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Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children

Sibylle Koletzko[1]*, Nicola L. Jones[2]*, Karen J. Goodman[3], Benjamin Gold[4], Marion Rowland[5], Samy Cadranel[6], Sonny Chong[7], Richard B. Colletti[8], Thomas Casswall[9], Yoram Elitsur[10], Jeannette Guarner[11], Nicolas Kalach[12], Armando Madrazo[13], Francis Megraud[14], Giuseppina Oderda[15] on behalf of the *H. pylori* working groups of ESPGHAN and NASPGHAN

[1]Dr. v. Haunersches Kinderspital, Ludwig Maximilians University, Munich, Germany,
[2] Division of GI/ Hepatology and Nutrition, SickKids, University of Toronto, Canada
[3] Department of Medicine, University of Alberta, Edmonton, Canada.
[4] Children's Center for Digestive Healthcare, Atlanta, USA
[5] Children's Research Centre, Our lady's Hospital for Sick Children, Crumlin, Ireland
[6] Queen Fabiola Children's Hospital, Brussels, Belgium
[7]Queen Mary's Hospital for Children, Carshalton, Surrey, UK.
[8]Department of Pediatrics, University of Vermont, Burlington, VT, USA
[9]Division of Paediatrics, Karolinska University Hospital, Stockholm, Sweden
[10] Department of Pediatrics, Marshall University, Huntington, WV, USA
[11] Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA
[12] St Antoine Pediatric Clinic, Faculté Libre de Médecine, Lille-France.
[13] Hospital de Pediatria, Centro Medico Nacional Siglo XXI, Mexico City, Mexico
[14] Laboratoire de Bactériologie, Hôpital Pellegrin,Bordeaux, France
[15] Scienze Mediche, Clinica Pediatrica, Universita degli Studi di Novara, Novarra, Italy

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Author for correspondence and reprint request:

Professor Dr. Sibylle Koletzko, MD
Dr. v. Haunersches Kinderspital
Ludwig-Maximilians-University of Munich
Lindwurmstraße 4
D – 80337 München
Germany

Tel. +49 - 89 - 5160 7854
Fax +49 - 89 - 5160 7898
E-mail: sibylle.koletzko@med.uni-muenchen.de

*Sibylle Koletzko and Nicola Jones contributed equally to the manuscript

Abstract

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 in order to develop updated recommendations for children in North American and Europe in the following four areas: who to test, how to test, who to treat and how to treat. This document outlines the methods employed, the 21 recommendations generated by the joint committee and discussion regarding the supporting evidence and the rationale for the recommendations.

Synopsis

The current recommendations for managing *H. 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, where other causes have been ruled out, testing for *H. pylori* infection may be considered. 5) There is currently 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 ITP, and short stature. 6) For the diagnosis of *H. pylori* infection during esophagogastroduodenoscopy (EGD), it is recommended to obtain gastric biopsies (antrum and corpus) for histopathology. 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 on a positive culture. 8) The ^{13}C-urea breath (UBT) test is a reliable non-invasive test to determine whether *H. pylori* has been eradicated. 9) A validated ELISA test for detection of *H. pylori* antigen in stool is a reliable non-invasive 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 to wait at least 2 weeks after stopping PPI therapy and 4 weeks after stopping antibiotics to perform biopsy based and non-invasive tests (UBT, stool test) for *H. pylori*. 12) In the presence of *H. pylori*-positive pep-

tic ulcer disease, eradication of the organism is recommended. 13) When *H. pylori* infection is detected by biopsy based methods in the absence of peptic ulcer disease, *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: triple therapy with a proton pump inhibitor+ amoxicillin+ clarithromyin or an imidazole; or bismuth salts + amoxicillin + an imidazole; or sequential therapy. 18) Antibiotic susceptibility testing for clarithromycin is recommended prior to initial clarithromycin-based triple therapy in areas/populations with a known high resistance rate (>20%) of *H. pylori* strains in children. 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 non-invasive test for eradication is recommended at least 4 to 8 weeks following completion of therapy. 21) If treatment has failed there are 3 options recommended: a) EGD, with culture and susceptibility testing including alternative antibiotics, if not performed before to guide therapy; b) fluorescence in situ hybridization (FISH) on previous paraffin embedded biopsies if clarithromycin susceptibility testing has not been performed before to guide therapy; c) modification of therapy by adding an antibiotic, using different antibiotics, adding bismuth and/or increasing the dose and/or duration of therapy

