Approach to *Helicobacter pylori* infection in paediatric population

Matjaž Homan

Unit of Gastroenterology and Hepatology, Division of Paediatrics, University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence:
Matjaž Homan, e: matjaz.homan@guest.arnes.si

Key words:
antibiotic susceptibility; children; eradication; Helicobacter pylori

Received: 26. 8. 2017
Accepted: 28. 11. 2017

Abstract

Prevalence of *Helicobacter pylori* infection has decreased significantly in recent years, especially in the developed world where it dropped below 20 %. In the majority of cases in children, *Helicobacter pylori* causes asymptomatic chronic gastritis. Systematic reviews and meta-analysis showed that recurrent abdominal pains in children are not associated with bacterial infection. Therefore "test and treat" strategy is not recommended in paediatric population. Eradication therapy should be prescribed according to antimicrobial sensitivity of the bacterial strain obtained during endoscopy. The article summarizes recent recommendations and guidelines of the joint North American and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN, ESPGHAN) published this year and based on the systemic review of published studies from the field.

Cite as: Homan M. [Approach to Helicobacter pylori infection in paediatric population]. Zdrav Vestn. 2018;87(7–8):378–84.

DOI: 10.6016/ZdravVestn.2646

1 Introduction

Helicobacter pylori (*H.pylori)* infection most frequently occurs in childhood. It remains one of the most common infections in man although in developed countries its prevalence has been decreasing steadily and is currently 15–20 % (1,2). Unlike in adults in whom *H. pylori* infection is an important cause of gastric cancer, in children the infection is mostly asymptomatic and may even have beneficial effects on their immune system (3). Because of overuse of antibiotics and the associated widespread antibiotic resistance, the efficacy of *H. pylori* infection treatment in children has declined below the acceptable level of 90 % (4). Extensive research on the subject failed to confirm the association between *H. pylori* infection and chronic gastric pain in children without endoscopic evidence of upper gastrointestinal erosions or ulcers (5). Therefore treatment of *H. pylori* infection in children differs significantly from that in adults. In the paediatric population the diagnostic evaluation and treatment are not always necessary. The paper deals with relevant conclusions of the 2018 guidelines for *H. pylori* management in the developed world. The prevalence of infection in developing countries is signi-

ficantly higher: it affects more than 80 % of the population on average.

2 »Test and treat » strategy in children is not sensible

The so-called »test and treat« approach is used in adults infected with *H. pylori.* Individuals with chronic upper gastrointestinal symptoms are assessed by a non-invasive test for detection of *H. pylori*, either by a stool antigen test or urea breath test. Patients with positive test results are started on empirical eradication therapy. However, there is no evidence regarding health benefits to children from testing for *H. pylori.* Extensive research on the subject has provided no evidence to confirm the association between chronic abdominal pain and *H. pylori* infection in children without evidence of upper gastrointestinal ulcerations and erosions (3). Peptic ulcer disease in children is very rare. Eradication therapy is not invariably recommended in children without ulcer disease who have endoscopically diagnosed upper gastrointestinal *H. pylori* infection. There are several reasons for this strategy: a)according to the studies conducted hithero, successful *H. pylori* eradication will most probably provide no improvement of gastrointestinal symptoms; b) it is most unlikely that within the ensuing ten year a child not treated for *H. pylori* infection will develop a serious disease, such as duodenal ulcer od MALT lymphoma; and c) children infected with *H. pylori* are less likely to develop allergic diseases or asthma (6). During eradication treatment, half of the patients complain of adverse side-effects, such as headache, diarrhoea, nausea and metallic taste in the mouth. It should be borne in mind that infection may recur despite successful eradication therapy. According to the results of the German study based on the epidemiological data comparable to those for Slovenia, the probable reinfection rate is 2.3 % per year (7). If *H. pylori* is detected by chance, the reasons against eradication treatment are explained to the infected child or the child‘s parents and the decision to either treat or only monitor the infection is made together with them.

