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Is Helicobacter pylori Anyway Pathogen in Children?

Marco Manfredi, MD, PhD[1], Pierpacifico Gismondi, MD, PhD[2], and Silvia Iuliano, MD[3]

Abstract

Helicobacter pylori (*H. pylori*) infection is a continuous challenge for both gastroenterologists and pediatricians. The international guidelines regarding diagnostic and treatment pathways differ between adults and children. The pediatric guidelines are more restrictive because children are rarely affected by serious consequences, particularly in Western countries. Therefore, infected children should be treated only after a careful case-by-case evaluation by a pediatric gastroenterologist. In any case, recent studies are confirming an increasingly all-around pathological role of *H. pylori* even in asymptomatic children. For these reasons, following the current evidence, we feel that *H. pylori*-infected children could be treated starting in pre-adolescence, particularly in Eastern countries, because their stomachs have already begun to develop the biomarkers of gastric damage. Therefore, we believe that *H. pylori* is anyway pathogen in children. Nevertheless, the possible beneficial role of *H. pylori* in humans has not yet been conclusively disproved.

Keywords

Helicobacter pylori, children, infection, management, adolescence

What is already known about this topic?
Current Western pediatric international guidelines on the management of *H. pylori* infection have a restrictive approach in both diagnosis and therapy compared to the guidelines for adults. In infected young adult patients without alarm signs, a "test and treat" strategy is recommended.

How our research contributes to the field?
Our research is based on the most recent evidence-based knowledge in the field and could contribute, at least in part, to raising questions about such a restrictive approach in infected children, encouraging new related studies.

Implications for theory, practice, or policy?
Our study should motivate researchers to better evaluate why treatment should not necessarily be ruled out for *H. pylori*-infected children with no alarm signs, considering the possible risks linked to ongoing infection, despite the fact that they are clinically paucisymptomatic or asymptomatic. Treating Western children with *H. pylori* infection, although they have a low risk of developing *H. pylori*-related gastric cancer, could prevent the onset of certain related minor diseases such as iron deficiency anemia, chronic idiopathic thrombocytopenic purpura, and failure to thrive.

Helicobacter pylori (*H. pylori*) infection remains an important cause of gastrointestinal and non-gastrointestinal diseases such as iron deficiency anemia, idiopathic thrombocytopenic purpura.[1-6] This infection is predominantly acquired during infancy or childhood and the primary transmission route is by close person-to-person contact, mainly within the same household.[7]

The latest ESPGHAN/NASPGHAN guidelines recommend that before deciding to investigate *H. pylori* infection in children with abdominal pain, we should carefully evaluate whether upper gastrointestinal endoscopy is needed to better study all possible causes and not merely focus on *H. pylori* infection.[8] On the other hand, *H. pylori* infection must be treated in children with peptic ulcer disease or in the event of a first-degree relative with gastric cancer. The guidelines do not recommend the "test and treat" strategy in children. Similarly, if *H. pylori* infection is incidentally diagnosed during upper digestive endoscopy performed for an unrelated clinical suspicion, the subsequent eradication treatment should be considered only after a careful discussion of the risks and benefits with parents. In fact, eradication does not always improve symptoms and may increase the risk of

developing gastroesophageal reflux disease, allergic diseases, and asthma.[8] This is because the prevalence of neoplastic complications of *H. pylori* infection during childhood is very low, especially in Western countries. On the contrary, in some Asian countries like China and Japan, where the prevalence of *H. pylori*-associated gastric cancer is high, the benefits of eradication outweigh the risks linked to treatment in children.[8]

It is known that *H. pylori* infection causes a chronic low-grade inflammatory response in the gastro-duodenal mucosa, which may persist lifelong if the infection is not treated.[2,9] So in any case, infected children will have gastric inflammation, although with inter-individual variability of severity, and they can also develop several associated diseases.[8,10] For example, many studies have confirmed a strong association between *H. pylori* infection and iron deficiency anemia.[11-14] Chronic immune thrombocytopenic purpura in adults can be resolved by *H. pylori* eradication, but the effect of antibiotic treatment for pediatric patients has not yet been fully clarified.[2,11,12,15-17]

However, there are discordant results regarding the association between *H. pylori* infection and failure to thrive in children. Yang et al[18] reported that successful eradication of *H. pylori* during childhood increases growth and restores serum acylated ghrelin levels. Another study reported a higher percentage of delayed growth in children infected with *H. pylori* compared with controls, while others reported no causative effect.[19-22] A very recent meta-analysis by Wei et al[10] suggests that "preventing and detecting *H. pylori* infection in children may be critical to ensure normal growth and development during childhood."

