REVISTA CHILENA DE PEDIATRÍA
www.revistachilenadepediatria.cl
www.scielo.cl

Rev Chil Pediatr. 2020;91(5):809-827
DOI: 10.32641/rchped.vi915.2579

SCIENTIFIC SOCIETY RECOMMENDATION

Adaptation to the reality of Latin America of the NASPGHAN/ESPGHAN 2016 Guidelines on the Diagnosis, Prevention and Treatment of *Helicobacter pylori* Infection in Pediatrics

Adaptación a la realidad de Latinoamérica de la Guía Clínica NASPGHAN/ESPGHAN 2016 sobre Diagnóstico, Prevención y Tratamiento de Infección por *Helicobacter pylori* en Pediatría

Paul R. Harris[a], Otto Gerardo Calderón-Guerrero[b], José Fernando Vera-Chamorro[c], Yalda Lucero[d,e], Margarita Vásquez[f], Silvio Kazuo Ogata[g], Diana Angulo[h], Armando Madrazo[i], José Gonzáles[j], Anelsy Rivero[k], Juan Cristóbal Gana[a], a nombre de la Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición Pediátrica (SLAGHNP/LASPGHAN).

[a]Departamento de Gastroenterología y Nutrición Pediátrica, Escuela de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile
[b]Universidad del Valle. Cali, Colombia
[c]Sección de Gastroenterología, Hepatología y Nutrición Pediátrica, Hospital Universitario Fundación Santa Fe de Bogotá y Universidad de los Andes. Colombia
[d]Programa de Microbiología y Micología, Instituto de Ciencias Biomédicas (ICBM), y Departamento de Pediatría Norte, Hospital Roberto del Río, Facultad de Medicina, Universidad de Chile. Santiago, Chile
[e]Unidad de Gastroenterología Infantil, Departamento de Pediatría, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo. Santiago, Chile
[f]Hospital Universitario Pediátrico Agustín Zubillaga. Venezuela
[g]Disciplina de Gastroenterología Pediátrica, Universidade Federal de São Paulo - Escola Paulista de Medicina. Brasil
[h]Hospital Nacional Docente Madre Niño San Bartolomé y Universidad Científica del Sur. Lima, Perú
[i]Universidad Nacional Autónoma de México. México
[j]Instituto Nacional de Salud del Niño Breña. Lima, Perú
[k]Hospital Central de Valencia. Estado Carabobo, Venezuela

Received: May 27, 2020; Approved: June 22, 2020

What do we know about the subject matter of this study?

There are multiple recent Clinical Guidelines for diagnosis and management of H. pylori infection in adult medicine, from the U.S., Europe, LA and Asia Pacific. In pediatrics the joint Clinical Guidelines NASPGHAN and ESPGHAN 2011, were updated on 2016, but questions have arisen from LA regarding applicability of the same and in particular with some situations specifics related to the prevention of gastric cancer.

What does this study contribute to what is already known?

The Latin American Society of Gastroenterology, Hepatology and Pediatric Nutrition (SLAGHNP/LASPGHAN) formed a study group with experts from 6 countries to analyze the current NASPGHAN/ ESPGHAN 2016 guidelines and offers an analysis document based on current data and reality from Latin America.

Correspondence:
Paul R. Harris
pharris@med.puc.cl

How to cite this article: Rev Chil Pediatr. 2020;91(5):809-827. DOI: 10.32641/rchped.v91i5.2579

Abstract

Introduction: The latest joint *H. pylori* NASPGHAN and ESPGHAN clinical guidelines published in 2016, contain 20 statements that have been questioned in practice regarding their applicability in Latin America (LA); in particular in relation to gastric cancer prevention. **Methods:** We conducted a critical analysis of the literature, with special emphasis on LA data and established the level of evidence and level of recommendation of the most controversial claims in the Joint Guidelines. Two rounds of voting were conducted according to the Delphi consensus technique and a Likert scale (from 0 to 4) was used to establish the "degree of agreement" among a panel of SLAGHNP experts. **Results:** There are few studies regarding diagnosis, treatment effectiveness and susceptibility to antibiotics of *H. pylori* in pediatric patients of LA. Based on these studies, extrapolations from adult studies, and the clinical experience of the participating expert panel, the following recommendations are made. We recommend taking biopsies for rapid urease and histology testing (and samples for culture or molecular techniques, when available) during upper endoscopy only if in case of confirmed *H. pylori* infection, eradication treatment will be indicated. We recommend that selected regional centers conduct antimicrobial sensitivity/resistance studies for *H. pylori* and thus act as reference centers for all LA. In case of failure to eradicate *H. pylori* with first-line treatment, we recommend empirical treatment with quadruple therapy with proton pump inhibitor, amoxicillin, metronidazole, and bismuth for 14 days. In case of eradication failure with the second line scheme, it is recommended to indicate an individualized treatment considering the age of the patient, the previously indicated scheme and the antibiotic sensitivity of the strain, which implies performing a new endoscopy with sample extraction for culture and antibiogram or molecular resistance study. In symptomatic children referred to endoscopy who have a history of first or second degree family members with gastric cancer, it is recommended to consider the search for *H. pylori* by direct technique during endoscopy (and eradicate it when detected). **Conclusions:** The evidence supports most of the general concepts of the NASPGHAN/ESPGHAN 2016 Guidelines, but it is necessary to adapt them to the reality of LA, with emphasis on the development of regional centers for the study of antibiotic sensitivity and to improve the correct selection of the eradication treatment. In symptomatic children with a family history of first or second degree gastric cancer, the search for and eradication of *H. pylori* should be considered.

Keywords:
H. pylori;
Rapid Urease Test;
Latin America;
C13 Urea Breath Test;
Fecal Antigen Test;
Gastric Cancer

Abbreviations	
Helicobacter pylori	*H. pylori*
Rapid Urease Test	RUT
Upper Gastrointestinal Endoscopy	UGE
Functional Gastrointestinal Disorders	FGIDs
Latin America	LA
Functional Abdominal Pain Disorder	FAPD
Urea Breath Test C13	UBT-C13
Stool antigen test	HpSAg
Proton pump inhibitors	PPI
Gastric Cancer	GC
Gastric Ulcer	GU
Duodenal Ulcer	DU
Gastroduodenal Ulcer	GDU
Nodular Gastropathy	NG
Polymerase Chain Reaction	PCR
Clarithromycin	CLA
Metronidazole	MET
Amoxicillin	AMO

Introduction

Helicobacter pylori (*H. pylori)* infection in Latin America (LA) continues to be a relevant problem due to its prevalence and the medical and social impact of its associated pathologies[1]. The study of this infection in LA has been led by adult specialists and with a predominant focus on the sequelae produced by the infection and particularly on the prevention of gastric cancer (GC), but it scarcely addresses issues specific to the pediatric population.

There are multiple recent Clinical Guidelines in adult medicine from the USA, Europe, LA and Asia Pacific[2-7]. In pediatrics the first attempts were led by the Canadian group studying *H. pylori*[8] and later by the joint NASPGHAN and ESPGHAN Clinical Guidelines of 2011, which were updated in 2016[9]. With the publication of the 20 statements of these guidelines (table 1), questions have risen from LA regarding their applicability and in particular with some specific situations related to GC prevention.

Therefore, the Latin American Society of Pediatric Gastroenterology, Hepatology and Nutrition (LAS-

PGHAN) has formed a study group with experts from 6 countries (Brazil, Chile, Colombia, Mexico, Peru and Venezuela) to analyze the current NASPGHAN/ESPGHAN 2016 guidelines (published in 2017) and offer a document of analysis based on current data and Latin American reality.

Methodology

First step

Based on the 20 statements contained in the NASPGHAN/ESPGHAN 2016 Guidelines, those that were feasible to evaluate/reconsider at the Latin American level were defined, and are presented in table 1. Each member of the panel (Study Group) identified statements individually and then selected by consensus those that should be evaluated for LA. In this way, the statements of interest in relation to diagnosis, prevention, and treatment of *H. pylori* infection in pediatrics were identified by consensus, following Delphi methodology[10], and with a panel of 10 experts plus a methodological advisor. Highly controversial statements were considered 2a, 4, 9a, 9b and 14; moderately controversial statements 2b, 11, 12, 15 and 16; and minimally or non-controversial statements were the following: 1, 2c, 3, 5a, 5b, 6, 7, 8, 10 and 13.

Second step

Once the statements to be evaluated were selected, a critical analysis of the literature was performed, with special emphasis on LA data, and the level of evidence and level of recommendation of the statement was established. One or two responsible people were assigned for each statement, and they were in charge of presenting it to the panel in a standard format (described below).

Levels of evidence and levels of recommendation

The evaluation of the quality of evidence supporting each statement was done in a descriptive manner, based on the type of study design, adapted from the recommendations made by the U.S. Preventive Services Task Force[11,12]. Evidence was stratified according to the design of each study (table 2). Each category represents a level of quality. Each level is ordered in decreasing order, so that randomized controlled trials and systematic reviews of randomized trials correspond to the highest quality of evidence; observational trials correspond to an intermediate level of evidence; pathophysiological trials and expert opinion correspond to the lowest quality of evidence. For each question we recommended describing the most relevant studies in terms of design and their results (with their respective confidence intervals and/or p-values). The recommendation level was established according to table 3.

Each expert was asked to review the assigned statement using the references in a structured search in MEDLINE and SCIELO. Based on the information collected, the expert had to review each statement or sub-affirmation (since some of them are subdivided) with no limit on the number of references. The response should be based on the best available evidence in the literature and should culminate in a brief, concise and accurate recommendation, to which a "level of evidence" and "level of recommendation" (according to the criteria previously described) should be assigned.

