeding ulcer in those who failed bacterial eradication (115). Although there are differences in the etiologies and clinical presentation and frequency of PUD in children compared with adults (1,116), it can be assumed that recurrence of *H pylori*-related PUD can be prevented in children by eradication of the infection. Therefore, eradication of the infection is recommended in a child with *H pylori* infection and PUD. The indication applies also for healed ulcers or a history of PUD.

Recommendation 13 When *H pylori* infection is detected by biopsy-based methods in the absence of PUD, *H pylori* treatment may be considered.

Agree: 79% (A+ 29%, A 50%, D- 21%). Grade of evidence: low.

Comment on Recommendation 13:

The finding of *H pylori*-associated gastritis in the absence of PUD during diagnostic endoscopy poses a dilemma for the endoscopist (see comment for recommendations 1, 2, and 3). As outlined in the comments for recommendations 1 and 2, there is inadequate evidence supporting a causal relation between *H pylori* gastritis and abdominal symptoms in the absence of ulcer disease. Therefore, eradication of the organism in the absence of ulcers may not result in improvement of symptoms. As reviewed in the comment for recommendation 3, *H pylori* is a risk factor for the development of gastric malignancies; however, only a fraction of infected individuals develop cancer. The carcinogenic risk is modified by strain-specific bacterial factors, host responses, and/or specific host-microbe interactions. (117). Current evidence suggests that in high-risk populations such as in China, the eradication of *H pylori* may have the potential to decrease the risk of gastric cancer in a subset of individuals without precancerous lesions (39). Prospective intervention trials are of variable quality and results may not be generalizable from 1 population to another. As noted in the comment to recommendation 12, eradication of *H pylori* can prevent recurrence of PUD. In adults with nonulcer dyspepsia, eradication of *H pylori* may reduce the development of peptic ulcers (118). A potential benefit of chronic infection with certain *H pylori* strains cannot be excluded (119). Therefore, the decision to treat *H pylori*-associated gastritis without duodenal or gastric ulcer is subject to the judgment of the clinician and deliberations with the patient and family, taking into consideration the potential risks and benefits of the treatment in the individual patient.

Recommendation 14 A “test and treat” strategy is not recommended in children.

Agree: 80% (A+ 47%, A 20%, A- 13%, D- 13%, D 7%). Grade of evidence: moderate.

Comment on Recommendation 14:

The primary goal of testing is to diagnose the cause of clinical symptoms. By definition, a “test and treat” strategy (the detection of the presence of *H pylori* infection by a noninvasive test followed by treatment in the case of a positive test) will not provide this information in children (see comments on recommendations 1 and 2). Therefore, in contrast to current guidelines for adults (8,120), current evidence does not support this practice in children.

3.5. Which Treatment Should Be Applied in Which Situation?

Recommendation 15 In children who are infected with *H pylori* and whose first-degree relative has gastric cancer, treatment can be offered.

Agree: 93% (A+ 20%, A 47%, A- 27%, D+ 6%). Grade of evidence: low.

Comment on Recommendation 15:

Please refer to the comment on recommendation 3.

Recommendation 16 Surveillance of antibiotic resistance rates of *H pylori* strains in children and adolescents is recommended in different countries and geographic areas.

Agree: 100% (A+ 60%, A 20%, A- 20%). Grade of evidence: not applicable.

Comment on Recommendation 16:

Several European studies have documented high resistance rates to clarithromycin and metronidazole in pediatric and adult populations (1,121–123). Increasing rates of primary clarithromycin resistance have been reported from several countries (124–126). A prospective US multicenter study in adults and children also documented similar high resistance rates (127). In 2 small studies from the United States (Michigan and West Virginia), a high proportion of isolates were resistant to clarithromycin (128,129). Antibiotic resistance is an important factor in treatment success (130). Indeed, eradication rates in children treated with standard therapy are also decreasing over time, in part related to increased antibiotic resistance. *H pylori* antibiotic susceptibility data are not available for most geographic regions. Therefore, it is recommended that continuous surveillance of resistance rates be undertaken to effectively guide initial empiric therapy with the aim of improving treatment outcomes.

Recommendation 17 First-line eradication regimens are the following: triple therapy with a PPI + amoxicillin + imidazole; or PPI + amoxicillin + clarithromycin; or bismuth salts + amoxicillin + imidazole; or sequential therapy.

Agree: 100% (A+ 36%, A 40%, A- 14%). Grade of evidence: moderate.

Recommendation 18 Antibiotic susceptibility testing for clarithromycin is recommended before initial clarithromycin-based triple therapy in areas/populations with a known high resistance rate (>20%) of *H pylori* to clarithromycin.

Agree: 93% (A+ 33%, A 40%, A- 20%, D- 7%). Grade of evidence: moderate.

Recommendation 19 It is recommended that the duration of triple therapy be 7 to 14 days. Costs, compliance, and adverse effects should be taken into account.

Agree: 93% (A+ 27%, A 40%, A- 27%, D- 6%). Grade of evidence: moderate.