In recent years, the literature on the composition and alteration of the intestinal microbiota in general, and the gastric microbiota in particular, has grown exponentially. Several recent studies focusing on the gastric microbiota have shown that when *H. pylori* is present, it represents the dominant species in the stomach and its interaction with other microbes may play a pivotal role in *H. pylori*-associated diseases, increasing gastric inflammation and promoting *H. pylori*-associated carcinogenesis.[1,23,24] In this regard, other studies have shown that *H. pylori* infection is associated with a shift of the intestinal microbiota toward a *Prevotella*-dominated microbiome.[25] The longer the changes in the gastric microbiota settle into the stomach, the higher the risks for the patient, even though these risks have not yet been fully understood.[26-30]

In addition, several studies have shown that infected children also present serum biomarkers associated with gastric damage compared to healthy ones.[31-34] Although these changes in the gastric microbiota are not enough to cause gastric cancer, they do seem to represent a step in the initiation of the carcinogenic cascade starting from *H. pylori*.[1,35] *H. pylori*, mainly certain specific serotypes, is probably the prime mover in the gastric carcinogenic cascade together with dietary, environmental, and genetic factors, as well as non-*H. pylori* bacteria.[35] It is well known that dietary patterns play a pivotal role in gastric carcinogenesis. Some types of foods seem to have a protective role, such as fruits, vegetables and vitamin intake; others such as coffee, alcohol, spicy and fried foods, and red meat seem to increase the risk of developing gastric cancer.[36,37] Gastric cancer is the fifth most common type of cancer and the third leading cause of cancer death worldwide, and it has been reported that more than 70% of gastric cancers can be attributed to *H. pylori* infection.[36,38,39] Although gastric cancer is a rare event before age 50, the risk increases with age, showing the highest incidence between the sixth and seventh decades of life. In addition, the incidence rates are 2 to 3 times higher in men than in women.[36] Though many studies support the beneficial role of *H. pylori* eradication in reducing the risk of developing gastric cancer in the adult population, data are still lacking for children.[39-43]

Another essential factor involved in *H. pylori*-related consequences is the alteration of the microbiota. Though researchers have only just begun to study and understand the effect of modifications of the microbiota on humans, a higher microbiota diversity is generally associated with better health, playing an essential role in human well-being.[44] *H. pylori* infection significantly modifies the bacterial composition of the gastric microbiota, the strongest association being with *Prevotella copri* and members of the Clostridiales family, whereas it depletes the abundance of *Clostridium, Coprococcus*, and *Ruminococcus*, even in asymptomatic children. *Prevotella copri* is considered an immune-relevant gut microbe that has also been associated with the development of various inflammatory diseases.[45-47] Hence, the abundance of *Prevotella copri* in *H. pylori*-positive children could be related to changes in the intestinal immune environment, making them susceptible to inflammation and diseases.[34,45] This would support the affirmation expressed by David Y. Graham that *H. pylori* is not a good bacterium in any case and its presence cannot be wholesome.[48] In addition, studies demonstrating that infected children have serum biomarkers of gastric damage confirm the pathological role of *H. pylori*, even in pediatric age.[29-33,48] Over the course of their lives, *H. pylori*-positive children will almost surely be affected by minor pathologies such as peptic ulcers,

[1]Azienda USL-IRCCS di Reggio Emilia, Maternal and Child Department, Pediatric Unit, Sant'Anna Hospital, Castelnovo ne Monti, Reggio Emilia, Italy
[2]Week Hospital, Pietro Barilla Children's Hospital, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy
[3]Pediatric Gastroenterology, Pietro Barilla Children's Hospital, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

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Corresponding Author:
Marco Manfredi, Azienda USL-IRCCS di Reggio Emilia, Maternal and Child Department, Pediatric Unit, Sant'Anna Hospital, via Roma, 2 - Castelnovo ne Monti, Reggio Emilia 42122, Italy.
Email: marco.manfredi@ausl.re.it

anemia, thrombocytopenic purpura, and failure to thrive, and possibly even gastric malignancies.[2] Therefore, if these alterations could be prevented, patients would be less susceptible to these conditions.