Third step

A first round of voting was held where, according to the Delphi consensus technique, the coordinators in charge of the project received the information sent by each expert and a document was generated that included each of the responses to the statements. The levels of evidence and recommendations were reviewed centrally to standardize criteria and the document was sent back to the experts, who had to vote and give their opinion on all the statements in the place indicated as "degree of agreement" and using a Likert scale from 0 to 4 (0: Completely disagree; 1: Disagree; 2: Doubtful or with reservations; 3: Agree; 4: Completely agree). In case of voting 0, 1 or 2, each expert had to insert a short text explaining his/her reasons or place a new example of statement.

The information obtained from the first round was analyzed, a document was prepared with the answers of the panel of experts to each of the statements and they were asked to make the required changes according to the opinions regarding the question they had to analyze.

Fourth step

A second round of voting was held, using the methodology described in the first round. Finally, the information was integrated after the second round of voting, which was the basis for this publication.

Final manuscript

The final manuscript was evaluated and approved by each of the experts who made up the Study Group. This document was reviewed and approved by the LASPGHAN Board of Directors.

Recommendations

The following LASPGHAN recommendations refer to the original statements published by NASPGHAN/ESPGHAN[9] and use the same correlative number to facilitate their identification (table 1).

Table 1. Summary of NASPGHAN/ESPGHAN Recommendations* and level of controversy for LA according to LASPGHAN expert panel consensus

Nº	Recommendation	Level of controversy for LA
1	We recommend that the primary goal of clinical investigation of gastrointestinal symptoms should be to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection.	No controversy
2a	We recommend that during endoscopy additional biopsies for RUT and culture should only be taken if treatment is likely to be offered if infection is confirmed.	Highly controversial
2b	We suggest that if *H. pylori* infection is an incidental finding at endoscopy, treatment may be considered after careful discussion of the risks and benefits of *H. pylori* treatment with the patient/parents.	Moderately controversial
2c	We recommend against a "test and treat" strategy for *H. pylori* infection in children.	No controversy
3	We recommend that testing for *H. pylori* be performed in children with gastric or duodenal ulcers. If *H. pylori* infection is identified then treatment should be advised and eradication be confirmed.	No controversy
4	We recommend against diagnostic testing for *H. pylori* infection in children with functional abdominal pain.	Highly controversial
5a	We recommend against diagnostic testing for *H. pylori* infection as part of the initial investigation in children with iron deficiency anemia.	No controversy
5b	We suggest that in children with refractory IDA in which other causes have been ruled out, testing for *H. pylori* during upper endoscopy may be considered.	No controversy
6	We suggest that noninvasive diagnostic testing for *H. pylori* infection may be considered when investigating causes of chronic immune thrombocytopenic purpura (ITP).	No controversy
7	We recommend against diagnostic testing for *H. pylori* infection when investigating causes of short stature.	No controversy
8	We recommend that before testing for *H. pylori*, waiting at least 2 weeks after stopping proton pump inhibitor (PPI) and 4 weeks after stopping antibiotics.	No controversy
9a	We recommend that the diagnosis of *H. pylori* infection should be based on either (a) histopathology (*H. pylori*–positive gastritis) plus at least 1 other positive biopsy-based test or (b) positive culture.	Highly controversial
9b	We recommend that for the diagnosis of *H. pylori* infection at upper gastrointestinal endoscopy, at least 6 gastric biopsies be obtained.	Highly controversial
10	We recommend against using antibody-based tests (IgG, IgA) for *H. pylori* in serum, whole blood, urine, and saliva in the clinical setting.	No controversy
11	We recommend that antimicrobial sensitivity be obtained for the infecting *H. pylori* strain (s), and eradication therapy tailored accordingly.	Moderately controversial
12	We recommend that the effectiveness of first-line therapy be evaluated in national/regional centers.	Moderately controversial
13	We recommend that the physician explain to the patient/family the importance of adherence to the anti–*H. pylori* therapy to enhance successful eradication.	No controversy
14	We recommend first-line therapy for *H. pylori* infection as listed in Table 2.	Highly controversial
15	We recommend that the outcome of anti–*H. pylori* therapy be assessed at least 4 weeks after completion of therapy using one of the following tests. (a) The 13C-urea breath (13C-UBT) test or (b) a 2-step monoclonal stool antigen test.	Moderately controversial
16	We recommend that when *H. pylori* treatment fails, rescue therapy should be individualized considering antibiotic susceptibility, the age of the child, and available antimicrobial options.	Moderately controversial

*Reference 9.

Table 2. Level of evidence*

Level of evidence	Description
Type I	Evidence from at least one well-designed randomized controlled study1 or a systematic review of randomized clinical studies
Type II	II-1 Evidence from non-randomized controlled trials[1] II-2 Evidence from observational[2] cohort or case-control studies, ideally from several centers II-3 Evidence from case series
Type III	Opinion of authorities on the subject based on experience, expert committees, case reports, physiopathological or basic science studies

[1]A controlled study is one in which the intervention is managed by the investigator. [2]An observational study is one in which the intervention is not controlled by the investigator. *Adapted from ref 10-12.

Table 3. Recommendation Level*

Recommendation	Language
A	The consensus strongly recommends the indicated intervention or ser-vice. This recommendation is supported by high quality evidence, with categorical benefit outweighing risk
B	The consensus recommends routine clinical use of the indicated inter-vention or service. The recommendation is supported by evidence of moderate quality, with benefit exceeding risk
C	The consensus does not recommend either for or against the interven-tion or service. A categorical recommendation is not made since the evidence, of at least moderate quality, does not show a satisfactory risk/benefit ratio. A decision must be made on a case-by-case basis
D	The consensus recommends against the intervention or service. The recommendation is supported by at least moderate quality evidence that shows no benefit or that the risk or harm outweighs the benefits of the intervention
I	The consensus concludes that the evidence is insufficient, either be-cause of low quality studies, heterogeneous results, or the risk/benefit balance cannot be determined

*Adapted from ref 10-12.

Indication of taking biopsies to identify the presence of *H. pylori* in children undergoing upper endoscopy (Recommendations 2a and 2b)

Practical points:

a. During an upper endoscopy (UGE) of a patient who has a condition that justifies giving eradication therapy, biopsies should be taken for histological study and Rapid Urease Test (RUT), to confirm diagnosis. Taking an additional biopsy for antibiotic resistance/sensitivity study will be discussed at length at a later date.
b. According to current evidence, sampling and eradication is only justified in case of gastric or duodenal erosion or ulcer (GDU) or family history of GC. The presence of nodular gastropathy (NG) is still a subject of debate and will be addressed at length later on.
c. About offering treatment to eradicate *H. pylori* in children without the lesions described above, the physician should explain that *H. pylori* infection is not the cause of the symptoms and that after treatment the symptoms should probably not be expected to disappear. In addition, the potential risk of developing infection-related complications (GDU, GC) at a later age should be discussed with parents and older children, and the risks of treatment should be explained, including treatment failure, adverse effects from antibiotics such as diarrhea, allergic reactions, and intestinal microbial abnormalities, among others.

Comments

In general, in the absence of peptic lesions, diagnosis of infection by endoscopic biopsy-dependent methods for the sole purpose of identifying *H. pylori* infection is not appropriate. However, *H. pylori* infection may be found incidentally when UGE is performed to diagnose other pathologies such as inflammatory bowel disease or celiac disease, especially in areas of high prevalence of this infection. In LA, where the possibility of performing UGE is not entirely easy, in certain areas and populations, it is essential to rely on clinical findings.

Eradicating *H. pylori* in children is only justified if the benefit is greater than the risk and cost of

treatment, especially considering that the treatment does not eliminate the symptoms, with the exception of GDU[13]. In a study of *H. pylori* infection associated with histological gastritis without erosive lesions in the gastric or duodenal mucosa, it was observed that this rarely leads to disease progression or complication during childhood[13]. This may be explained by the different immune response to the infection. Compared to adults, infected children present a mucosal immune response with greater involvement of regulatory T cells and their anti-inflammatory effect[14,15]. Additionally, the rate of reinfection by *H. pylori* after eradication appears to be quite high in LA[16]. A bolivian study conducted in cities with high prevalence and low resource populations, observed a re-infection rate of 20% one year after eradication in children under 10 years old[17]. Finally, the risk of GC or MALT lymphoma associated with *H. pylori* infection during childhood is extremely low in Europe and North America and probably also low in LA in the absence of a family history of GC (this aspect will be discussed at length below).

One aspect under study is the inverse relationship between *H. pylori* infection and allergic diseases, where there would be a potential beneficial role of infection in early childhood, which would be an additional argument to avoid unjustified eradication of the bacteria[18].

Recommendation 2a LASPGHAN: We recommend taking biopsies for RUT and histology (and biopsies for culture or molecular techniques, when available) during upper endoscopy, only if treatment will be administered when the infection is confirmed.

Level of evidence:	II-2
Recommendation level:	B
Degree of agreement AVERAGE:	3.4

Recommendation 2b LASPGHAN: We recommend that if *H. pylori* infection is an incidental finding in endoscopy, treatment can be considered with detailed discussion with the patient and parents.

Level of evidence:	III
Recommendation level:	C
Degree of agreement AVERAGE:	3.4

Indication of eradication on the finding of *H. pylori* in children with asymptomatic or functional digestive symptoms (Recommendation 4)

Practical points

a. Rome IV has established that functional gastrointestinal disorders of children and adolescents (FGIDs) do not simply constitute the absence of organic disease. We should consider diagnosing some FGIDs if after an adequate medical clinical evaluation, the symptoms cannot be attributed to any medical condition of organic origin[19]. A positive diagnosis of FGIDs may require some very specific diagnostic test (or none at all) and must meet a set of clinical criteria for inclusion of symptoms that Rome IV has proposed and are already defined in publications[20]. There will always be the possibility of the coexistence of FGIDs and some organic condition of disease.
By more rigorously defining the inclusion criteria, the diagnostic requirement for different types of Functional Abdominal Pain (FAPD) is better established. It is then possible to establish a list of questions and generate surveys applicable to different populations of children and adolescents in various countries of the world[21]. Some recent studies in LA that have used the Rome III diagnostic criteria suggest that the prevalence of FAPD in different cities, of varied economic status and of different populations, is comparable to that of more developed countries[22-24].

b. *H. pylori* infection in children and adolescents may be expressed by digestive and extra-digestive manifestations or may be, more often, silent[25]. In LA, the prevalence of infection in the general population is high, and the first infection may occur at an early age. It seems that the natural history of the infection is somewhat different from that seen in children in more developed countries[26] and should be considered when evaluating the possibility of diagnosing and eradicating the bacteria. Follow-up studies of children infected with *H. pylori* in LA, diagnosed by different procedures, both in rural and urban environments, establish a high annual recurrence rate of infection in our population[27]. In Mexico, re-infection or recurrence is 11.7% to 18%, a situation associated with low socioeconomic level[28]. The reappearance of the bacteria in Peru after treatment is due to 80% reinfection and 20% recurrence, according to bacterial DNA typing tests. Re-infection rates in Lima in recent years have decreased from 70% to 30% in patients of low socioeconomic level[27]. A high prevalence of infection has put pressure on the indiscriminate use of antibiotics with increasing presence of antimicrobial resistance[29].