Comment on Recommendations 17–19:

The goal of treatment is at least a 90% eradication rate on a per-protocol basis at the first attempt. A high initial eradication rate will prevent the development of antibiotic resistance and spread of resistant *H pylori* strains in the population. For individual patients, a high initial success rate will reduce the need for further treatments and procedures, including endoscopies.

The combination of 2 antibiotics and a PPI has been the recommended first-line therapy since the first published pediatric guidelines (6,14,15). Studies comparing the various treatment options in the pediatric population remain limited. In 2000, Oderda et al (131) performed a systematic review of the published eradication treatment studies in children. Because of the marked heterogeneity and the limited number of well-designed studies, it was difficult to make definitive recommendations. In 2001, the first randomized double-blind trial comparing dual therapy of amoxicillin and clarithromycin with triple therapy including omeprazole in children confirmed that in intention-to-treat analysis, triple therapy was far superior to dual therapy with eradication rates of 74.2% versus 9.4% (132).

A recent meta-analysis of eradication treatment efficacy in children concluded that, in general, the methodological quality of the studies was poor and that additional well-designed randomized

trials are needed (7). Thus, current recommendations remain mainly extrapolated from adult studies.

Recent data indicate a falling rate of *H pylori* eradication in response to treatment. For example, the European pediatric treatment registry reported results from the use of 27 different regimens in 518 children with *H pylori* (133). The overall eradication rate was 65.6%, lower than previously reported, but was higher in children with peptic ulcers (79.7%). One potential reason for this decline is antibiotic resistance (134). Based on the negative effect of antibiotic resistance on treatment outcomes, the rates of resistance in the area where the child lives or comes from should be taken into account when deciding on the initial therapeutic regimen for eradication (1).

Clarithromycin resistance adversely affects eradication rates in children (135,136). Studies in children addressing the role of susceptibility testing to target initial therapy are limited; however, 3 studies in children suggest that tailoring therapy based on antibiotic susceptibility testing can enhance eradication rates (137–139). In a study of 58 German children, clarithromycin and metronidazole susceptibility testing was used to guide standard triple therapy and resulted in a high eradication rate of 93% (137). An earlier study of 2 consecutive groups of 75 *H pylori*-infected children treated with either triple therapy, including amoxicillin and clarithromycin (group 1), or antibiotic therapy, guided by susceptibility testing (group 2), demonstrated enhanced eradication in the group with susceptibility-guided therapy (93% vs 81%) (138). Therefore, clarithromycin-based triple therapy can only be recommended as first-line therapy if susceptibility testing in the individual patient revealed a clarithromycin-susceptible strain or if the clarithromycin resistance rate in this area is known to be low. In the absence of these conditions, clarithromycin-based triple therapy cannot be recommended as first-line therapy.

Declining eradication rates with these standard triple regimens have led to the development of alternate treatment options (134). Sequential therapy involves dual therapy with a PPI and amoxicillin for 5 days followed sequentially by 5 days of triple therapy (a PPI with clarithromycin and metronidazole/tinidazole). In fact, this regimen can be considered as quadruple therapy provided in a sequential manner. It is speculated that the initial use of amoxicillin reduces the bacterial load and provides protection against clarithromycin resistance. In 2005, 74 children were randomized to receive either sequential treatment (omeprazole + amoxicillin for 5 days, followed by omeprazole + clarithromycin + tinidazole for another 5 days) or triple therapy for 1 week (140). Successful eradication was achieved in 97.3% of children receiving sequential therapy compared with 75.7% on standard triple therapy. In a subsequent study evaluating adjunctive probiotic supplementation, eradication of 82.5% was obtained from a group of 40 children receiving sequential therapy (141). Based on these studies suggesting that sequential therapy is at least as effective as standard therapy, sequential therapy was recommended as a first-line treatment option. It is important to note that the data in children are mostly limited to Italian studies, and therefore additional studies in North America and different European countries are needed to confirm that the findings apply to other locations. Furthermore, clarithromycin resistance has a negative effect on eradication success even with this regimen, although less so compared with standard triple therapy (136,142,143).

Bismuth-based triple therapy is also recommended as an alternate first-line therapy. Although there are no well-designed randomized studies directly comparing this regimen with the alternate recommended first-line therapies, in a study reported by the European pediatric treatment registry, bismuth-containing triple therapies were more efficacious than PPI-containing ones (77% versus 64%) when used as first-line treatment (133).