On the other hand, as *H. pylori* has existed in humans for a very long time, some authors believe it could be a possible commensal of the gastric microbiota, thus with a supposed beneficial role.[49,50] Several studies have found an inverse correlation (called "protective") between *H. pylori* and certain pathologies, such as asthma, allergic diseases, and gastroesophageal reflux, but the "hygiene hypothesis" has failed to prove this positive association.[51-56] Many studies have shown that *H. pylori* represents a surrogate for the hygiene hypothesis; it has been shown that in regions where *H. pylori* has a low prevalence, the prevalence of asthma, atopy, and gastroesophageal reflux is also low. In fact, in Malaysia, Zanzibar and Java, for example, *H. pylori prevalence* is low, and at the same time obesity, asthma, and gastroesophageal reflux are uncommon.[52,57,58] Therefore, it could be argued that the proposition that *H. pylori* in children should not be eradicated because the incidence of asthma and gastroesophageal reflux might increase should be rejected. Nevertheless, as Thomas Henry Huxley wrote, "the great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact." In fact, an increase in hygienic and economic conditions associated with a decrease in infectious diseases during childhood may be the cause of the rise of asthma, rhinitis and atopy.[59]

Without a doubt, *H. pylori* increases the risk of gastric cancer, but it can also cause several minor pathologies which often implicate a heavy burden on both patients and the healthcare system; therefore, it is unlikely to think it could be useful for humans, even for children.[10,53,59,60] It is thus probable that *H. pylori* is always harmful and that humans are better off without it, as clearly expressed in the statement: "The only good *H. pylori* is a dead H. pylori."[48]

The "wait and see" attitude, leaving the decision to eradicate the infection to adult gastroenterologists, may underestimate the related minor sequelae in relation to children. Although there is no consensus on the age for screening for *H. pylori* infection in children, recent studies suggest that the ideal age to treat *H. pylori*-positive children could be about 10 to 12 years of age, because these children already have biomarkers of gastric damage.[9,29] The infection is most frequently acquired in childhood, and according to the experimental work of Cao et al the earlier the acquisition of infection, the higher the risk of onset of carcinogenesis.[61,62] Moreover, some studies have demonstrated that eradication therapy has proven to be effective in restoring the gastric mucosal layer in both adults and children following the appearance of pre-malignant lesions, such as gastric atrophy and intestinal metaplasia.[63] Nevertheless, additional studies are needed to better evaluate and investigate this matter.

The ESPGHAN/NASPGHAN guidelines state that the primary goal of clinical investigation is to identify the underlying cause of upper gastrointestinal symptoms.[8] The authors stated that if *H. pylori* is found, even in asymptomatic children (ie, family members of positive patients), it should not necessarily be treated, because the symptoms do not often actually improve after eradication. However, in our opinion, persistent symptoms could be due to associated functional gastrointestinal disorders or alterations of the microbiota following antibiotic therapy, so they would not disappear quickly after eradication. Nevertheless, *H. pylori*, a known significant human pathogen, would be eliminated from the stomach.

We also believe that gastroscopy should not be performed on all *H. pylori*-positive children, particularly if the antimicrobial susceptibility test is not available. But as many authors and studies related to adults suggest, also for children we could consider them infected when 2 or more non-invasive tests are positive (therefore the negative predictive value would be very low). Then we might treat infected children using the "test and treat" strategy, based either on local or personal antibiotic history, even if there are no alarm signs (right upper or right lower quadrant pain, dysphagia, odynophagia, persistent vomiting, gastrointestinal blood loss, involuntary weight loss, deceleration of linear growth, delayed puberty, unexplained fever, and a family history of inflammatory bowel disease, celiac disease, anemia, first-degree relative of patient with gastric cancer, previous peptic ulcer disease).[29] We could reserve gastroscopy as a second option, if the first-line therapy fails, performing a histology culture and better choosing the antibiotic based on the susceptibility of the strain.[2,64] Furthermore, by eradicating *H. pylori*, not only will its direct effects on gastric inflammation decrease, but also by acting on the remaining parietal cells, acid secretion can increase toward more normal stages.[29]

In addition, although *H. pylori* eradication therapy can lead to a short-term dysbiosis of the gut microbiota, the gastric microbial composition returns close to that of *H. pylori*-negative children within about 1 year after eradication.[35,65,66] In any case, in this regard many authors suggest a combination therapy with multiple selected probiotic strains to reduce the related side effects of poly-antibiotic therapy and quickly restore the microbiota.[8,67]

Certainly, making the right choice of eradication treatment has been a continuous challenge for pediatricians because of the limited antibiotic availability for children compared to adults.