3 Indications for active testing for *H. pylori* in children

A child with alarm upper gastrointestinal signs or symptoms should have upper gastrointestinal endoscopy to determine the causes of the health problem. If gastric/duodenal ulceration or erosion is found, it is imperative to collect two to four gastric mucosa biopsy samples for diagnosis and culture of *H. pylori*. Efficacy of eradication therapy should be assessed at one month after the completion of treatment using non-invasive tests. Gastric or duodenal ulcer is very likely to recur if *H. pylori* has not been successfully eradicated (8). Testing for bacterial infection is not required in children with chronic abdominal pain without alarm signs and symptoms. This pain is most probably functional and will not be relieved by successful eradication of *H. pylori.*

Active testing for H. pylori is necessary in a child presenting with chronic immune thrombocytopenic purpura (cITP). As demonstrated by the studies published hitherto, platelet count tends to improve once *H. pylori* has been succcessfully eradicated (9-11). The efficacy of therapy seems to depend on the presence of virulence gene cagA in the genome of *H. pylori* strains. Molecular structure of cagA is very similar to that of platelet peptide with a molecular mass

Table 1: Recommended body-weigh-tailored doses

Medication	Body weight	Morning	Evening
PPI	15 to 24 kg	20 mg	20 mg
	25 to 34 kg	30 mg	30 mg
	> 35 kg	40 mg	40 mg
AM	15 to 24 kg	500 mg (750 mg*)	500 mg (750 mg*)
	25 to 34 kg	750 mg (1000 mg*)	750 mg (1000 mg*)
	> 35 kg	1000 mg (1500 mg*)	1000 mg (1500 mg*)
CL	15 to 24 kg	250 mg	250 mg
	25 to 34 kg	500 mg	250 mg
	> 35 kg	500 mg	500 mg
ME	15 to 24 kg	250 mg	250 mg
	25 to 34 kg	500 mg	250 mg
	> 35 kg	500 mg	500 mg

PPI –proton pump inhibitor, AM – amoxycillin, CL – clarithromycin, ME – metronidazole
* high-dose AM

of 55 kDa. After successful bacteria eradication, antibodies to cagA protein are no longer detectable; antiplatelet antibodies disappear, and as a result, platelet count rises. In Slovenia, 61.2 % of children are infected with *H. pylori* strains with cagA in their genome (12,13). Only exceptionally, non-invasive tests, such as stool antigen test or urea breath test, can be used for the diagnosis of *H.pylori* infection in children with cITP. Thrombocytopenia increases the risk of complications (bleeding) during upper gastrointestinal endoscopy and biopsy sample collection for bacterial culture.

Iron-deficiency anaemia is a frequent childhood disorder due to high iron requirements during growth periods, and is usually well managed by iron replacement therapy. Anaemia that is not responding to iron supplementation may be due to blood loss associated with *H.pylori*-caused ulcer disease (14). *H.pylori* is known to feed on dietary iron. If anaemia fails to improve despite iron replacement therapy, it is sensible to perform endoscopy and institute appropriate treatment if *H.pylori* infection is diagnosed.

There is no sufficient evidence to confirm that chronic *H.pylori* infection impairs growth. Since short stature and bacterial infection are associated with low socioeconomic status, infection is more likely to occur in children with short stature. Numerous studies, most of them conducted in low-income countries, failed to confirm that short stature in childhood is an evidence-based argument for initiating testing for *H.pylori* infection (15).

4 Diagnosis of bacterial infection

Unlike in adult patients, in children definitive diagnosis of *H.pylori* infection should always be based on the results

of upper gastrointestinal endoscopy and gastric mucosal biopsy. The diagnosis should be ultimately confirmed by another test of gastric mucosal biopsy specimen, i.e. fast urease test or molecular test (polymerase chain reaction). Molecular test is the most reliable test for detecting active bleeding in the digestive tract (16). Identification of *H.pylori* from bacterial culture is the only method with a 100 % reliability. Prevalence of *H.pylori* infection in children has been decreasing, therefore all other tests have become less reliable. The diagnosis should not be based on a positive histopathological test alone. In children younger than five years, the reliability of fast urease test is lower, most probably because of small number of bacteria present on the gastric mucosa. Serological tests for determination of IgA or IgG in the serum, blood, saliva or urine are no longer recommended, not even in epidemiology.