Comments

The presence of abdominal pain in children and adolescents located in the upper abdomen is a frequent reason for consultation. The intensity of the pain can be varied. The coexistence of patients with abdominal pain and clinical behavior of FAPD and the existence in our environment of a high prevalence of *H. pylori* infection opens the reasonable question of causality or

simple coexistence. Jaime et al.[30] in a cross-sectional study, with 358 children, found no difference in any variant of FGIDs in infected versus non-infected children; however, in multivariate analysis, the presence of isolated abdominal pain was related to *H. pylori* infection (OR 1.55, 95% CI [1.02, 2.36]).

We do not know whether in our environment, where there is a high rate of recurrent infection, these episodes of reinfection have clinical expression or are, as might be assumed, mostly silent. In a population such as LA, with a high rate of reinfection, the presence of symptomatic episodes of pain may coexist or exacerbate the symptoms of a patient diagnosed with FAPD[31,32].

Nodular gastropathy (NG) is more frequent in childhood and adolescence compared to the adult population. It was not described in the original reports of gastric pathology associated with *H. pylori* infection by the Sydney group[33]. Recently it has been reported that *H. pylori* NG is a more common finding in the child population (44-67% in children vs 0.19-13% in adults)[34,35]. It is an endoscopic finding and its presence has been related to a higher microbial density[36]. There are no long-term follow-up studies and we do not know if NG generates pain symptoms or if its presence establishes any particular risk condition, or if it only suggests intense immune reactivity and it is unknown if it exposes to future risks[37]. In a study of LA in 48 adults in Chile, NG was not associated with preneoplastic lesions, but was associated with an increased bacterial load without a concomitant increase in mucosal inflammatory response[38]. In another study of 172 cases and 172 controls in adults in Colombia, the cases had more frequent premalignant gastric lesions (OLGA II; 6.5 vs 1.2%, p = 0.01). In that study the association of NG with gastric cancer was not demonstrated, however, there was one case of a neoplastic lesion in the NG group[39]. The indication for eradication in a child infected with NG is still a matter of debate and should be considered on an individual basis.

In conclusion, the presence of FAPD is now clearly defined in diagnostic terms thanks to Rome IV, however, the possible simultaneous association with chronic *H. pylori* gastritis cannot be excluded. In populations with a high prevalence of *H. pylori* infection, it is still necessary to identify which groups of children and under which risk factors evolve to conditions of greater severity of gastric mucosal involvement such as the presence of ulcer (low prevalence in pediatric population).

Apart from the conditions identified as alarm signs recognized by the NASPGHAN/ESPGHAN consensus[9], the most important characteristic to discuss when making the decision to perform an UGE when there is abdominal pain is the severity of epigastric pain reported by the patient or family. It is possible to consider recommending an UGE if epigastric pain is severe, associated with weight loss, or wakes the child up at night.

Recommendation 4 LASPGHAN: In children with functional abdominal pain, in the absence of alarm signals, testing for *H. pylori* is not recommended. In children with dyspepsia or abdominal pain with alarm signs, according to the Rome IV criteria, it is recommended as a first option to perform upper endoscopy to determine the presence of lesions and other causes of abdominal pain. If any lesions are identified (ulcers or erosions), it is recommended to take biopsies for RUT and histology and if available, also biopsies for culture or molecular techniques. In case of identifying *H. pylori*, eradication treatment should be considered.

Level of evidence:	III
Recommendation level:	B
Degree of agreement AVERAGE:	2.4

Techniques available to diagnose *H. pylori* infection (Recommendations 9a and 9b)

Practical points

a. To investigate *H. pylori*-associated "disease" in children, an UGE should be performed with biopsies for histology, RUT, and ideally culture, and should not be based on non-invasive tests such as the UBT-C13 Urea Test, HpSAg, or other non-invasive methods.
b. The histopathological diagnosis of *H. pylori* gastritis should be made using the updated Sydney classification[40]. At least 5 gastric biopsies should be taken in an UGE to detect *H. pylori* infection. Two antrum biopsies and two body biopsies for histopathological evaluation using the updated Sydney classification[40], and one antrum biopsy for RUT.
c. If available, at least 1 antrum biopsy and 1 body biopsy should be taken for culture and 1 antrum biopsy for molecular tests such as PCR or fluorescent in situ hybridization[41-42] for antimicrobial sensitivity study but not for clinical diagnostic purposes. In LA, culture and/or PCR is performed for research purposes in several countries: Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Mexico, Paraguay, Peru, Uruguay and Venezuela[43]. In some cities in Colombia and Chile, a culture is carried out for antimicrobial sensitivity studies of *H. pylori* for clinical purposes[44,45].
d. Biopsies taken during a GI bleeding episode can give false negative results for histology, culture, RUT or molecular tests[41-42].

e. Biopsies for culture and molecular tests should be placed in special media, refrigerated if necessary and transported as soon as possible, to the processing center to improve its performance.

Comments

The objective of invasive research based on UGE and biopsies is to detect the cause of the symptoms and not only the presence of *H. pylori*, since evidence in children indicates that *H. pylori* infection is not associated with symptoms in the absence of GDU[46]. None of the available diagnostic tests have 100% sensitivity and specificity. According to a 2017 NIHR (National Institute for Health Research) report, the sensitivity and specificity for histology is 66-86% and > 98%, respectively. Currently, the detection of *H. pylori* infection in histology has been improved by adding immunohistochemical tests (marked anti-*H. pylori* antibodies), with sensitivity and specificity > 97% and 100%, respectively[47,48].

The sensitivity and specificity for RUT is 80-95% and 97-99%, respectively[48]. According to some studies, RUT requires a minimum of two gastric biopsies (body and antrum) and a high bacterial load to ensure optimal accuracy. However, the positive predictive value of the tests increases, if the prevalence of infection is high as it is in LA countries[49], so that, in general, a single positive test is sufficient. For an adequate interpretation of RUT, it should be considered that sensitivity is lower in children under 4 years of age and increases with age and with the greater number of biopsies, this due to the low bacterial density in young children, compared with adolescents and adults[50].

The sensitivity and specificity of the culture is 60% and 100%, respectively[9,44,48,51]. Biopsy-dependent molecular tests (PCR or fluorescent in-situ hybridization) will be discussed in a later section.

Recommendation 9a LASPGHAN: The diagnosis of *H. pylori* infection should be made in symptomatic patients based on biopsies obtained through UGE, with at least two of the following positive tests: RUT, histology, or culture.

Level of evidence:	I
Grade recommended:	A
Grade of agreement AVERAGE:	4

Recommendation 9b LASPGHAN: At least 5 gastric biopsies should be taken for the diagnosis of *H. pylori* infection in UGE. Two biopsies should be obtained from the antrum and two biopsies from the body for histopathological evaluation using the Sydney classification and one antrum biopsy for RUT; ideally additional biopsies could be taken if techniques for antimicrobial sensitivity study (culture or molecular techniques) are available.

Level of evidence:	III
Grade of recommendation:	A
Degree of agreement AVERAGE:	3.6

H. pylori antimicrobial susceptibility evaluation (Recommendation 11)

Practical points

a. Despite the recognized importance of *H. pylori* antimicrobial susceptibility testing both for the regional antimicrobial resistance pattern and for the customization of the eradication treatment, at least in LA, there is no surveillance system and it is generally not routinely performed.
b. Antimicrobial susceptibility methods based on molecular and culture studies are available only in large cities and as research studies, generally not as routine laboratory tests.
c. Antimicrobials available for pediatric prescription are limited.

Comments

Ideally, susceptibility testing should be performed on each and every patient infected with *H. pylori*, and eradication treatment should be individualized for each patient. The superiority of treatment guided by susceptibility testing rather than empirical first-line antimicrobial treatment is well known, as well as for rescue treatment[52,53]. The benefits of successful eradication (when indicated) are well known, preventing the development of serious diseases associated with *H. pylori* infection, mainly GC in adulthood[54].

On the other hand, failure to eradicate increases the risk of secondary antimicrobial resistance, and the persistence of infection has numerous health and economic implications for the patient[55]. For these reasons, we fully agree that antimicrobial susceptibility should ideally be determined for all infecting strains.

However, some adjustments are necessary in the context of LA: i) molecular and culture techniques based on biopsies are not available in our countries, and even when they are available they are limited to research laboratories in large cities[7]; ii) when studies are conducted in countries with large territorial extension such as Argentina and Brazil[56], or even a little smaller ones such as Bolivia, Chile, Colombia, Mexico and Venezuela, researchers cannot claim that an antimicrobial susceptibility study conducted in a specific region or city of the country represents the resistance pattern of the whole country[57].