It is known that the best way to obtain a good eradication rate is by using antimicrobial susceptibility testing, but in the empirical regimen, a better antibiotic combination should be chosen based on local antimicrobial resistance and on the previous personal use of antibiotics.[8,64,68] Recently, a new non-invasive method on stools has been introduced that can determine antibiotic susceptibility and therefore make it possible to treat *H. pylori*-infected patients without gastroscopy.[69]

An eradication therapy using potassium-competitive acid blockers and a high-dose dual therapy (probably with lesser impact on the microbiota) have demonstrated higher effectiveness in adults and children.[65,70,71]

Conclusions

We know that *H. pylori* infection does not cause the same effects in children as in adults. However, as children represent the first stage of the acquisition of the infection, in our opinion eradication in children should be considered.

Many biomarkers with a consistent role in carcinogenesis, previously detected in adults with *H. pylori*-related gastric cancer, have also been observed in infected children, confirming the pathogenic role of *H. pylori* during the early stages of infection and supporting the evaluation of treatment for infected children.[29,72] In fact, following eradication, the biomarkers of gastric damage disappear and the gastric microbiota can be restored to a similar composition as in healthy people, so this can only be beneficial and favorable.

Western pediatric guidelines are so restrictive in recommending eradication also because of the known risk of developing antibiotic resistance. But are we sure that the risk of *H. pylori*'s increasing antibiotic resistance has a greater impact on healthcare costs than the efforts to diagnose and treat subsequent non-cancer-linked *H. pylori*-related diseases?

We believe that a good compromise, supported by actual evidence, could be to treat infected children starting in preadolescence, particularly in Eastern countries where the risk of developing gastric cancer still remains high.

Author's Declaration

MM conceived the manuscript and wrote it together with SI. PG collected the literature data. All authors approved the final version

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Ethics and Informed Consent Statement

Our study did not require an ethical board approval because it is a commentary.

ORCID iD

Marco Manfredi https://orcid.org/0000-0003-4473-1123

References

1. Yang L, Zhang J, Xu J, et al. *Helicobacter pylori* infection aggravates dysbiosis of gut microbiome in children with gastritis. *Front Cell Infect Microbiol*. 2019;9:375. doi:10.3389/fcimb.2019.00375
2. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence consensus report. *Gut*. 2017;66(1):6-30. doi:10.1136/gutjnl-2016-312288
3. Graham DY. History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer. *World J Gastroenterol*. 2014;20:5191-5204. doi:10.3748/wjg.v20.i18.5191
4. Sonnenberg A, Turner KO, Genta RM. Associations between gastric histopathology and the occurrence of colonic polyps. *Colorectal Dis*. 2020;22:814-817.
5. Manfredi M, de'Angelis GL. eds *Helicobacter pylori: Detection Methods, Diseases, and Health Implications*. Nova Science Publishers; 2013.
6. Deretzi G, Zavos C, Polyzos SA, et al. Chapter 11: Neurological disorders and *Helicobacter pylori* infection. In: Manfredi M and de'Angelis GL (eds) *Helicobacter pylori: Detection Methods, Diseases, and Health Implications*. Nova Science Publishers; 2013;201-222.
7. Kayali S, Manfredi M, Gaiani F, et al. *Helicobacter pylori*, transmission routes and recurrence of infection: state of the art. *Acta Biomed*. 2018;89(8-S):72-76. doi:10.23750/abm.v89i8-S.7947
8. 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. doi:10.1097/MPG.0000000000001594
9. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut*. 2015;64(9):1353-1367. doi:10.1136/gutjnl-2015-309252
10. Wei S, Dang Y, Peng L, Li X, Tang L, Zhang G. Association between *Helicobacter pylori* infection and delayed growth in children: a meta-analysis. *Exp Ther Med*. 2020;19:3814-3828. doi:10.3892/etm.2020.8654
11. Okuda M, Lin Y, Kikuchi S. *Helicobacter pylori* infection in children and adolescents. *Adv Exp Med Biol*. 2019;1149:107-120.
12. 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;20:1379-1401.
13. Muhsen K, Cohen D. *Helicobacter pylori* infection and iron stores: a systematic review and meta-analysis. *Helicobacter*. 2008;13:323-340.
14. Qu XH, Huang XL, Xiong P, et al. Does *Helicobacter pylori* infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol*. 2010;16:886-896.
15. Blanchette VS, Price V. Childhood chronic immune thrombocytopenic purpura: unresolved issues. *J Pediatr Hematol Oncol*. 2003;25(Supplement 1):S28-S33.
16. Russo G, Miraglia V, Branciforte F, et al. Effect of eradication of *Helicobacter pylori* in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. *Pediatr Blood Cancer*. 2011;56:273-278. doi:10.1002/pbc.22770
17. Treepongkaruna S, Sirachainan N, Kanjanapongkul S, et al. Absence of platelet recovery following *Helicobacter pylori* eradication in childhood chronic idiopathic thrombocytopenic purpura: a multicenter randomized controlled trial. *Pediatr Blood Cancer*. 2009;53:72-77. doi:10-1002/pbc.21991
18. Yang YJ, Sheu BS, Yang HB, Lu CC, Chuang CC. Eradication of *Helicobacter pylori* increases childhood growth and serum acylated ghrelin levels. *World J Gastroenterol*. 2012;18:2674-2681.

