THERAPEUTIC ADVANCES in
Gastroenterology

Review

Helicobacter pylori in children: think before you kill the bug!

Ther Adv Gastroenterol

2023, Vol. 16: 1–10

DOI: 10.1177/17562848231177610

M Ravikumara

***Abstract*:** Since the discovery of *Helicobacter pylori* (*H. pylori*) as the causative organism for gastric and duodenal ulcers four decades ago and subsequent recognition as class 1 gastric carcinogen, countless numbers of studies have been conducted and papers published, on the efficacy of various management strategies to eradicate the infection. In adults, a global consensus by the experts in the field concluded that *H. pylori* gastritis is an infectious disease and requires treatment irrespective of the presence or absence of symptoms due to the potential for serious complication like peptic ulcer disease and gastric neoplasia. However, although more than half the world's population harbors *H. pylori*, these serious complications occur only in a small minority of the infected population, even less so in childhood. More importantly, there is accumulating evidence for beneficial role of *H. pylori* against many chronic health conditions, from several epidemiological and laboratory studies. No doubt, eradication therapy is indicated in children with *H. pylori*-related peptic ulcer disease. Even though the pediatric guidelines from various learned societies recommend against a "test and treat" strategy, this is not always adhered to. With the accumulating evidence of the possible beneficial role of *H. pylori*, it is time to pause and think, are we causing more harm than good by eradicating *H. pylori* in every child who has this bug?

Keywords: Asthma and allergies, benefits, children, eosinophilic esophagitis, gastroesophageal reflux, *Helicobacter pylori*, inflammatory bowel disease, obesity

Received: 11 January 2023; revised manuscript accepted: 6 May 2023.

Introduction

Helicobacter pylori (*H. pylori*), a gram-negative bacterium that colonizes the gastric mucosa, is one of the most common gastrointestinal infections, infecting more than half the world's population.[1] The prevalence varies from 24% to 73% depending on geographical region and economic development.[2] The infection is mostly acquired in childhood and persists for life in the infected host unless treated.[3] Since the discovery of *H. pylori* by Warren and Marshall in 1983,[4] its causative role in peptic ulcer disease (PUD) and gastric cancers is well established. Eradication of *H. pylori* heals the ulcer, reduces the ulcer recurrence,[5] and might confer long-term protection against gastric cancer in high-risk populations.[6] In addition, iron deficiency anemia[7–9] and idiopathic thrombocytopenic purpura[10] are found to be strongly associated with the infection. There also appears to be growing interest in the potential role of *H. pylori* in other extragastric conditions including cardiovascular, respiratory, neurological, dermatological, and metabolic diseases.[11,12] An excellent recent review summarizes the extra gastric diseases associated with *H. pylori*.[12] With this background, various guidelines have evolved and updated by several professional bodies, endorsing testing and treating *H. pylori* infection in the adult population.[13–15]

However, children are not little adults, and this is true with respect to *H. pylori* infection too. The prevalence is lower; children have a low rate of severe disease associated with *H. pylori* and almost an absence of gastric malignancies.[16] Infection is generally asymptomatic in children. Several studies have shown a lack of evidence of relation between abdominal pain or other abdominal

Correspondence to:
M Ravikumara
Department of Gastroenterology, Perth Children's Hospital, Hospital Avenue, Nedlands, Perth, WA 6009, Australia
Madhur.Ravikumara@health.wa.gov.au

symptoms in children and *H. pylori* infection.[17–21] There is no evidence that eradication of *H. pylori*, in the absence of PUD, is beneficial in improvement of abdominal symptoms. In addition, there is increasing antibiotics resistance, particularly to Clarithromycin.[22–24]

Recognizing these differences, pediatric guidelines from many learned societies including that from the European Society of Pediatric Gastroenterology Hepatology and Nutrition and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition on the management of *H. pylori* in Children recommend against a 'test and treat strategy'. The primary goal of clinical investigation should be to identify the cause of abdominal symptoms rather than look for *H. pylori* infection.[25] Unfortunately, in real life, guidelines are not always adhered to.[26] It is all too common to see inappropriate tests (e.g., *H. pylori* serology or breath test) being used to diagnose the infection and any positive test leading to eradication treatment (authors personal experience). No doubt, eradication treatment should be done in children with PUD. What is not clear is whether treating *H. pylori* infection without PUD is beneficial at all. On the contrary, there is accumulating evidence that this may even be harmful, by exposing children to greater risks of various chronic conditions, as discussed in the following sections.