Scope and Purpose

1.1. Introduction and aims

Children differ from adults with respect to *H. pylori* infection on 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 to adults, peptic ulcer disease is found less often in infected children undergoing upper endoscopy. In a large European multicenter study including 1233 symptomatic children with *H. pylori* infection, peptic ulcer disease was diagnosed in less than 5% of children below 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 are different. Children are often unable to give precise descriptions of the location and the character of the pain (4;5). Some disorders, like idiopathic thrombocytopenic purpura, which have been associated with *H. pylori* infection in adults, do not show a relation in children, probably due to 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. Very 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 very common in certain geographic areas like

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 corresponding impact on health care resources in industrialized compared to 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 for other continents, particularly developing countries with a high *H. pylori* infection rate in children and with very 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 participants

In 2000, the Pediatric Task Force of the *H. pylori* study group of ESPGHAN had published consensus statements on *H. pylori* infection in children (14). Shortly thereafter, a working group of 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 participants from Canada, the US 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 in order to have the same recommendations for North America and Europe.

The following four areas were identified and covered by four subgroups which formulated the critical questions for each area.

- Who should be tested? (Differentiating between screening, surveillance and clinically-based testing)

- What tests should be used?
- Who should be treated?
- What treatment regimens are most appropriate?

Each society assigned one chair (Benjamin Gold for NASPGHAN and Sibylle Koletzko for ESPGHAN). At least two members from each society were assigned to the subgroups for the four 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 participants 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 the years 2000 through August 2007. The search included publications of all types presenting or reviewing data on *H. pylori* in subjects under 20 years of age, selecting on MeSH terms as listed in Table 1, with no language restrictions. The search identified 1,979 unique publications and an additional 63 publications were generated from the citations of relevant reviews. Of these 2,042 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 publications that did not present relevant data in an English abstract; 19 non-systematic reviews. The total number of selected papers was 490, including 80 reviews. The papers were grouped according to the review fo-

cus 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.

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

In addition, within each subgroup, the members were asked to search the literature with respect to their topics in order 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 sources. Grading 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 four subgroups presented the statements during the annual meeting of the ESPGHAN Pediatric Task Force meeting 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 two iterations of each of the consensus statements. Statements were revised based on feedback provided from the participants, 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 votes were anonymous. A six-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 disagree strongly (D+). Agreement with the statement (the sum of voting for A+, A, or A–) by three-quarters (i.e. = 75%) of the voting members was defined *a priori* as consensus. The level of agreement in the final vote is given 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:

- High: Further research is unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Very low: Any estimate of effect is uncertain.

The designation 'not applicable' was employed for situations where 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 USA, 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 to the recorded electronic voting slides. The statements were presented at the World Congress of Pediatric Gastroenterology in Iguaçu 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 two epidemiologists Karen Goodman and Marion Rowland. Due to 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 September 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 to the version presented in August 2008 at the World congress. The new literature was implemented in the final draft, which then circulated to all members of the consensus group and their input was worked into the manuscript.

3. Results

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 one, and others were 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 given for every statement.