19. Thomas JE, Dale A, Bunn JE, et al. Early *Helicobacter pylori* colonisation: the association with growth faltering in the Gambia. *Arch Dis Child*. 2004;89:1149-1154.
20. Perri F, Pastore M, Leandro G, et al. *Helicobacter pylori* infection and growth delay in older children. *Arch Dis Child*. 1997;77:46-49.
21. Fialho AMN, Braga ABC, Queiroz DMM, Rodrigues MN, Herbster ID, Braga LLBC. The association between *Helicobacter pylori* infection and height in children from an urban community in North-East Brazil. *Ann Trop Pediatr*. 2007;27:55-61.
22. Patel P, Mendall MA, Khulusi S, Northfield TC, Strachan DP. *Helicobacter pylori* infection in childhood. Risk factors and effect on growth. *BMJ*. 1994;309:1119-1123.
23. Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, Mantilla A, Torres J. Stomach microbiota composition varies between patients with non-atrophic gastritis and patients with intestinal type of gastric cancer. *Sci Rep*. 2014;4(1): 4202. doi:10.1038/srep04202
24. Rizzato C, Torres J, Kasamatsu E, et al. Potential role of biofilm formation in the development of digestive tract cancer with special reference to *Helicobacter pylori* infection. *Front Microbiol*. 2019;10:846. doi:10.3389/fmicb.2019.00846
25. Frost F, Kacprowski T, Rühlemann M, et al. *Helicobacter pylori* infection associates with fecal microbiota composition and diversity. *Sci Rep*. 2019;9(1):20100.
26. Miftahussurur M, Yamaoka Y, Graham DY. *Helicobacter pylori* as an oncogenic pathogen, revisited. *Expert Rev Mol Med*. 2017;19(e4):1-11. doi:10.1017/erm.2017.4
27. Wang C, Weber A, Graham DY. Age, period, and cohort effects on gastric cancer mortality. *Dig Dis Sci*. 2015;60: 514-523. doi:10.1007/s10620-014-3359-0
28. Balakrishnan M, George R, Sharma A, Graham DY. Changing trends in stomach cancer throughout the world. *Curr Gastroenterol Rep*. 2017;19:36. doi:10.1007/s11894-017-0575-8
29. Lucero Y, Lagomarcino AJ, Torres JP, et al. Effect of *Helicobacter pylori* eradication therapy on clinical and laboratory biomarkers associated with gastric damage in healthy school-aged children: a randomized non-blinded trial. *Helicobacter*. 2021;26:e12853. doi:10.1111/hel.12853
30. Okuda M, Lin Y, Mabe K, et al. Serum pepsinogen values in Japanese junior high school students with reference to *Helicobacter pylori* infection. *J Epidemiol*. 2020;30(1): 30-36.
31. de'Angelis GL, Cavallaro LG, Maffini V, et al. Usefulness of a serological panel test in the assessment of gastritis in symptomatic children. *Dig Dis*. 2007;25(3):206-213.
32. Guariso G, Basso D, Bortoluzzi CF, et al. GastroPanel: evaluation of the usefulness in the diagnosis of gastro-duodenal mucosal alterations in children. *Clinica Chimica Acta*. 2009;402(1-2):54-60.
33. Isabel Lopes A, Palha A, Lopes T, Monteiro L, Oleastro M, Fernandes A. Relationship among serum pepsinogens, serum gastrin, gastric mucosal histology and *H. pylori* virulence factors in a paediatric population. *Scand J Gastroenterol*. 2006;41(5):524-531.
34. Zhang XY, Zhang PY, Aboul-Soud MA. From inflammation to gastric cancer: role of *Helicobacter pylori. Oncol Lett*. 2017;13(2):543-548. doi:10.3892/ol.2016.5506