Method: Review of beneficial effects of *H. pylori* infection in children.

Asthma and allergies

The prevalence of allergic diseases and asthma had been increasing in many countries in recent decades,[27,28] which coincided with increased hygiene and socioeconomic conditions along with decrease in many infectious diseases.[29] The prevalence of *H. pylori* infection, both in children and adults, is decreasing in the western world as well as in some developing countries, as *H. pylori*-associated disease has led to aggressive diagnostic and eradication strategies. This contrasts with increase in childhood asthma and allergic diseases.[2,30–32] Though opposite prevalence trends of *H. pylori* infection and allergies have been reported, accumulating evidence supports an inverse relationship between *H. pylori* and the risk of asthma. After the first report by Chen and Blaser who found an inverse association between *H. pylori* seropositivity and asthma in children,[33] several studies and meta-analyses have confirmed this negative association. A recent meta-analysis of 18 observational studies reported the exact same conclusion that *H. pylori* infection, particularly CagA +ve infection, is inversely associated with the risk of childhood asthma. All 18 studies included in this analysis were of moderate to high quality and included a total of 17,196 children.[34] In a hospital-based case-control study, Elias *et al.* concluded that *H. pylori* infection and related gastric inflammation may have a protective role against pediatric asthma.[35] This inverse relationship with pediatric asthma is seen even in a high *H. pylori* prevalence population.[36] A recent cross-sectional study again demonstrated a significant inverse association between *H. pylori* infection and pediatric asthma.[37] There is also report that *H. pylori* not only protects against childhood asthma but also inversely correlates to its clinical and functional severity.[38] Chen *et al.* in their meta-analysis of 24 studies, which included both pediatric and adult subjects, concluded that the accumulated evidence supports that *H. pylori* infection (especially Cag A positive *H. pylori*) is inversely associated with the risk of asthma.[39]

Similar to asthma, systematic reviews and meta-analyses have reported an inverse correlation of *H. pylori* infection with atopy.[40–43] Children, in particular, appear to benefit from their *H. pylori* infection in that the inverse correlation with allergy is strongest in pediatric cohorts.[40] Though causality is not proven in humans, animal studies have shown a direct protective effect of *H. pylori* via regulatory T cells (Tregs).[44–46]

However, not all studies have demonstrated this inverse relationship with asthma. In their review of relevant surveys, cohort studies, meta-analyses, and studies testing the protective hypothesis of *H. pylori* against atopy, allergy, and asthma, Miftahussurur *et al.* reported that the meta-analyses showed a significant but weak inverse correlation, but studies directly testing the protection hypothesis in relation to asthma failed to confirm a protective effect[47]

Eosinophilic esophagitis (EoE), a chronic immune-mediated inflammatory disease of the esophagus, is increasing in frequency.[48] Interestingly, large cross-sectional analyses of several populations have identified an inverse relationship with EoE and the presence of

H. pylori.[49–51] In their comprehensive meta-analysis of 11 observational studies comprising data on 377,795 individuals worldwide, Shah *et al.* reported that exposure to *H. pylori* was associated with a 37% reduction in odds of EoE, irrespective of study location, prevalence of *H. pylori* in the population, time period, or whether studies were performed in pediatric or adult population.[52]

There are several proposed mechanisms as to how *H. pylori* infection in children could reduce the risk of asthma and allergies. It has been shown that the Tregs induced by *H. pylori* were able to skew adaptive immune response toward immune tolerance.[53] Other mechanisms include regulating Th1/Th2 and Th17/Tregs balance, inhibition of dendritic cells and Heat shock protein 70, activation of Toll-like receptors, reduction of gastroesophageal reflux, hygiene hypothesis, and gut–lung axis theory.[54] However, others have concluded that *H. pylori* is inversely related to good hygiene and its presence just serves as a biomarker rather than any specific prevention role for *H. pylori* or *H. pylori* antigens.[47] Also, research on molecular mechanisms of the "hygiene hypothesis" and genetic analysis have highlighted that the allergies and asthma are not due to a single mechanism but multifactorial diseases with complex interplay between the organism and environment.[55]