The effectiveness of eradication therapy should be determined one month after the completion of treatment. Non-invasive tests, such as urease breath test (^{13}C-UBT) or stool antigen test are employed. Other non-invasive methods have been shown to have insufficent reliability. In children aged less than six years, urea breath test may yield false positive results because of the child's small lung volume and different level of carbon dioxide production (17). Moreover, it is difficult to get small children to cooperate in testing.

5 Treatment of *H.pylori* infection

5.1 First-line treatment

Eradication therapy is based on the determination of antibiotic sensitivity of bacterial strains. In order to improve bacterial culture sensitivity, a special transport medium is used for transporting gastric mucosal samples to the microbiology laboratory. Sensitivity of the method for detecting mixed-strain infection is improved by taking at least two mucosal specimens, one from the gastric antrum and another from the gastric body. One transport medium can be used for transporting both specimens to the microbiology laboratory for analysis.

Despite the use of targeted antibiotic therapy – based on antibiotic susceptibility testing – the eradication treatment success rate remains below the acceptable level of 90 % (18). In the Slovenian study published in 2017, the rate of bacterial eradication was 85.9 % (19). Poor treatment compliance was identified as the main reason for low success rate of eradication therapy. The results of the study indicate that at least 90 % of the prescribed medications should be taken for *H.pylori* eradication to be successful (20). Poor treatment adherence is attributable to a large number of drugs prescribed, a 14-day regimen and high incidence of side effects. Prior to treatment, the child or the child's parents should be given a clear explanation of the treatment plan and possible side effects, and the importance of full adherence to the prescribed medications should be stressed.

Children with *H.pylori* infection are treated for 14 days. Body-weight-tailored drug doses are indicated in Table 1.

Guidelines for the first-line treatment of *H.pylori* based on antibiotic sensitivity testing.

1. Proton pump inhibitor (PPI), amoxycillin (AM), clarithromycin (CL) (non-resistant strain).
2. PPI, AM, metronidazole (ME) (CL-resistant strain).
3. PPI, AM, CL (ME-resistant strain).
4. PPI, AM (high-dose) (Table 1), ME (CL- and ME-resistant strain).
5. PPI, AM (high-dose) (Table 1), ME (strain sensitivity test not available).

The effectiveness of therapy depends to the largest extent on the antibiotic sensitivity of the isolated strain. In Slovenia, the rate of resistance to CL in children exceeds 20 %; it is slightly lower for the adult population. ME resistance rate of > 20 % is found in both children and adults (19,21,22). When data on antibiotic susceptibility are not available, CL is not included in the first-line therapy because of the high CL-resistance rate reported for the paediatric population in Slovenia.

Sequential regimen is one of the treatment options in patients infected with *H.pylori*. It consists of a 10-day treatment comprising PPI and AM for the first five days, followed by a combination of CL and ME for the remaining five days. A 10-day sequential regimen has not proved effective in children infected with CL resistant bacterial strain. It can be used as an alternative therapy to the recommended first-line treatment with PPI, AM and CL for children infected with a bacterial strain that is not resistant neither to ME nor to CL.

The eradication regimen comprising a bismuth preparation (PPI, two antibiotics) can be prescribed in children as an alternative regimen for double resistant strains, or in case bacterial strain culture is not available.

Most meta-analyses investigating the role of probiotics in the treatment of *H.pylori* infection in adults showed that including adequate amounts of specific probiotic preparations in standard eradication regimens has beneficial effects on the success rate of bacterial eradication (23). The role that probiotic supplementation may play in improving the efficacy of eradication and decreasing the incidence of eradication therapy-related side effect in children has not yet been clarified. For now, there is not enough high-quality research to support the use of supplementary probiotics in the standard treatment of children with specific probiotic bacterial strains.

5.2 *H.pylori* treatment in children not responding to first-line therapy

The efficacy of treatment should always be assessed using an appropriate urea breath test or monoclonal stool antigen test. When treatment failure is confirmed, switching to a new eradication regimen is necessary. In the paediatric population, fewer treatment options are available than in adults, which makes choosing the most appropriate first-line therapy even more important.