3.1. 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 like 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 performed endoscopy in children with epigastric pain and symptoms suggestive of gastroesophageal reflux disease (17). After treatment, improvement of epigastric pain correlated with improvement of reflux disease, but was not related to *H. pylori* eradication. Abdominal complaints might also be part of a functional gastrointestinal disorder (18). Children below 8 years of age, or even as old as 12 years, may not be able to give accurate descriptions of the degree, character and location of pain (4). Whether *H. pylori* gastritis causes abdominal pain in the absence of peptic ulcer disease is still debatable. Several studies from the 1990s applied different non-invasive 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 – 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 relationship between *H. pylori* infection and abdominal pain. In a study of 1221 children from Germany, Bode et al identified in a multivariable logistic regression analysis that social and familial

factors (single parent household, family history of peptic ulcer disease or functional pain) were significantly associated with abdominal pain, but not the *H. pylori* status of the child, as assessed by the 13C-urea breath test (22). Tindberg et al. reported no significant association of recurrent abdominal pain with *H. pylori* infection in 695 school children between 10 and 12 years of age (23). In fact, an inverse relation was noted for *H. pylori* positivity and the occurrence of any abdominal pain after adjustment for selected possible confounders (OR 0.5, 95% 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 very short follow up period of a few weeks only (27). These uncontrolled intervention studies provide very weak evidence of a causal relationship between *H. pylori* infection and abdominal pain, particularly because functional abdominal pain resolves in 30 – 70% of patients by 2 – 8 weeks after diagnosis accompanied by reassurance of the child and the parents (28;29).

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

In summary, at present there is inadequate evidence supporting a causal relationship 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 work up 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 relationship 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 two decades of life. While *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 – 3 in *H. pylori* infected individuals. The risk is further increased if only non-cardia carcinomas are considered. However, the risk of gastric cancer depends not only on the infection itself, but is strongly modified by the presence of bacterial virulence factors (35), and other factors such as the genetic make up 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 intervention trial in adults, subgroup analysis suggested that eradication may be beneficial in persons without precancerous lesions (39). However, the time point for an effective intervention, and therefore screening strategy, is not yet clear (40). In previous studies of

patients with gastric cancer below 45 years of age, *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 shares not only 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 non-invasive test or with biopsy-based methods, treatment 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 as a marker of *H. pylori* independency, but this marker is found in only half of the MALT lymphomas 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 where 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, where 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 non-invasive diagnostic tests are not able to find the cause and/or if the iron deficiency is refractory to oral iron therapy, 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). Since 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 relationship. The first randomized placebo-controlled study included only 22 *H. pylori* infected pediatric patients randomized into three treatment arms: iron only,

eradication therapy only, or both (48). Eradication therapy increased hemoglobin levels even without iron substitution while iron therapy alone did not. In a study from Turkey of 140 children between 6 and 16 years of age, 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 a recent intervention trial in children living in Alaska (50). 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 currently 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 ITP, 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 relationship for these associations in children is not compelling (51-62)

3.2. Which diagnostic test should be applied in which situation?

Numerous tests that detect *H. pylori* are available. They are divided into non-invasive and invasive tests. Invasive tests require gastric tissue for detecting the organism and include cul-

ture, rapid urease test, histopathology, PCR, and fluorescence in situ hybridization (FISH). (63). Non-invasive 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 ^{13}C-urea breath test (UBT). The sensitivities and specificities obtained in different pediatric studies have been reviewed by the four members of the guideline subgroup and recently published (63).

All diagnostic tests are generally feasible in children. However, tests requiring patient cooperation, like 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, pre-school and school-aged 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 which 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 two tests are needed to define the *H. pylori* infection status. For non-invasive 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 two or three 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 non-invasive tests, should be the reference.

All tests are suitable for the detection of infection prior to 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 proton pump inhibitors (PPI), should be discontinued prior to testing for at least 4 weeks 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 to obtain gastric biopsies (antrum and corpus) for histopathology.

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 plus positive rapid urease test, or on a positive culture.

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

Comment on recommendations 6 and 7

For histology two biopsies should be obtained from both the antrum and the corpus, and the findings should be reported according to the updated Sydney classification (70). Since 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, since 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 *H. heilmannii* infection (72).