Inflammatory bowel disease

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing worldwide, both in pediatric and adult populations.[56,57] A steady rise in the incidence of IBD is observed in *H. pylori* endemic regions, which corresponds to the beginning of anti-*H. pylori* therapy for PUD.[58] Although a small number of studies reported no association between *H. pylori* and IBD, the overwhelming majority of the studies to date, both epidemiological and basic experimental, strongly suggest a protective role of *H. pylori* infection against IBD. Luther *et al.* reported a protective effect of *H. pylori* against IBD in their meta-analysis and systematic review.[59] Sonnenberg and Genta compared the presence of *H. pylori* in more than 1000 IBD subjects with 65,000 control subjects and found that control subjects harbored *H. pylori* twice as frequently as IBD patients, confirming an inverse association between *H. pylori* and IBD.[60] Several meta-analyses and systematic reviews subsequently have confirmed this significant negative association between *H. pylori* and IBD, both in the pediatric and adult populations.[61–67] Kayali *et al.* reported a striking inverse association between *H. pylori* and IBD prevalence, independent of IBD subtypes and geographical regions.[63] Others reported evidence of *H. pylori* conferring more protection against Crohn's compared to UC and also more protective effect in East Asian population compared to Mediterranean regions,[67] nonetheless protective against any type of IBD. Roka *et al.* observed that the occurrence of *H. pylori* gastritis is less frequent in children with IBD compared to controls.[68] It has also been shown that *H. pylori* is associated with less fistulizing and less active colitis in patients with Crohn's disease.[69] A study from Taiwan, where *H. pylori* infection rate approaches 80% in the general population, reported that the treatment of *H. pylori* infection was associated with a significant increase in the risk of autoimmune diseases including IBD.[70] As opposed to this, a recent study, utilizing a large electronic medical records database from 26 major integrated health-care systems in the United States, showed that *H. pylori* eradication therapy is not associated with the development of IBD in the first 5 years after therapy, but it did confirm lower prevalence of IBD in the presence of *H. pylori*.[71] Studies indicate that *H. pylori* colonization reduces the risk of IBD by 38–52%![61,62]

It could be argued that this protective effect may just be apparent rather than real, just an epidemiological association, reflecting the "hygiene hypothesis," *H. pylori* being a surrogate marker for other phenomena such as reduced infections and improved socioeconomic conditions. But then, a systematic review and meta-analysis found that the closely related bacteria including enterohepatic Helicobacter species and campylobacter species increase the risk of IBD, suggesting an immunomodulatory effect specific to *H. pylori*.[72] Similarly, another systematic review of gastrointestinal infections and incident IBD found that *Salmonella* species, *Campylobacter* species, and *Clostridioides difficile* demonstrated consistent positive association with the risk of incident IBD, whereas *H. pylori* and helminth infections were associated with a reduced risk of IBD.[73] This protective role of *H. pylori* is replicated in several animal studies and in vitro experimental studies too. Mice that were colonized with *H. pylori* prior to the induction of Salmonella typhimurium experimental colitis experienced markedly less severe

inflammation compared to mice that were not colonized with *H. pylori*.[74] It has also been shown that prior oral administration of 20–50 μg *H. pylori* DNA ameliorated the severity of dextran sulfate-sodium-induced acute or chronic colitis in mice, in terms of both pathology and symptoms such as bleeding and weight loss.[75] This protective effect could be attributed to *H. pylori*-induced systemic immune tolerance and suppression of inflammatory response. Tolerogenic phenotype dendritic cells and immunosuppressive Tregs are thought to be involved in this protective mechanism.[76–78] Taking all these into consideration, it could be argued strongly that *H. pylori* is a potent modulator of the immune system and prevents IBD.

Gastroesophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma

Several epidemiological studies have demonstrated a negative association between *H. pylori* and gastroesophageal reflux disease (GERD) and related complications like Barrett's esophagus and esophageal adenocarcinoma in the adult population. Just about two decades after the discovery of *H. pylori*, a systematic review found that the prevalence of *H. pylori* infection was significantly lower in those with gastroesophageal reflux than those without.[79] This inverse relationship between GERD and *H. pylori* has been reported in several subsequent studies.[80] This is also true for Barrett's esophagus and esophageal adenocarcinoma.[81–83] The relationship between *H. pylori* and GERD is not as clear cut in the pediatric population however. Some studies reported higher prevalence of reflux esophagitis in *H. pylori*-infected children[84,85] and others reported the contrary.[86,87] The reason for this disparity may lie in that the determinants affecting GERD in *H. pylori* are the location of gastric inflammation and CagA positivity in both children and adults.[88] It is well established that gastric acid secretion is a key factor in the pathophysiology of reflux esophagitis. Depending on the type of gastritis related to *H. pylori*, acid secretion may either increase or decrease. Gastritis in corpus leads to hypoacidity, while antrum gastritis leads to hyperacidity. In adults, HP infection is often associated with atrophic gastritis in the corpus, whereas in children, it is often associated with antral predominant gastritis. Depending on the type of gastritis, the *H. pylori* eradication may either aggravate or alleviate GERD.