Unfortunately, there are few pediatric reports. A systematic review in LA yielded 59 studies of *H. pylori* antimicrobial resistance (56 in adults, 2 in children, and 1 in both groups), where pediatric reports were too few to summarize by meta-analysis[43]. Resistance to

metronidazole (MET) and clarithromycin (CLA) appears to be the main cause of eradication failure, with controversial data regarding the relative importance of each. Some recent studies in pediatric patients show a high prevalence of CLA resistance in Chilean (21%) and Brazilian (19.5%) children[53,54], however, a recent study in Bogotá, Colombia, found only 8% of strains associated with CLA resistance[58].

The approach of the IV Brazilian Consensus on *H. pylori* infection is probably the best adapted clinical guide to LA, since it highlights that susceptibility testing is not widely available in our environment, and for that reason they do not recommend routine susceptibility testing. However, after the second or third eradication failure there is a recommendation that susceptibility testing should be performed[6].

In children, on the other hand, the supply of antimicrobials is lower, for example: the use of tetracycline and levofloxacin is not recommended. Therefore, knowing the pattern of antimicrobial resistance and customizing the eradication treatment to optimize the outcome becomes crucial in pediatrics

Recommendation 11a LASPGHAN: Ideally, where and when susceptibility testing is available, the pattern of antimicrobial resistance should be determined to guide the first attempt to eradicate the infection.

Level of evidence:	I
Level of recommendation:	A
Degree of agreement AVERAGE:	4

Recommendation 11b LASPGHAN. When available, antimicrobial susceptibility testing should be conducted in pediatric patients to improve the effectiveness of eradication therapy, particularly if there is a high prevalence (> 20%) of CLA resistance.

Level of evidence:	I
Grade of recommendation:	A
Grade of Agreement AVERAGE:	4

Evaluation of antimicrobial susceptibility of *H. pylori* to failure of eradication treatment at the regional level (Recommendation 12)

Practical points

a. As antimicrobial susceptibility testing is not available in all centers, we propose that the effectiveness of *H. pylori* eradication regimes in children and adolescents be evaluated, if possible at the regional level.

Comments

We support the original NASPGHAN/ESPGHAN statement, in particular, that failure of *H. pylori* eradication treatment in clinical practice is often associated with inadequate choice of treatment regimen, lack of adherence, or antimicrobial resistance. To avoid further research, and the induction of secondary resistance in the infecting *H. pylori* strains, the primary success rate for eradication should be more than 90% in the analysis per protocol. This goal is not achieved in most currently published treatment trials in children[57,59]. Therefore, benchmarking is a necessity to evaluate the local performance of prescribed regimens and to minimize the risk of treatment failure. This is particularly important in areas where antimicrobial susceptibility testing is not available.

Martinez et al. conducted a review of 35 publications (1996 to 2012) that grouped in total 3358 isolated samples, 3262 from adult patients and 96 from children in different countries: Brazil 9, Colombia 8, Mexico 5, Chile 4, Peru, Costa Rica, Argentina, Ecuador, Jamaica, Paraguay, Uruguay and Venezuela[57]. The techniques used to determine the antibiotic sensitivity of *H. pylori* were: the E-test (epsilon test) in 17 studies (48%), dilution in agar 14 studies (37%) and diffusion in disc 3 (8%). The studies showed considerable heterogeneity and differences among the countries of the region and even in studies conducted in the same country. In vitro resistance for MET was 65.7%, for AMO 6.5%, for CLA 14%, for tetracycline 8.3%, for levofloxacin 39% and for furazolidone 6.9%. Studies based on molecular techniques and more recent studies in pediatric patients show a high prevalence of resistance to CLA in Chilean (21%) and Brazilian (19.5%) pediatric patients[60,61], however, in symptomatic pediatric patients in Colombia resistance to CLA was only 8%[58].

A prospective, multicenter European study studied the antibiotic resistance of more than 1,000 children with UGE; 24% of primary resistance to clarithromycin was detected, higher in males, in children under 6 years compared to those over 12 years, and in patients from southern Europe (Greece, Italy, Spain and Portugal). Resistance to MET was 25%, higher in children born outside Europe. Resistance to AMO was exceptional, 0.6%, and double resistance to CLA and MET, 6.9%[62].

No epidemiological studies were found regarding cost and availability of techniques to assess antimicrobial sensitivity in regional or national reference centers in LA countries; therefore, NASPGHAN/ESPGHAN recommendation 12 should also be applied in LA.

H. pylori is an infectious agent and the therapeutic objective should always be 100%, with a theoretical efficacy threshold established (excellent > 95%, good 90-95%, fair 85-89%, poor 81-84% and unacceptable 80%)[63]. The ideal scenario, therefore, would be to know in advance the susceptibility of the microorganism to antibiotics by means of bacterial culture or another molecular technique, in order to design a tailor-made treatment for each strain of *H pylori*. As

mentioned above, the reality is that the vast majority of eradication treatments are prescribed empirically[63-65]. Therefore, this choice must be made taking into account variables dependent on the bacterium and the individual. The rates of resistance to local antibiotics should be known, and in case they are not known, an estimation of them should be made according to the local efficacy of the treatments used[63,65].

Recommendation 12 LASPGHAN: We recommend that the antimicrobial sensitivity or resistance study of *H. pylori* be evaluated at selected regional centers acting as reference centers for all LA countries.

Level of evidence:	III
Grade of recommendation:	B
Degree of agreement AVERAGE:	4

Selection of antibiotic treatment to eradicate *H. pylori* (Recommendation 14)

Practical points

a. If the strain is susceptible to CLA and MET, the preferred option is triple therapy (PPI, AMO, CLA) for 14 days. In case of treatment failure, a switch to PPI, AMO and MET can be made without further susceptibility testing.
b. Sequential therapy for 10 days (PPI with AMO for 5 days, followed by PPI with CLA and MET for 5 days, according to doses in table 4) is equally effective as triple therapy in patients infected with fully susceptible strains. However, it has the disadvantage of exposing the child to 3 different antibiotics. Sequential therapy should not be given if the strain is resistant to MET or CLA, or if sensitivity testing is not available. In adults, however, the latest guidelines recommend the use of sequential therapy as first or second line therapy.
c. PPI and antibiotic doses should be calculated according to body weight (table 4).
d. A higher degree of acid suppression improves the success rate of AMO and CLA-based therapy. Younger children need a higher dose of PPIs per kg body weight compared to adolescents and adults to obtain sufficient acid suppression.
e. Esomeprazole and rabeprazole are less susceptible to degradation by rapid metabolizers with genetic polymorphism of CYP2C19, and therefore may be preferred when available. Rapid metabolizers are more frequent in the Caucasian population (56-81%) compared to Asians. We do not have published data on the pediatric population in LA, but a study in Chilean adults showed 79.5% of rapid metabolizers[66].
f. The PPI dose given in table 4 refers to esomeprazole and omeprazole and should be adapted if other PPIs are used. PPIs should preferably be administered at least 15 minutes before a meal.
g. For children under 8 years of age, bismuth quadruple therapy refers to bismuth, PPI, AMO, and MET. In children over 8 years old, bismuth quadruple therapy refers to bismuth, IPP, MET and tetracycline.
h. Current evidence does not support routinely adding individual or combined probiotics to eradication therapy to reduce side effects and/or improve eradication rates.

Table 4. Standard dosing regime

Medication	Weight range	Morning Dose (mg)	Evening Dose (mg)
PPI	15-24 kg	20	20
	25-34 kg	30	30
	> 35 kg	40	40
Amoxicillin	15-24 kg	500	500
	25-34 kg	750	750
	> 35 kg	1.000	1.000
Clarithromycin	15-24 kg	250	250
	25-34 kg	500	250
	> 35 kg	500	500
Metronidazole	15-24 kg	250	250
	25-34 kg	500	250
	> 35 kg	500	500
Bismuth	< 10 years	262 QID	
	>10 years	524 QID	

*PPI, Proton Pump Inhibitor.

Comments

The recommended scheme in case of unknown antimicrobial susceptibility of *H. pylori* includes high dose (14 days) PPI-AMO-MET or quadruple bismuth therapy. The few studies reporting in vitro resistance to different antibiotics have already been described above[57,60,61,67,68].

Ramirez-Bulla carried out a systematic review to determine the prevalence of *H. pylori* resistance to tetracycline, finding 8% in Central and South America[69], data to be considered in treatment schemes for children over 8 years. Thiebaud carried out a retrospective study in Honduras in children under 11 years of age with *H. pylori* disease who were treated with AMO 60 mg/kg/day, CLA 20 mg/kg/day and lanzoprazol 30 mg/day for 14 days. Seventy-nine.2% of patients reported clinical improvement and negative stool antigen after treatment[70].

The findings of Martinez et al. described in the previous section[57] and the lack of publications with updated data regarding *H. pylori* antibiotic resistance in LA and the assessment of the efficacy of first line schemes would make the scheme recommended in the NASPGHAN/ESPGHAN guide, in the absence of knowledge of antimicrobial susceptibility, not applicable in the Latin American pediatric population.

Recommendation 14 LASPGHAN: We recommend using the information presented in table 5 to plan the first-line treatment for *H. pylori* infection if antimicrobial susceptibility is known. If the susceptibility is not known, we recommend the PPI-AMO-CLA regimen for 14 days at standard doses (except in countries with CLA resistance > 20%).

Level of evidence: II
Grade of recommendation: B
Degree of agreement AVERAGE: 4

How to evaluate the eradication of *H. pylori* after antibiotic treatment (Recommendation 15)

Practical points

a. There is evidence of a growing resistance of *H. pylori* to the antibiotic schemes currently used, which may result in failure to eradicate the infection with the complications that result from chronic infection[46,57,71]. We believe it is prudent to verify the eradication of the infection after treatment. Mera and colleagues published a 16-year follow-up study in Colombian adults in a region of high incidence of *H. pylori* showing how effective treatment of eradication led to a decrease in pre-malignant lesions and even regression of them[72].
b. To prove the effective eradication of the infection, invasive methods are recognized using UGE with biopsy taking for histology, RUT and culture. Because of their invasiveness and high costs they are considered unfavourable in children and non-invasive methods are preferred[73].
c. Queiroz et al. reported a concordance study, carried out in Brazil, comparing UBT-C13 and HpSAg, using a commercial ELISA test (Premier Platinum HpSa Plus Assay with multiple murine monoclonal antigens) finding a 94.9% concordance between the two tests[74].
d. The non-invasive tests include the UBT-C13 which has demonstrated a sensitivity and specificity of over 95%, especially in children over 6 years of age (Sensitivity: 96.6%, specificity: 97.7%). In children under 6 years of age its accuracy is lower (sensitivity: 95%, specificity: 93.5%) possibly due to lower endogenous CO2 production[73-77].
e. HpSAg has proven to be as efficient as UBT-C13 and has some advantages as the sample is easily taken, can be transported and processed if kept refrigerated at reference sites far from its capture site[76-78]). Polyclonal antigen detection methods and one-step monoclonal antigen methods are not recommended because of their inaccuracy[76].