In children with suspected *H. pylori* infection it is highly recommended to take not only biopsies for histopathology, but also one 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 one diagnostic test is based on the sensitivity results of invasive tests, which ranges from 66 – 100% for histology, and from 75 – 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 two 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, a non-invasive test (UBT or stool test) should be applied. One exception from the rule of two concordant test results is a positive culture, which is 100% specific and therefore in itself is sufficient to diagnose *H. pylori* infection. Another exception is the presence of a bleeding peptic ulcer, in which case one 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 peptic ulcer disease clearly indicated that active bleeding decreases the sensitivity of invasive diagnostic tests, but the specificity is very high (73).

Recommendation 8: The 13C-urea breath test is a reliable non-invasive 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 cut off levels, this test has a high accuracy, sensitivity and specificity (63;64). When the UBT is performed, the patient should have an empty stomach prior to 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 given to the child in order 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 less than 6 years of age compared to older children (74;76;80-84). False positive results can also occur in young children due to the lower distribution volume and a different CO_2 production rate, which can be adjusted for (85).

Recommendation 9: A validated ELISA for detection of *H. pylori* antigen in stool is a reliable non-invasive 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 non-invasive method that seems very suitable for both clinical use and epidemiological studies. Several methods are available for the detection of *H. pylori* antigen in stool: 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 five days, nor freezing for months or even years seems to influence the accuracy of the stool tests (86-89). In most countries an enzyme immunoassay (EIA) would be less costly than the UBT. In addition, the EIA stool test is the only diagnostic non-invasive test which has not shown an age dependency on the accuracy of the test results (64;87). Therefore, validation studies in adults may be extrapolated to children.

The first commercial EIA tests to detect *H. pylori* antigen in stool was the Premier Platinum HpSA® (Meridian Diagnostics, Cincinatti, USA). This test is based on polyclonal antibodies. There is a wide range for sensitivity and specificity of the test in children, both pre-treatment (86;90-98) and post-treatment (89;91;92;95). However, testing the same stool samples with different production lots of the polyclonal test indicated inter-assay 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, Italy) was recently evaluated against invasive methods, but this 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 non-invasive 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 immunochromography using monoclonal antibodies have been evaluated in children (102;105). However, the accuracy was lower compared to 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 will only apply to the tests which 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 varies 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 20–50 % 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 cut-off values obtained in validation studies in adults results in a failure to detect a large proportion of infected children, especially in children below the age of 6–8 years. Oliveira *et al*. used a second-generation EIA in comparison with biopsy-based methods and found a low sensitivity of 44% in children aged 2–6 years (107). Sensitivity increased to 77% in children aged 7–11 years, and to 93 % in adolescents, which is comparable with results in adults. When two 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). However, in a European multicenter study a more recent third generation EIA seem to perform better, with sensitivity just below 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 enzyme immunoassays. Therefore, these tests cannot be recommended in children of any age group (63).

Recommendation 11: It is recommended to wait at least 2 weeks after stopping PPI therapy and 4 weeks after stopping antibiotics to perform biopsy based and non-invasive 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 proton pump inhibitor therapy can cause false negative test results due to a reduction in bacterial load without eradication of the bacterium (69;110;111). Therefore, it is recommended that testing be performed at least four weeks after completion of antibiotic treatment and two weeks following cessation of PPI therapy.

Recommendation 12: In the presence of *H. pylori*-positive peptic ulcer disease, 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 peptic ulcer disease (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 one randomized controlled pediatric trial in *H. pylori* infected children with PUD (n=106) has been published. However, this trial compared the eradication rate of *H. pylori* and the cure rate of PUD with three 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 to 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 peptic ulcer disease, *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 peptic ulcer disease during diagnostic endoscopy poses a dilemma for the endoscopist (see comment for recommendations 1, 2 and 3). As outlined in the comments for recommendation 1 and 2, there is inadequate evidence supporting a causal relationship 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 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 one population to another. As noted in the comment to recommendation 12, eradication of *H. pylori* can prevent recurrence of peptic ulcer disease. 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 can not 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 non-invasive 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.