TABLE 1. First-line treatment recommendations for *H pylori* eradication in children

PPI (1–2 mg · kg ⁻¹ · day ⁻¹) + amoxicillin (50 mg · kg ⁻¹ · day ⁻¹) + metronidazole (20 mg kg day)*
PPI (1–2 mg · kg ⁻¹ · day ⁻¹) + amoxicillin (50 mg · kg ⁻¹ · day ⁻¹) + clarithromycin (20 mg · kg ⁻¹ · day ⁻¹)*
Bismuth salts (bismuth subsalicylate or subcitrate 8 mg · kg ⁻¹ · day ⁻¹) + amoxicillin (50 mg · kg ⁻¹ · day ⁻¹) + metronidazole (20 mg · kg ⁻¹ · day ⁻¹)*
PPI (1–2 mg · kg ⁻¹ · day ⁻¹) + amoxicillin (50 mg · kg ⁻¹ · day ⁻¹) for 5 days then PPI (1–2 mg · kg ⁻¹ · day ⁻¹) + clarithromycin (20 mg · kg ⁻¹ · day ⁻¹) + metronidazole (20 mg · kg ⁻¹ · day ⁻¹) for 5 days

Maximum daily dose for amoxicillin 2000 mg, for metronidazole 1000 mg, for clarithromycin 1000 mg/day. PPI = proton pump inhibitor.

* Administered twice daily for 10 to 14 days.

In addition, bismuth-based triple therapy may be less costly than the other options; however, concerns regarding the palatability of bismuth potentially affecting adherence should also be considered.

Conflicting data exist regarding the benefit of longer duration of therapy for first-line regimens in adults (142,144). A systematic review of therapy in children found no benefit from longer duration of therapy (131). In contrast, a recent meta-analysis of studies in children suggested that longer duration of therapy was associated with improved eradication rates (7). Similarly, a meta-analysis comparing sequential therapy with standard triple therapy showed higher eradication rates with longer duration of triple therapy up to 14 days (142). Therefore, based on these data, recommended duration of therapy is 7 to 14 days, taking into consideration cost, compliance, and side effects. Suggested doses are given in Table 1.

Recommendation 20 A reliable noninvasive test for eradication is recommended at least 4 to 8 weeks following completion of therapy.

Agree: 93% (A + 53%, A 27%, A– 13%, D– 7%). Grade of evidence: low.

Comment on Recommendation 20:

Even when children become asymptomatic after treatment, it is recommended that the success of treatment regardless of the initial endoscopic findings be evaluated. The absence of symptoms does not necessarily mean the infection has been eradicated (30). Particularly in children who had PUD, persistence of infection would warrant additional treatment. Reliable tests to monitor successful eradication include the ¹³C-UBT and a monoclonal ELISA for detection of *H pylori* antigen in stool. A follow-up endoscopy is not routinely indicated unless other causes of ulceration (eg, eosinophilic gastroenteropathy, Crohn disease) are suspected or if biopsies are needed for culture and antibiotic susceptibility testing.

Recommendation 21 If treatment has failed, there are 3 options recommended:

1. EGD, with culture and susceptibility testing, including alternate antibiotics if not performed before guide therapy.
2. FISH on previous paraffin-embedded biopsies if clarithromycin susceptibility testing has not been performed before guide therapy.

3. Modify therapy by adding an antibiotic, using different antibiotics, adding bismuth, and/or increasing dose and/or duration of therapy.

Agree: 100% (A + 29%, A 43%, A– 28%) Grade of evidence: not applicable.

Comment on Recommendation 21:

Primary antibiotic resistance adversely affects treatment outcomes (see comment for recommendation 20). In addition, a 12-year observational study from Belgium demonstrated secondary resistance following treatment in 39 of 87 strains obtained from children who had failed initial therapy (122). The present study suggests that development of secondary antibiotic resistance may be common in children. Thus, if possible, primary culture with antibiotic sensitivity testing should be performed to guide second-line therapy in an *H pylori*-infected child who has failed initial therapy.

If primary culture and sensitivity testing is not available, then the choice of second-line therapy must take into account the initial therapy administered and avoid readministering an antibiotic that was previously provided (145). Another option available at some centers is FISH to detect primary clarithromycin resistance on previously obtained biopsies (65,129,146). Clarithromycin should only be used as part of second-line therapy if the strain is found to be sensitive.

If it is not possible to perform a primary culture, then the following therapeutic regimens are suggested as second-line or salvage therapy.

- Quadruple therapy: PPI + metronidazole + amoxicillin + bismuth. Quadruple therapy is the recommended second-line therapy in most guidelines (8,15); however, this regimen is complicated to administer. Furthermore, bismuth salts are not universally available.
- Triple therapy: PPI + levofloxacin (moxifloxacin) + amoxicillin. Evaluation of regimens using fluoroquinolones, including levofloxacin, as second-line therapy in children is limited. In adult studies, this regimen appears to be effective. In a recent meta-analysis of studies in adults (147), triple therapy with levofloxacin appeared to be as efficacious as quadruple therapy for second-line treatment; however, there are concerns regarding increasing rates of quinolone resistance (145). Therefore, this regimen should not be used if the child has received fluoroquinolones previously. Although the studies on the ideal duration of therapy for second-line treatment are not conclusive, a longer duration of therapy of up to 14 days is recommended.

4. CONCLUSIONS

These clinical guidelines represent updated, best-available evidence, and expert opinion regarding the management of *H pylori* infection in children in Europe and North America developed through a rigorous standardized process. The goal of these recommendations is to improve the care of children and adolescents with *H pylori* infection. As the clinical implications of *H pylori* infection in the pediatric setting continue to evolve, these guidelines will need to be updated.

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