Comments

Verifying that the treatments in place in our patients are effective in eradicating *H. pylori* is a desirable goal in order to decrease the complications of the infection such as GDU, gastrointestinal bleeding, iron deficiency anemia and the possibility of developing GC.

Non-invasive methods, UBT-C13 and monoclonal

Table 5. First-line therapy for *H. pylori* infection with known susceptibility

Susceptibility	Suggested treatment
Susceptible to CLA* and MET**	IBP^-AMO***-CLA 14d at standard doses
Resistant to CLA, susceptible to MET	IBP-AMO-MET 14d or bismuth scheme
Resistant to MET, susceptible to CLA	IBP-AMO-CLA 14d or bismuth scheme
Resistant to CLA and MET	IBP-AMO-MET with high doses of AMO or bismuth scheme

*Clarithromycin, **Metronidazole, ***Amoxicillin, ^Proton Pump Inhibitor.

HpSAg in stool have been shown to have a sensitivity and specificity of about 95% in most of the studies consulted, and are easier to perform in children. The use of antibiotics and/or PPIs during the month prior to endoscopy can induce false negatives by decreasing the population of *H. pylori* or by decreasing the production of gastric acid[79].

In some countries of LA, methods for detecting UBT-C13 are available that can be taken in the office and transported to the laboratory to be performed. In Colombia and Chile the test is available in commercial form with an average value of US$ 70-100 for the end user.

Recommendation 15a LASPGHAN It is recommended that the success of *H. pylori* treatment be verified using UBT-C13 or HpSAg.

Level of evidence:	I
Grade of recommendation:	A
Degree of agreement AVERAGE:	4

Recommendation 15b LASPGHAN: Testing should be performed at least 4 weeks after receiving antibiotic treatment and suspension of proton pump inhibitors.

Level of Evidence:	I
Grade of Recommendation:	A
Grade of Agreement AVERAGE:	4

Selection of second-line antibiotic treatment to eradicate *H. pylori* (Recommendation 16)

Practical points

a. Although the ideal is to have the antibiotic susceptibility profile of *H. pylori* from the beginning, so as to be able to indicate a first-line treatment according to it, in practice this is difficult to achieve in much of LA. In general, antibiotic susceptibility studies are reserved for large centers and research purposes.
b. The rate of eradication of first-line treatment in children is lower than that reported for adults and ranges from 64% to 77%[80-82]. In addition, the repertoire of antibiotics that can be administered in children is smaller than at later ages, for safety reasons, which reaffirms the need for an antimicrobial susceptibility study in cases of failure of first-line treatment, so that the most appropriate antibiotic scheme can be chosen.

Comments

We agree with NASPGHAN/ESPGHAN statement 16, although we are aware that its implementation in the current health context in LA is difficult. Evidence in adults shows that antibiogram-guided treatment is more effective than both first-line[52] and rescue[83] empirical treatment. Although common sense suggests that this strategy is also recommended in children, there are no pediatric studies that have explored the effectiveness of personalized treatment according to antimicrobial susceptibility compared to empirical.

The implementation of this recommendation involves performing a new UGE with gastric biopsy for culture and antibiotic susceptibility study. The culture of *H. pylori* requires its sowing in special media and incubation for 7-10 days, followed by 24-48 h of incubation of the antimicrobial susceptibility test. In practice, this study is carried out in a few tertiary centers in LA and generally for research purposes. We strongly recommend that the culture and antibiotic technique for *H. pylori* be available in every center where pediatric UGE is performed and that it be taken at least in every patient who has failed second-line treatment. This in order to choose the most adequate scheme to achieve effective eradication after failure of second line therapy.

Since some of the antibiotics included in *H. pylori* eradication schemes may have adverse reactions in children, which do not occur in adults (such as quinolones and tetracyclines), their use should be fully supported and reserved only for cases with demonstrated resistance to the safer antimicrobials. Based on the resistance profiles described in LA[57,60,84] and other latitude[85-88] children, it is recommended that at least susceptibility to AMO, CLA, MET, tetracycline and ciprofloxacin (or other quinolone) be included in the study.

The most recent guide published in LA for case management in adults is the Brazilian guide, which considering the practical difficulties of implementing the susceptibility study for *H. pylori*, suggests first, second and third line empirical schemes, reserving culture and antibiogram for case management after a third treatment failure[6]. We discourage this practice in children and recommend supporting the choice of antibiotics with a susceptibility study from the second treatment failure, because the indiscriminate use of antibiotics can have serious impact on the health of the patient, his microbiota and favor the appearance of secondary resistance.

Recommendation 16a LASPGHAN: In case of failure to eradicate *H. pylori* with first-line treatment, we recommend empirical treatment with quadruple bismuth therapy. In children under 8 years of age, we recommend a scheme with PPI, AMO, MET and bismuth for 14 days. In children 8 years and older, consideration may be given to replacing MET with tetracycline in this same regimen.

Level of evidence:	I (adult)
Recommendation level:	A
Degree of agreement AVERAGE:	3.8

Recommendation 16b LASPGHAN: In case of failure of eradication with the second line therapy, it is recommended to consider an individualized treatment, ideally using the antibiotic sensitivity of the strain (which implies performing a new endoscopy with sample extraction for culture and antibiogram or molecular resistance study), the previously indicated scheme and the age of the patient.

Level of evidence:	I (in adults)
Recommendation level:	A
Degree of agreement AVERAGE:	3.8

Prevention of Gastric Cancer in infected children

The 2011 NASPGHAN/ESPGAHN clinical guidelines stated "Consider testing in the setting of family history of gastric cancer or MALT". However, in the new version 2016, they remove this recommendation: "Removal of recommendation for testing of the setting of family history of gastric cancer or MALT, as rarely encountered".

Practical points

a. According to reports from the Global Cancer Observatory (Globocan), there are more than 900,000 new cases of CG each year and more than 700,000 deaths per year, making it the 5th cause in annual incidence of malignant tumors and the 3rd cause in cancer mortality in the world and in LA with serious socio-economic implications (https://gco.iarc.fr/). Incidences adjusted for age and sex are significantly higher in developing countries compared to developed countries. Currently 3 countries concentrate 60% of the world's total GC, corresponding to Japan, China and Korea. In LA, the incidence of GC accounts for 6-7% of the total world incidence, doubling that of Europe and tripling that of the USA[89].

b. The relationship between prevalence of *H. pylori* infection and incidence of GC has been well established[90]. The incidence of GC is generally in direct proportion to the prevalence of *H. pylori* infection, although there are higher incidences of GC in Asian countries compared with other countries with similar prevalence of infection[91]. Strain virulence has been established as one of the central factors in the development of GC[92].

c. There is evidence of intra-family transmission of *H. pylori* infection, particularly from parent to child, so that children receive strains with similar virulence characteristics to their parents. Bacterial genotyping studies make it possible to trace the origin of the infection in children[93-96]. But also, these children inherit from their parents "risk factors" for the development of GC, such as cytokine polymorphism (IL-17A-197A, IL-17F 7488CC, MMP9-1562 C/T, EGF +61 A>G, CTLA-4 -1661A/G; rs9904341; IL1-RN VNTR; among others)[97-100]. Finally, these children share environmental risk factors such as diet, exposure to contaminants or other geographical factors. Therefore, those children with first-degree (parents or siblings) or second-degree (grandparents or aunts) infected relatives represent a unique group since they acquire *H. pylori* from their parents and at the same time share genetic and environmental risk factors.
Recent studies suggest that the risk of developing GC in subjects with a family history of GC is high with ORs ranging from 1.5 (95% CI 1.3-1.8) to 10.1 (95% CI 6.1-16.8)[100]. In a recent 2017 meta-analysis, from both Asian and non-Asian countries, with 26 studies exclusively analyzing GC history in first-degree relatives, the risk was 2.71 (95% CI 2.08-3.53; $p < 0.00001$)[100]. Furthermore, among people with a family history of GC, the highest risk of developing GC was: current or past *H. pylori* infection, having two or more affected first-degree relatives, and being female[101].

d. *H. pylori* eradication appears to be the most important strategy to prevent GC in first-degree relatives of GC patients, particularly those in their 20s and 30s, and to prevent progression to intestinal metaplasia[101], but no data are available on first- or second-degree relatives. A study of 750 children (390 infected, 52%) showed a higher prevalence of family history of GC in infected children and that in those infected with atrophy (6.2%) and intestinal metaplasia (2.8%), eradication was able to reverse both findings[102].

e. A meta-analysis of RCTs on *H. pylori* eradication studied the effect on the subsequent occurrence of GC in the general adult population. It provides evidence of limited and moderate quality that the search for and eradication of *H. pylori* reduces the incidence of GC in healthy asymptomatic infected Asian individuals, but these data cannot necessarily be extrapolated to other populations[103,104]. A model projecting the possible reduction of lifetime risk of GC and associated costs in a high-risk region in China found that eradication at ages 20 to 30 is more cost-effective compared to older ages[105]. The LA consensus[7] postulated that eradication of *H. pylori* in primary prevention of GC in adults is desirable, but recognized that there is not yet sufficient evidence to implement it on a large scale in the general population (Level of Evidence Type I, Grade of Recommendation C). Meta-analyses of those RCTs aimed at GC prevention suggest that *H. pylori* eradication significantly reduces the risk