Guidelines for a 14-day second-line treatment, depending on the antibiotic susceptibility of bacterial strains and the first-line eradication regimen:

1. PPI, AM, ME (non-resistant bacterial strain; first-line therapy included PPI, AK, CL)
2. PPI, AM, CL (non-resistant bacterial strain; first-line therapy included PPI, AM, ME)
3. PPI, AM (high-dose; see Table 1), ME or repeat endoscopy (therapy based on antibiotic sensitivity test results), (non-resistant bacterial strain; first--line treatment - sequential regimen).

4. PPI, AM (high-dose;see Table 1), ME (CL-resistant bacterial strain; first-line treatment included PPI, AM, ME).
5. PPI, AM (high-dose, see Table 1), ME or repeat endoscopy (further treatment based on antibiotic sensitivity testing results); (ME-resistant strain; first-line therapy included PPI. AM, CL).
6. PPI, AM (high-dose; see Table 1). ME or repeat endoscopy (further treatment based on the results of antibiotic sensitivity testing), (antibiotic sensitivity test not available, first-line treatment included PPI, two antibiotics).

After failure of the first-line eradication, it is mandatory that the second-line regimen is determined on the basis of antibiotic sensitivity tests and initial therapy. Studies in adult patients have demonstrated that it is sensible to increase the dose of PPI and ME (24). In children, PPI in doses higher than those recommended in the 2011 guidelines, was included already in the first-line regimen (25). According to a study published in 2011, high-dose PPI in AM should be given to children with bacterial strains resistant to ME and CL. These recommendations were taken into account in proposing *H.pylori* treatment modalities (26).

6 Conclusions

The efficacy of *H.pylor* infection treatment was well below the recommended level of 90 %. These findings underscore the importance of selecting a 14-day eradication regimen on the basis of the infecting strain antibiotic sensitivity. High-dose PPI should be used. Before initiating treatment, the child or the child's parents should be given a detailed explanation of the treatment plan stressing the importance of full adherence to the prescribed medications. Treatment with CL is indicated in patients who are confirmedly not infected with a CL-resistant bacterial strain. When antibiotic susceptibility of a given bacterial strain is not known, or testing cannot be performed, a triple therapy including high-dose PPI, ME and AM is prescribed. One month after the completion of treatment, urea breath test or stool antigen test for *H.pylori* should be done to assess the efficacy of eradication therapy. Selecting appropriate eradication regimen after failure of the first-line treatment is not easy: only a limited number of antibiotics are available for paediatric use, and there is a paucity of relevant studies of more complex eradiction regimens for children.

Studies of new treatment modalities, such as prospective bismuth-containing treatment, triple antibiotic therapy and treatment with specific probiotic strains would help us optimise second-line eradication regimens for children. Last but not least, the development of vaccine against *H.pylori* infection holds great promise for the future.

References

1. Jones NL, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, et al.; ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr. 2017 Jun;64(6):991–1003.
2. Homan M, Hojsak I, Kolaček S. Helicobacter pylori in pediatrics. Helicobacter. 2012 Sep;17 Suppl 1:43–8.
3. Sierra MS, Hastings EV, Goodman KJ. What do we know about benefits of H. pylori treatment in childhood? Gut Microbes. 2013 Nov-Dec;4(6):549–67.

4. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut. 2010 Aug;59(8):1143–53.
5. Spee LA, Madderom MB, Pijpers M, van Leeuwen Y, Berger MY. Association between helicobacter pylori and gastrointestinal symptoms in children. Pediatrics. 2010 Mar;125(3):e651–69.
6. Holster IL, Vila AM, Caudri D, den Hoed CM, Perez-Perez GI, Blaser MJ, et al. The impact of Helicobacter pylori on atopic disorders in childhood. Helicobacter. 2012 Jun;17(3):232–7.
7. Feydt-Schmidt A, Kindermann A, Konstantopoulos N, Demmelmair H, Ballauff A, Findeisen A, et al. Reinfection rate in children after successful Helicobacter pylori eradication. Eur J Gastroenterol Hepatol. 2002 Oct;14(10):1119–23.
8. Bontems P, Kalach N, Vanderpas J, Iwanczak B, Casswall T, Koletzko S, et al. Helicobacter pylori Infection in European children with gastro-duodenal ulcers and erosions. Pediatr Infect Dis J. 2013 Dec;32(12):1324–9.
9. Brito HS, Braga JA, Loggetto SR, Machado RS, Granato CF, Kawakami E. Helicobacter pylori infection & immune thrombocytopenic purpura in children and adolescents: A randomized controlled trial. Platelets. 2015;26(4):336–41.
10. Russo G, Miraglia V, Branciforte F, Matarese SM, Zecca M, Bisogno G, et al.; AIEOP-ITP Study Group. Effect of eradication of Helicobacter pylori in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. Pediatr Blood Cancer. 2011 Feb;56(2):273–8.
11. Ferrara M, Capozzi L, Russo R. Effect of Helicobacter pylori eradication on platelet count in children with chronic idiopathic thrombocytopenic purpura. Hematology. 2009 Oct;14(5):282–5.
12. Homan M, Luzar B, Kocjan BJ, Orel R, Mocilnik T, Shrestha M, et al. Prevalence and clinical relevance of cagA, vacA, and iceA genotypes of Helicobacter pylori isolated from Slovenian children. J Pediatr Gastroenterol Nutr. 2009 Sep;49(3):289–96.
13. Homan M, Šterbenc A, Kocjan BJ, Luzar B, Zidar N, Orel R, et al. Prevalence of the Helicobacter pylori babA2 gene and correlation with the degree of gastritis in infected Slovenian children. Antonie van Leeuwenhoek. 2014 Oct;106(4):637–45.
14. Thankachan P, Muthayya S, Sierksma A, Eilander A, Thomas T, Duchateau GS, et al. Helicobacter pylori infection does not influence the efficacy of iron and vitamin B(12) fortification in marginally nourished Indian children. Eur J Clin Nutr. 2010 Oct;64(10):1101–7.
15. Goodman KJ, Correa P, Mera R, Yepez MC, Cerón C, Campo C, et al. Effect of Helicobacter pylori infection on growth velocity of school-age Andean children. Epidemiology. 2011 Jan;22(1):118–26.
16. Rimbara E, Sasatsu M, Graham DY. PCR detection of Helicobacter pylori in clinical samples. Methods Mol Biol. 2013;943:279–87.
17. Leal YA, Flores LL, Fuentes-Pananá EM, Cedillo-Rivera R, Torres J. 13C-urea breath test for the diagnosis of Helicobacter pylori infection in children: a systematic review and meta-analysis. Helicobacter. 2011 Aug;16(4):327–37.
18. 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 e3; Discussion e12–3.
19. Butenko T, Jeverica S, Orel R, Homan M. Antibacterial resistance and the success of tailored triple therapy in Helicobacter pylori strains isolated from Slovenian children. Helicobacter. 2017;22(5):e12400.
20. Schwarzer A, Bontems P, Urruzuno P, Kalach N, Iwanczak B, Roma-Giannikou E, et al. Sequential Therapy for Helicobacter pylori Infection in Treatment-naïve Children. Helicobacter. 2016 Apr;21(2):106–13.
21. Tepeš B, Vujasinović M, Šeruga M, Stefanovič M, Forte A, Jeverica S. Randomized clinical trial comparing 10-day sequential, 7-day concomitant and 7-day standard triple therapies for Helicobacter pylori eradication. Eur J Gastroenterol Hepatol. 2016 Jun;28(6):676–83.
22. Jeverica S, Tepeš B, Ihan A, Skvarč M. Primarna odpornost bakterije Helicobacter pylori. Zdrav Vestn. 2010;79(1):25–30.
23. Zhu R, Chen K, Zheng YY, Zhang HW, Wang JS, Xia YJ, et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. World J Gastroenterol. 2014 Dec;20(47):18013–21.
24. Molina-Infante J, Lucendo AJ, Angueira T, Rodriguez-Tellez M, Perez-Aisa A, Balboa A, et al.; European Registry on H. pylori management (Hp–EuReg). Optimised empiric triple and concomitant therapy for Helicobacter pylori eradication in clinical practice: the OPTRICON study. Aliment Pharmacol Ther. 2015 Mar;41(6):581–9.
25. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, et al.; H pylori Working Groups of ESPGHAN and NASPGHAN. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011 Aug;53(2):230–43.
26. Zeng M, Mao XH, Li JX, Tong WD, Wang B, Zhang YJ, et al. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 Oct;386(10002):1457–64.