35. Miao R, Wan C, Wang Z. The relationship of gastric microbiota and *Helicobacter pylori* infection in pediatrics population. *Helicobacter*. 2020;25:e12676. doi:10.1111/hel.12676
36. Eusebi LH, Telese A, Marasco G, Bazzoli F, Zagari RM. Gastric cancer prevention strategies: a global perspective. *J Gastroenterol Hepatol*. 2020;35:1495-1502. doi:10.1111/jgh.15037
37. Luu MN, Quach DT, Hiyama T. Screening and surveillance for gastric cancer: does family history play an important role in shaping our strategy? *Asia Pac J Clin Oncol*. 2022;18:353-362. doi:10.1111/ajco.13704
38. Chiang TH, Chang WJ, Chen SL, et al. Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. *Gut*. 2021;70:243-250.
39. Muzaheed. *Helicobacter pylori* oncogenicity: mechanism, prevention, and risk factors. *Sci World J*. 2020;2020(24):1-10. doi:10.1155/2020/3018326
40. Yan L, Chen Y, Chen F, et al. Effect of *Helicobacter pylori* eradication on Gastric Cancer Prevention: updated report from a randomized controlled trial with 26.5 years of follow-up. *Gastroenterology*. 2022;163:154-162.e3.
41. Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut*. 2020;69:2113-2121.
42. Ford AC, Yuan Y, Forman D, Hunt R, Moayyedi P. *Helicobacter pylori* eradication for the prevention of gastric neoplasia. *Cochrane Database Syst Rev*. 2020;7:CD005583. doi:10.1002/14651858.cd005583.pub3
43. Lin Y, Kawai S, Sasakabe T, et al. Effects of *Helicobacter pylori* eradication on gastric cancer incidence in the Japanese population: a systematic evidence review. *Jpn J Clin Oncol*. 2021;51:1158-1170.
44. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell*. 2012;148:1258-1270. doi:10.1016/j.cell.2012.01.035
45. Lapidot Y, Reshef L, Cohen D, Muhsen K. *Helicobacter pylori* and the intestinal microbiome among healthy school-age children. *Helicobacter*. 2021;26:e12854. doi:10.1111/hel.12854
46. Korecka A, Arulampalam V. The gut microbiome: scourge, sentinel or spectator? *J Oral Microbiol*. 2012;4:9367.
47. Pianta A, Arvikar S, Strle K, et al. Evidence of the immune relevance of Prevotella copri, a gut microbe, in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2017;69(5):964-975.
48. Graham DY. The only good *Helicobacter pylori* is a dead *Helicobacter pylori*. *Lancet*. 1997;350(9070):70-71. doi:10 .1016/S0140-6736(05)66278-2
49. Blaser MJ, Crabtree JE. CagA and the outcome of *Helicobacter pylori* infection. *Am J Clin Pathol*. 1996;106:565-567.
50. Maixner F, Krause-Kyora B, Turaev D, et al. The 5300-year-old *Helicobacter pylori* genome of the Iceman. *Science*. 2016;351(6269):162-165. doi:10.1126/science.aad2545
51. Aguilera Matos I, Diaz Oliva SE, Escobedo AA, Villa Jiménez OM, Velazco Villaurrutia YDC. *Helicobacter pylori* infection in children. *BMJ Paediatr Open*. 2020;4:e000679. doi:10.1136/ bmjpo-2020-000679
52. Lee YY, Mahendra Raj S, Graham DY. *Helicobacter pylori* infection–a boon or a bane: lessons from studies in a low-prevalence population. *Helicobacter*. 2013;18:338-346. doi: 10.1111/hel.12058

53. Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y. *Helicobacter*, hygiene, atopy, and asthma. *Front Microbiol*. 2017;8:1034. doi:10.3389/fmicb.2017.01034
54. Cullinan P, Harris JM, Newman Taylor AJ, et al. Can early infection explain the sibling effect in adult atopy? *Eur Respir J*. 2003;22:956-961. doi:10.1183/09031936.03.00039102
55. Lee SP, Lee SY, Kim JH, et al. Correlation between *Helicobacter pylori* infection, IgE hypersensitivity, and allergic disease in Korean adults. *Helicobacter*. 2015;20:49-55. doi:10.1111/hel.12173
56. den Hollander WJ, Sonnenschein-van der Voort AM, Holster IL, et al. *Helicobacter pylori* in children with asthmatic conditions at school age, and their mothers. *Aliment Pharmacol Ther*. 2016;43:933-943. doi:10.1111/apt.13572
57. Lee YY, Raj SM, Sharif SE, Salleh R, Ayub MC, Graham DY. Incidence of esophageal carcinoma among Malays in northeastern Peninsular Malaysia: an area with an exceptionally low prevalence of *Helicobacter pylori* infection. *Dig Dis Sci*. 2011;56:1438-1443.
58. Raj SM, Choo KE, Noorizan AM, Lee YY, Graham DY. Evidence against *Helicobacter pylori* being related to childhood asthma. *J Infect Dis*. 2009;199:914-915.
59. Robinson K, Atherton JC. The spectrum of *Helicobacter*-mediated diseases. *Annu Rev Pathol*. 2021;16:123-144. doi:10.1146/annurev-pathol-032520-024949
60. Hudak L, Jaraisy A, Haj S, Muhsen K. An updated systematic review and meta-analysis on the association between *Helicobacter pylori* infection and iron deficiency anemia. *Helicobacter*. 2017;22:1-16. doi:10.1111/hel.12330
61. Sherman PM. Appropriate strategies for testing and treating *Helicobacter pylori* in children: when and how? *Am J Med*. 2004;117(5):30-35. doi:10.1016/j.amjmed.2004.07.015
62. Cao X, Tsukamoto T, Nozaki K, et al. Earlier *Helicobacter pylori* infection increases the risk for the N-methyl-N-nitrosourea-induced stomach carcinogenesis in Mongolian gerbils. *Jpn J Cancer Res*. 2002;93:1293-1298.
63. Cam S. Risk of gastric cancer in children with *Helicobacter pylori* infection. *Asian Pac J Cancer Prev*. 2014;15:9905-9908.
64. Manfredi M, Gismondi P, Maffini V, et al. Primary antimicrobial susceptibility changes in children with *Helicobacter pylori* infection over 13 years in northern Italy. *Gastroenterol Res Pract*. 2015;2015:717349. doi:10.1155/2015/717349
65. Zou PY, Hu J, Zhao JT, et al. 10-day and 14-day high-dose dual therapy for the treatment of *Helicobacter pylori*: a propensity score matching analysis. *Helicobacter*. 2021;26:e12833. doi:10.1111/hel.12833
66. Llorca L, Pérez-Pérez G, Urruzuno P, et al. Characterization of the gastric microbiota in a pediatric population according to *Helicobacter pylori* status. *Pediatr Infect Dis J*. 2017;36:173-178. doi:10.1097/INF.0000000000001383
67. Lü M, Yu S, Deng J, et al. Efficacy of probiotic supplementation therapy for *Helicobacter pylori* eradication: a meta-analysis of randomized controlled trials. *PLoS One*. 2016;11(10):e0163743. doi:10.1371/journal.pone.0163743
68. Jun JS, Seo JH, Park JS, Rhee KH, Youn HS. Changes in the treatment strategies for *Helicobacter pylori* infection in children and adolescents in Korea. *Pediatr Gastroenterol Hepatol Nutr*. 2019;22:417-430. doi:10.5223/pghn.2019.22.5.417
69. Shiotani A, Roy P, Lu H, Graham DY. *Helicobacter pylori* diagnosis and therapy in the era of antimicrobial stewardship. *Therap Adv Gastroenterol*. 2021;14:17562848211064080. doi:10.1177/17562848211064080
70. Kaji E, Yoden A, Otani M, et al. *Helicobacter pylori* test-and-treat strategy for second-year junior high school students aimed at the prevention of gastric cancer in Takatsuki City. *Helicobacter*. 2020;25:e12696. doi:10.1111/hel.12696
71. Kusano C, Gotoda T, Suzuki S, Ikehara H, Moriyama M. Safety of first-line triple therapy with a potassium-competitive acid blocker for *Helicobacter pylori* eradication in children. *J Gastroenterol*. 2018;53:718-724.
72. 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;11:90. doi:10.3389/fmicb.2020.00090