Table 6. Summary of Recommendations

Nº de Recommendation NASPGHAN/ESPGHAN	LASPGHAN proposal
2a y 2b	2a. We recommend taking biopsies for RUT and histology (and biopsies for culture or molecular techniques, when available) during upper endoscopy, only if treatment will be administered when the infection is confirmed 2b. We recommend that if *H. pylori* infection is a chance finding in endoscopy, treatment can be considered with a detailed discussion of it with the patient and parents
4	In children with functional abdominal pain, in the absence of alarm signals, testing for *H. pylori* is not recommended. In chil-dren with dyspepsia or abdominal pain with alarm signs, ac-cording to the Rome IV criteria, it is recommended as a first option to perform upper endoscopy to determine the presence of lesions and other causes of abdominal pain. If any lesions are identified (ulcers or erosions), it is recommended to take biopsies for RUT and histology and if available, also biopsies for culture or molecular techniques. In case of identifying *H. pylori*, eradication treatment should be considered
9a y 9b	9a. The diagnosis of *H. pylori* infection should be made in symptomatic patients based on biopsies obtained through UGE, with at least two of the following tests being positive: RUT, his-tology, or culture 9b. At least 5 gastric biopsies should be taken for the diagnosis of *H. pylori* infection in UGE. Two biopsies should be obtained from the antrum and two biopsies from the body for histopatho-logical evaluation using the Sydney classification and one an-trum biopsy for RUT; additional biopsies may ideally be taken if techniques for antimicrobial sensitivity study (culture or mo-lecular techniques) are available
11a y 11b	11a. Ideally, where and when susceptibility testing is available, the pattern of antimicrobial resistance should be determined to guide the first attempt to eradicate the infection 11b. When available, antimicrobial susceptibility testing should be performed in pediatric patients to improve the effectiveness of eradication therapy, particularly if there is a high prevalence (> 20%) of CLA resistance
12	We recommend that the *H. pylori* antimicrobial sensitivity or resistance study be evaluated at selected regional centers acting as reference centers for all LA countries
14	We recommend using the information presented in table 5 to plan the first-line treatment for *H. pylori* infection if antimicro-bial susceptibility is known. If the susceptibility is not known, we recommend the PPI-AMO-CLA regimen for 14 days at standard doses (except in countries with CLA resistance > 20%)
15	15a. It is recommended to check the success of the *H. pylori* treatment using the UBT-C13 or HpSAg 15b. The tests should be performed at least 4 weeks after receiving the antibiotic treatment and the suspension of the proton pump inhibitors
16	16a. In case of failure to eradicate *H. pylori* with first-line treatment, we recommend empirical treatment with quadruple bismuth therapy. In children under 8 years of age, we recom-mend a scheme with PPI, AMO, MET and bismuth for 14 days. In children 8 years and older, consideration may be given to replacing MET with tetracycline in this same regimen. 16b. In case of failure of eradication with the second line thera-py, it is recommended to consider an individualized treatment, ideally using the antibiotic sensitivity of the strain (which im-plies performing a new endoscopy with sample extraction for culture and antibiogram or molecular resistance study), the pre-viously indicated scheme and the age of the patient
Gastric cancer	In symptomatic children referred to endoscopy, with a history of first or second degree relatives with gastric cancer, we rec-ommend looking for *H. pylori* (and eradicating it when detect-ed), using direct technique during endoscopy

of GC (RR 0.6; 95%CI: 0.4-0.9), especially in high-risk populations, but there are no empirical data addressing the most appropriate age for interventions to eradicate *H. pylori* infection. The most recent 2017 meta-analysis shows that the relative risk reduction of GC occurrence was 0.67 (95% CI: 0.48-0.95)[106].

Comments

In a recent review by LA researchers, 37 GC biomarkers were identified, of which 24 are over-expressed, 3 are under-expressed, and 10 genes are significantly hyper-methylated in *H. pylori* infected children compared to non-infected children. Notably, 13 of these biomarkers (b-catenin, C-MYC, GATA-4, DAPK1, CXCL13, DC-SIGN, TIMP3, EGFR, GRIN2B, PIM2, SLC5A8, CDH1, and VCAM-1) are consistently unregulated in children and adults with GC. However, to date, it is not yet possible to identify which children relatives of patients with GC may be at increased risk of developing pre-neoplastic lesions[107].

As of 2013, there is already an important consensus (IARC 2013, Kyoto 2014)[108,109] that has provided additional arguments supporting the strategy of eradication in asymptomatic populations for the prevention of GC. In addition, major eradication studies are un-

derway, the results of which will be available in 2019 and 2020. However, there is no information on the effectiveness of eradication in first- and second-degree relatives of GC patients; it is highly likely that the benefits in the general population will be repeated or amplified in high-risk populations.

This year 2020, Choi et al. reported the result of a study of 1676 subjects with a family history of GC in first-degree relatives (9.2 years of follow-up) showing that among the 832 subjects infected with *H. pylori*, eradication of the bacteria reduced the risk of developing GC, compared to the 844 infected subjects who did not receive treatment (RR 0.27; 95% CI, 0.10-0.70)[110]. Considering the benefit to the general population of eradication, the pathogenesis associated with GC, and the high incidence of GC in LA, we opted to recommend eradication of the bacteria when it is found in an endoscopy of a symptomatic child referred to endoscopy with a history of first or second degree relatives with a history of gastric cancer.

LASPGHAN Recommendation: In symptomatic children referred to endoscopy with a history of first or second degree relatives with gastric cancer, we recommend looking for *H. pylori* (and eradicating it when it is detected), using direct technique during the endoscopy.

Level of evidence: I	II
Recommendation level:	B
Degree of agreement AVERAGE:	3.6

Conclusions

The expert panel has evaluated the current NASPGHAN/ESPGHAN 2016 recommendations, based on current LA data. The statements of interest regarding diagnosis, prevention and treatment of *H. pylori* infection in children were established by consensus and are summarized in Table 6. The evidence supports most of the general concepts set forth in the NASPGHAN/ESPGHAN 2016 Guidelines. However, it is necessary to adapt them to the reality of LA with emphasis on the development of regional centers for the study of antibiotic sensitivity and to improve the correct selection of eradication treatment. It is necessary to consider the search for *H. pylori* (and eradicate it when detected), by direct technique during endoscopy, in a symptomatic child referred to endoscopy with a history of first or second degree relatives with a history of GC.

It is unlikely that any regional clinical guidelines can be implemented globally, given the diverse socioeconomic realities or given the differential impact of GC on different continents and ages. However, the Clinical Guidelines should be continually reviewed and adapted to the available evidence. Finally, LA is a particular region where GC continues to be a relevant problem and new cohort studies are needed to evaluate the impact of *H. pylori* eradication on children and its impact on GC prevention.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Fondecyt Chile #1190456 (YL), Fondecyt Chile #1130387 (PRH).

References

1. Curado MP, de Oliveira MM, de Araújo Fagundes M. Prevalence of *Helicobacter pylori* infection in Latin America and the Caribbean populations: A systematic review and meta-analysis. Cancer Epidemiol. 2019;60:141-8.
2. Malfertheiner P, Megraud F, O'Morain CA, et al. and European Helicobacter and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. Gut. 2017;66:6-30.
3. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 2015;64:1353-67.
4. Kim SG, Jung HK, Lee HL, et al. and Korean College of *Helicobacter* and Upper Gastrointestinal Research. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol. 2014;29:1371-86.
5. Liu WZ, Xie Y, Lu H, et al and Chinese Society of Gastroenterology, Chinese Study Group on *H. pylori* and Peptic Ulcer. Fifth Chinese National Consensus Report on the management of Helicobacter pylori infection. Helicobacter. 2018;23(2):e12475.
6. Coelho LGV, Marinho JR, Genta R, et al. IVth Brazilian Consensus Conference on *H. pylori* infection. Arq Gastroenterol. 2018;55:97-121.
7. Rollan A, Arab JP, Camargo MC, et al. Management of *Helicobacter pylori* infection in Latin America: A Delphi technique-based consensus World J Gastroenterol 2014;20:10969-83.
8. Bourke B, Ceponis P, Chiba N, et al. and Canadian *Helicobacter* Study Group. Canadian *Helicobacter* Study Group Consensus Conference: Update on the approach to *Helicobacter* pylori infection in children and adolescents-an evidence-based evaluation. Can J Gastroenterol. 2005;19:399-408. Review. Erratum in: Can J Gastroenterol. 2005 Aug;19(8):478.
9. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). J Pediatr Gastroenterol Nutr. 2017;64:991-1003.
10. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey

technique. J Adv Nurs. 2000;32:1008-15.
11. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35.
12. Sawaya GF, Guirguis-Blake J, LeFevre M, Harris R, Petitti D; U.S. Preventive Services Task ForceUpdate on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med. 2007;147:871-5.
13. Sierra MS, Hastings EV, Goodman KJ. What do we know about benefits of *H. pylori* treatment in childhood? Gut Microbes 2013;4:549-67.
14. Harris PR, Wright SW, Serrano C, et al. *H. pylori* gastritis in children is associated with a regulatory T-cell response. Gastroenterology 2008;134:491-9.
15. Melo FF, Rocha AM, Rocha GA, et al. A regulatory instead of an IL-17 response predominates in *H. pylori* associated gastritis in children. Microb Infect 2012;14:341-7.
16. Morgan DR, Torres J, Sexton R, et al. Risk of recurrent *H. pylori* infection 1 year after initial eradication therapy in 7 Latin American communities. JAMA:2013;209:578-86.
17. Sivapalasingam S, Rajasingham A, Maugj T, et al. Recurrence of *H. pylori* infection in Bolivian children and adults after a population-based "screen and treat" strategy. Helicobacter 2014;19:343-8.
18. Blaser MJ, Chen Y, Reibmen J. Does *Helicobacter pylori* infection protect against asthma and allergy? Gut 2008;57:51-7.
19. Hyams J, Di Lorenzo C. Childhood Functional Gastrointestinal Disorders: Child/Adolescent. Gastroenterology 2016;150:1456-68.
20. Schmulson MJ, Drossman D. What Is New in Rome IV. J Neurogastroenterol Motil 2017;23:151-63.
21. Velasco-Benítez CA, Nichols-Vinueza D, Saps M. Spanish version of the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III (QPGS-RIII). J Pediatr Gastroenterol Nutr 2011;53 (suppl 1):E65.
22. Jativa E, Velasco-Benítez C, Saps M, et al. Prevalence of Functional Gastrointestinal Disorders in School children in Ecuador. J Pediatr Gastroenterol Nutr 2016;63:25-8.
23. Saps M, Nichols-Vinueza DX, Rosen JM, et al. Prevalence of functional gastrointestinal disorders in Colombian school children. J Pediatr. 2014;164:542-5. e1
24. Phatak UP, Pashankar DS. Prevalence of functional gastrointestinal disorders in obese and overweight children. Int J Obes (Lond) 2014;38:1324-7.
25. Pacifico L, Osborn JF, Tromba V, Romaggioli S, Bascetta S, Chiesa C. *Helicobacter pylori* infection and extragastric disorders in children: A critical update World J Gastroenterol 2014;20:1379-401.
26. Klein PD, Gilman RH, Leon-Barua R, Díaz F, Smith EO, Graham DY. The epidemiology of *Helicobacter pylori* in Peruvian children between 6 and 30 months of age. Am J Gastroenterol 1994;89:196-200.
27. Ramírez-Ramos, Alberto; Gilman, Robert H, Watanabe-Yamamoto, José; Rosas-Aguirre, Angel. Estudio de la epidemiología de la infección por el *Helicabacter pylori* en el Perú: 20 años. Acta Gastroenterol Latinoam 2004;34:69-78.
28. Gottrand F, Vincent P. What Can We Learn from *Helicobacter pylori* Reinfection in Childhood? J Pediatr Gastroenterol Nutr 2005;40:276-8.
29. Mégraud F, Lehours P. Review *Helicobacter pylor*i detection and antimicrobial susceptibility testing. Clin Microbiol Rev 2007;20:280-322.
30. Jaime F, Villagrán A, Hernández C, Ortiz M, Serrano C, Harris PR. Functional gastrointestinal disorders in children from low socio-economic status and *Helicobacter pylori* infection. Child Care Health Dev. 2018;44:319-25.
31. Begue RE, Gonzales JL, Correa-Gracian H, Tang SC. *H.* pylori infection in children with abdominal ailments in a developing country**.** Am J Med Sci. 1997;314:279-83.
32. Queiroz D, Rocha A, Crabtree JE. Unintended consequences of *Helicobacter pylori* infection in children in developing countries. Gut Microbes 2013;4:494-504.
33. Dixon MF, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20:1161-81.
34. Yang HR. Updates on the diagnosis of *Helicobacter pylori* infection in children: what are the differences between adults and children? Pediatr Gastroenterol Hepatol Nutr. 2016;19:96-103.
35. Mejia CR, Vera CA, Huiza-Espinoza L. Association between follicular gastritis and *Helicobacter pylori* children seen at a public hospital in Peru. Rev Gastroenterol Mex. 2016;81:80-5.
36. Bahú Mda G, da Silveira TR, Maguilnick I, Ulbrich-Kulczynski J. Endoscopic Nodular Gastritis: An Endoscopic Indicator of High-Grade Bacterial Colonization and Severe Gastritis in Children With Helicobacter pylori. J Pediatr Gastroenterol Nutr. 2003;36:217-22.
37. Ikuse T, Ohtsuka Y, Obayashi N. Host response genes associated with nodular gastritis in *H. pylori* infection. Pediatr Int 2018;60:446-54.
38. Mansilla R, Serrano C, Palma C, Vera C, Hernández C, Pizarro M, Torres J, Harris PR, Fuentes-López E, Riquelme A, Espino A. High *Helicobacter pylori* bacterial load and low cytokine expression levels are associated with nodular gastropathy. Digestive Diseases and Sciences 2020;65:565-75.
39. Marulanda H, Otero W, Gómez M. *Helicobacter pylori*, gastritis nodular y lesiones premalignas de estómago: un estudio de casos y controles. Rev Gastroenterol Peru. 2018;38:349-55.
40. Taha M, Hassan A, Samia I, et al. *Helicobacter pylori* chronic gastritis updated Sydney grading in relation to endoscopic findings and *H. pylori* IgG antibody: diagnostic methods. J Microsc Ultrastruct. 2016;4:167-74.
41. Rimbara E, Sasatsu M, Graham DY. PCR detection of *Helicobacter pylori* in clinical samples. Methods Mol Biol 2013;943:279-87.
42. Saez J, Belda S, Santibáñez M, et al. Real-time PCR for diagnosing *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding: comparison with other classical diagnostic methods. J Clin Microbiol 2012;50:3233-7.
43. Camargo MC, García A, Riquelme A, et al. The problem of *Helicobacter pylori* resistance to antibiotics: a systematic review in LatinAmerica. Am J Gastroenterol 2014;109:485-95.
44. Arévalo A, Otero W, Trespalacios A. *Helicobacter pylori*: resistencia múltiple en pacientes de Bogotá-Colombia. Biomédica. 2019;39:2-16.
45. Vesga FJ, Moreno Y, Ferrús MA, Campos C, Trespalacios AA. Detection of *Helicobacter pylori* in drinking water treatment plants in Bogotá, Colombia, using cultural and molecular techniques. Int J Hyg Environ Health. 2018;221:595-601.
46. Kotilea K, Kalach N, Homan M, Bontems P. *Helicobacter pylor*i Infection in Pediatric Patients: Update on Diagnosis and Eradication strategies. Paediatr Drugs 2018;20:337-51.
47. Lash RH, Genta RM. Routine anti-helicobacter immunohistochemical staining is significantly superior to reflex staining protocols for the detection of Helicobacter in gastric biopsy specimens. Helicobacter. 2016;21:581-5.
48. Nicholson BD, Abel LM, Turner PJ, Price CP, Heneghan C, Hayward G, Plüddemann A. Point-of-care *Helicobacter pylori* testing: primary care technology update. Br J Gen Pract. 2017;67:576-7.

49. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. Gastroenterol 2017;153:420-9.
50. Seo JH, Park JS, Yeom JS, et al. Correlation between positive rate and number of biopsy samples on urease test in childhood *Helicobacter pylori* infection. J Korean Med Sci 2014;29:106-9.
51. Atkinson NS, Braden B. *Helicobacter pylori* Infection: Diagnostic Strategies in Primary Diagnosis and After Therapy. Digestive diseases and sciences. 2016;61:19-24.
52. Chen H, Dang Y, Zhou X, Liu B, Liu S, Zhang G. Tailored therapy versus empiric chosen treatment for *Helicobacter pylori* eradication: A meta-analysis. Medicine 2016;95:1-10.
53. López-Góngora S, Puig I, Calvet X, et al. Systematic review and meta-analysis: susceptibility-guided versus empirical antibiotic treatment for *Helicobacter pylori* infection. J Antimicrobial Chemother 2015;70:2447-55.
54. Ford AC, Gurusamy KS, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive people. Cochrane Database Syst Rev. 2016;4:CD003840. doi: 10.1002/14651858.CD003840.pub5.
55. Axon A. *Helicobacter pylori* and public health. Helicobacter 2014;19(Suppl 1):68-73.
56. Vianna JS, Ramis IB, Ramos DF, Von Groll A, Silva PEA. Drug resistance in *Helicobacter pylori.* Arq Gastroenterol 2016;53I:215-23.
57. Martínez JD, Henao SC, Lizarazo JI. Antibiotic resistance of *Helicobacter pylori* in Latin america and the Caribbean. Rev Col Gastroenterol 2014;29:217-26.
58. Rosero YL, Arévalo-Jaimes BV, Delgado MP, et al. Evaluation of *Helicobacter pylori* infection and clarithromycin resistance in strains from symptomatic Colombian children. J Pediatr Gastroenterol Nutr 2018;67:601-4.
59. Arévalo A, Otero W, Trespalacios A. *Helicobacter pylori:* resistencia múltiple en pacientes de Bogotá, Colombia. Biomédica 2019;39 (Supl.1):125-34.
60. Serrano CA, León MA, Palma C, Vera M, Hernández C, Harris PR. *Helicobacter pylori*-clarithromycin resistance in symptomatic pediatric patients in a high prevalence country. J Pediatr Gastroenterol Nutr 2017;64:56-60.
61. Ogata SK, Godoy AP, da Silva Patricio FR, Kawakami E. High *Helicobacter pylori* resistance to metronidazole and clarithromycin in Brazilian children and adolescents. J Pediatr Gastroenterol Nutr 2013;56:645-8.
62. Koletzko S, Richy F, Bontems P, et al. Prospective multicenter study on antibiotic resistence of *Helicobacter pylori* strains obtained from children living in Europe. Gut 2006;55:1711-6.
63. Molina-Infante J, Corti R, Doweck J, McNicholl A, Gisbert J. Avances recientes en el tratamiento de la infección por *Helicobacter pylori*. Acta Gastroenterol Latinoam 2017;47(1):75-85.
64. Graham DY, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol 2014;12:177-86.
65. Molina-Infante J, Shiotani A. Practical Aspects in Choosing a *Helicobacter pylori* Therapy. Gastroenterol Clin North Am 2015;44:519-35.
66. Arenas A, Serrano C, Quiñones L, et al. High prevalence of clarithromycin resistance and effect on *Helicobacter pylori* eradication in a population from Santiago, Chile: cohort study and meta-analysis. Scientific Reports 2019;9:20070.
67. Yepes CA, Rodríguez A, Ruiz A, Ariza B. Resistencia antibiótica del *Helicobacter pylori* en el hospital universitario San Ignacio de Bogot**á**. Acta Médica Colombiana 2008;33:11-4.
68. Otth L, Wilson M, Fernández H, et al. Isolation of *Helicobacter pylori* in Gastric Mucosa and Susceptibility to Five Antimicrobial Drugs in Southern Chile. Braz J Microbiology 2011;42:442-7.
69. Ramírez-Bulla P, Mercado-Reyes M, Trespalacios-Rangel A, Ávila-Coy J, Otero-Regino W. Estado actual de la resistencia de *Helicobacter pylori* a tetraciclina: revisión sistemática de la literatura. www.javeriana.edu.co/universitas_scientiarum 2012, Vol. 17 N° 2:216-229.
70. Thiebaud L, Luque M, Sabillón L, Millares H, Bustillo K. Eficacia del tratamiento convencional para Helicobacter pylori en niños. Rev Med Hondur 2011;79:65-67.
71. Ogata S, Ortiz A, Da Silva F, Kawakami E. High *Helicobacter pylori* Resistance to Metronidazole and Clarithromycin in Brazilian Children and Adolescents. J Pediatric Gastroenterol Nutr 2013;56:645-8.
72. Mera Robertino, Bravo LE, Camargo MC, et al. Dynamics of *Helicobacter pylori* as a determinant of progression of gastric precancerous lesions: 16 -year follow-up of an eradication trial. Gut 2017;0:1-8.
73. Leal YA, Florez LL, Fuentes-Panama EM, et al. 13 C urea breath test for the diagnosis of *Helicobacter pylori* infection in children: a systematic review and meta-analysis. Helicobacter 2011;16:327-37.
74. Queiroz DM, Saito M, Rocha GA, et al. *Helicobacter pylori* infection in infants and toddlers in South America: concordance between [13C] urea breath test and monoclonal *H. pylori* stool antigen test. J Clin Microbiol 2013;51:3735-40.
75. Pacheco SL, Ogata SK, Machado RS, et al. Diagnosis of *Helicobacter pylori* infection By means of reduce-dose (13C) urea breath test and early sampling of exhaled breath. J Pediatric Gastroenterol Nutr 2013;57:607-11.
76. Zhou X, Su J, Xu G, et al. Accuracy of stool antigen test for the diagnosis of *Helicobacter pylori* infection in children: a meta-analysis. Clin Res Hepatol Gastroenterol 2014;38:629-38.
77. Raguza D, Machado RS, Ogata SK, et al. Validation of a monoclonal stool antigen for diagnosing *Helicobacter pylori* infection in young children. J Pediatr Gastroenterol Nutr. 2010;50:400-3.
78. De Carvalho Costa Cardinali L, Rocha G, et al. Evaluation of [13C] urea breath test and *Helicobacter pylori* stool antigen test for diagnosis of *H. pylori* infection in children from a developing country. J Clin Microbiol 2003;41:334-5.
79. Gatta L , Vakil N, Ricci C, et al. Effect of proton pump inhibitors and antacid Therapy on 13 C urea breath test for *Helicobacter pylori* infection. Am J Gastroenterol 2004;99:823-9.
80. Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: sequential therapy for *Helicobacter pylori* eradication in children. Aliment Pharmacol Ther. 2012;36:534-41.
81. Huang C-C, Tsai K-W, Tsai T-J, Hsu P-I. Update on the first-line treatment for *Helicobacter pylori* infection - a continuing challenge from an old enemy. Biomark Res. 2017;5:23.
82. Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for *Helicobacter pylori* eradication. Cochrane Database Syst Rev. 2016 Jun 28;(6):CD009034. doi: 10.1002/14651858.CD009034.pub2.
83. Kwon YH, Kim N, Lee JY, et al. Comparison of the efficacy of culture-based tailored therapy for *Helicobacter pylori* eradication with that of the traditional second-line rescue therapy in Korean patients: a prospective single tertiary center study. Scand J Gastroenterol. 2016;51:270-6.
84. Ogata SK, Gales AC, Kawakami E. Antimicrobial susceptibility testing for *Helicobacter pylori* isolates from Brazilian children and adolescents: comparing agar dilution, E-test, and disk diffusion. Braz J Microbiol Publ Braz Soc Microbiol. 2014;45:1439-48.
85. Mahmoudi S, Mamishi S, Banar M, et al. Antibiotic susceptibility of *Helicobacter pylori* strains isolated from Iranian children: High frequency of A2143G point mutation associated with clarithromycin resistance. J Glob Antimicrob Resist. 2017;10:131-5.
86. Maleknejad S, Mojtahedi A, Safaei-Asl

A, Taghavi Z, Kazemnejad E. Primary Antibiotic Resistance to *Helicobacter pylori* Strains Isolated From Children in Northern Iran: A Single Center Study. Iran J Pediatr. 2015;25(6):e2661. doi: 10.5812/ijp.2661.

87. Peretz A, Paritsky M, Nasser O, et al. Resistance of *Helicobacter pylori* to tetracycline, amoxicillin, clarithromycin and metronidazole in Israeli children and adults. J Antibiot (Tokyo). 2014;67:555-7.
88. Seo J-H, Jun J-S, Yeom JS, et al. Changing pattern of antibiotic resistance of *Helicobacter pylori* in children during 20 years in Jinju, South Korea: *H. pylori* and antibiotic resistance. Pediatr Int. 2013;55:332-6.
89. Ruíz-García E, Guadarrama-Orozco J, Vidal-Millán S, Lino-Silva LS, López-Camarillo C, Astudillo-de la Vega H. Gastric cancer in Latin America, Scandinavian Journal of Gastroenterology 2018;53:124-9.
90. International Agency for Research on Cancer. World Health Organization. Infection with Helicobacter pylori. In: Schistosomes, liver flukes and Helicobacter pylori. Lyon: IARC, 1994; 177-202.
91. Suzuki H, Mori H. World trends for *H. pylori* eradication therapy and gastric cancer prevention strategy by H. pylori test-and-treat. J Gastroenterol. 2018;53:354-61.
92. Chang WL, Yeh YC, Sheu BS. The impacts of *H. pylori* virulence factors on the development of gastroduodenal diseases. J Biomed Sci. 2018;25:68.
93. Osaki T, Konno M, Yonezawa M, Hojo F, Zaman C, Takahashi M, Fujiwara S, Kamiya S. Analysis of intra-familial transmission of *Helicobacter pylori* in Japanese familias. Journal of Medical Microbiology 2015;64:67-73.
94. Weyermann M, Rothenbacher D, Brenner H. Acquisition of *Helicobacter pylori* infection in early childhood: independent contributions of infected mothers, fathers, and siblings. Am J Gastroenterol 2009;104:182-9.
95. Goodman KJ, Correa P. Transmission of *Helicobacter pylori* among siblings. Lancet 2000;355:358-62.
96. Mamishi S, Eshaghi H, Mahmoudi S, Bahador A, Hosseinpour Sadeghi R, Najafi M, Farahmand F, Khodadad A, Pourakbari B. Intrafamilial transmission of *Helicobacter pylori*: genotyping of faecal samples. Br J Biomed Sci. 2016;73:38-43.
97. de Brito BB, da Silva FAF, de Melo FF. Role of polymorphisms in genes that encode cytokines and *Helicobacter pylori* virulence factors in gastric carcinogenesis. World J Clin Oncol. 2018;9:83-9.
98. Chmiela M, Karwowska Z, Gonciarz W, Allushi B, Stączek P. Host pathogen interactions in *Helicobacter pylori* related gastric cancer. World J Gastroenterol. 2017;23:1521-40.
99. Mommersteeg MC, Yu J, Peppelenbosch MP, Fuhler GM. Genetic host factors in *Helicobacter pylori*-induced carcinogenesis: Emerging new paradigms. Biochim Biophys Acta Rev Cancer. 2018;1869:42-52.
100. Choi YJ, Kim N. Gastric cancer and family history. Korean J Intern Med. 2016;31:1042-53.
101. Yaghoobi M, McNabb-Baltar J, Bijarchi R, Hunt RH. What is the quantitative risk of gastric cancer in the first-degree relatives of patients? A meta-analysis. World J Gastroenterol. 2017;23:2435-42.
102. Cam S. Risk of Gastric Cancer in Children with *Helicobacter pylori* Infection. Asian Pac J Cancer Prev 2014;15:9905-8.
103. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ. 2014;348:g3174. doi: 10.1136/bmj.g3174.
104. Ford AC, Forman D, Hunt R, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev. 2015;(7):CD005583.
105. Yeh JM, Kuntz KM, Ezzati M, Goldie SJ. Exploring the cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer in China in anticipation of clinical trial results. Int J Cancer. 2009;124:157-66.
106. Seta T, Takahashi Y, Noguchi Y, Shikata S, Sakai T, Sakai K, Yamashita Y, Nakayama T. Effectiveness of *Helicobacter pylori* eradication in the prevention of primary gastric cancer in healthy asymptomatic people: A systematic review and meta-analysis comparing risk ratio with risk difference. PLoS One. 2017;12(8):e0183321.
107. George S, Lucero Y, Torres JP, Lagomarcino AJ, O›Ryan M. Gastric Damage and Cancer-Associated Biomarkers in *Helicobacter pylori*-Infected Children. Front Microbiol. 2020 Feb 12;11:90. doi: 10.3389/fmicb.2020.00090. eCollection 2020.
108. International Agency for Research on Cancer. *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. Geneva, Switzerland: WHO Press, World Health Organization, 2014.
109. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P. Kyoto global consensus report on *Helicobacter pylor*i gastritis. Gut. 2015;64:1353-67.
110. Choi IJ, Kim CG, Lee JY, Kim YI, Kook MC, Park B, Joo J. Family history of gastric cancer and *Helicobacter pylori* treatment. N Engl J Med. 2020;382(5):427-36. doi: 10.1056/NEJMoa1909666.