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 the 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 two small studies from the US (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. Currently, *H. pylori* antibiotic susceptibility data is not available for most geographic regions. Therefore, it is recommended that continuous surveillance of resistance rates be undertaken in order to effectively guide initial empiric therapy with the aim of improving treatment outcomes.

Recommendation 17: First line eradication regimens are:

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 prior to initial clarithromycin-based triple therapy in areas/populations with known high resistance rate (>20%) of *H. pylori* strains in children.

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 spreading 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 two antibiotics and a proton pump inhibitor has been the recommended first line therapy since the first published pediatric guidelines (14)(15)(6). 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. Due to 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 ome -

prazole (OAC) 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 indicates 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, three 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 two 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% versus 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 metronidazol/tinidazol). In fact, this regimen can be considered as quadruple therapy given in 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 plus amoxicillin for 5 days, followed by omeprazole plus clarithromycin plus tinidazole for another 5 days) or triple therapy (OAM) 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. However 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 impact 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). 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 exists regarding the benefit of longer duration of therapy for first line regimens in adults (Luther J 2010; Gatta 2009). A systematic review of therapy in children found no benefit from longer duration of therapy (ODerda 2000). In contrast a recent meta-analysis of studies in children suggested that longer duration of therapy was associated with improved eradication rates (Khurana R 2007). 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 (Gatta 2009). Therefore based on this 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 non-invasive 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 to evaluate the success of treatment regardless of the initial endoscopic findings. 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 ^{13}C-UBT and a monoclononal ELISA for detection of *H. pylori* antigen in stool. A follow up endoscopy is not routinely indicated unless other

causes of ulceration (such as eosinophilic gastroenteropathy, Crohn's 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:

a) EGD, with culture and susceptibility testing, including alternate antibiotics if not performed before to guide therapy;

b) Fluorescence in situ hybridization (FISH) on previous paraffin embedded biopsies if clarithromycin susceptibility testing has not been performed before to guide therapy;

c) 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 twelve year observational study from Belgium demonstrated secondary resistance following treatment in 39 of 87 strains obtained from children who had failed initial therapy (122). This 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, the choice of second line therapy must take into account the initial therapy administered and avoid readministering an antibiotic that was previously given (144). Another option available at some centers is fluorescence in situ hybridization (FISH) to detect primary clarithromycin resistance on previously obtained

biopsies (65; 129; 145;). 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 (146), 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 (144). 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.

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 implica-

tions of *H. pylori* infection in the pediatric setting continue to evolve, these guidelines will need to be updated.

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Fig. 1 Proposed algorithm how to treat *H. pylori* infection in pediatric patients. EGD = Esophagogastroduodenoscopy; PUD = Peptic ulcer disease, CLA = Clarithromycin. * 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).

Table 1: First line treatment recommendations for *H. pylori* eradication in children (PPI = Proton pump inhibitor)

PPI (1-2 mg/kg/day) + amoxicillin (50 mg/kg/day)+ metronidazole (20 mg/kg/day)*
PPI (1-2 mg/kg/day) + amoxicillin (50 mg/kg/day) + clarithromycin (20 mg/kg/day)*
Bismuth salts (bismuth subsalicylate or subcitrate 8 mg/kg /day) + amoxicillin (50 mg/kg/day) + metronidazole (20 mg/kg/day)*
PPI (1-2 mg/kg/day) + amoxicillin (50 mg/kg/day) for 5 days then PPI (1-2 mg/kg/day) + clarithromycin (20 mg/kg/day) + metronidazole (20 mg/kg/day) for 5 days
** administered twice-daily for 10 to 14 days*
Maximum daily dose for amoxicillin 2000 mg, for metronidazole: 1000 mg, for clarithromycin: 1000 mg/d

Figure 1