Obesity

Obesity has become a major public health problem of global significance. The incidence of obesity in the general population has skyrocketed during the past 20 years, and more than doubled in children and quadrupled in adolescents in the past 30 years. Clearly, the most important risk factors are related to changes in the diet and lifestyle. Interestingly, an inverse relation with *H. pylori* infection has been reported by many studies, both in the adult and pediatric populations.[89–91] It has been postulated that *H. pylori*-induced gastritis modulates the levels of gastric hormones, ghrelin and leptin, that influence eating behavior. Ghrelin secreted by the stomach is an appetite-stimulating hormone. *H. pylori* is found to decrease ghrelin secretion by reducing the number of gastric ghrelin-producing cells.[92] Leptin, on the other hand, is an anorexigenic hormone. Though mainly produced by adipose tissue, it is also synthesized in the stomach. *H. pylori* infection upregulates gastric leptin secretion.[89] It has been shown that long-term eradication of *H. pylori* infection is associated with a significant increase in body mass index, lean, and fat mass along with a significant decrease in circulating ghrelin levels and an increase in leptin levels in prepubertal children.[93]

Discussion

There is increasing evidence suggesting beneficial role of *H. pylori* with several studies, systematic reviews, and meta-analyses showing an inverse association between *H. pylori* and various chronic health conditions, as discussed above. It could be argued, quite rightly, that these inverse associations could just reflect the significant socioeconomic improvements and the lifestyle changes seen in recent decades with improved sanitation, reduced infections, dietary habits, etc., *H. pylori* being just a surrogate marker of this. But then, several experimental studies directly showing potential benefits of *H. pylori* cannot be ignored. On the one hand, *H. pylori* is clearly demonstrated to cause PUD and gastric cancers, albeit, in a minority of the infected population. On the other hand, several epidemiological and experimental studies demonstrate beneficial aspects of this bacterium against various human health conditions. It is important to remember that *H. pylori* has coevolved with humans for several thousands of years. Though more than half of world's population is infected, clinical disease occurs only in a

small proportion of the infected subjects. The majority of the infected individuals show histologic chronic gastritis even though asymptomatic,[94] but only a small fraction of infected individuals develop *H. pylori*-associated diseases such as PUD and more rarely gastric carcinomas.[95] It has been estimated that the *H. pylori* infection is linked to gastric and duodenal ulcers in 1–10% of infected patients, gastric carcinoma in 0.1–0.3%, and gastric MALT lymphoma in less than 0.01%.[96] Therefore, there is an alternative point of view that *H. pylori* may be considered as a commensal symbiont, part of normal human stomach microbiome.[97–100] Unlike other pathogenic bacteria, *H. pylori* colonization in infancy leads to the development of immune tolerance.[98] Just as we do not attempt to eradicate the gut microbiome, so should be *H. pylori*, to be treated only if it causes problem, which, we know, happens only in a small minority of infected subjects.

In contrast to the pediatric guidelines, adult guidelines to date have recommended eradication of *H. pylori* in all patients with infection, regardless of the presence of PUD or background risk of gastric cancer. Interestingly however, in recent years, there has been increasing recognition of the beneficial role of *H. pylori*. Many experts have now questioned the unconditional recommendation to eradicate *H. pylori* in every case. Instead, they call for a more individualized treatment approach in the context of additional risk factors.[97,98,101,102]

From a practical point of view, what does this mean for pediatricians and pediatric gastroenterologists? On the face of it, it is simple enough, just follow the guidelines – do not "test and treat." What do we do, if during investigation of child's symptom, *H. pylori is* detected? Available evidence would suggest not to eradicate unless ulcer disease is present. Of course, this would need to be discussed with the family, explaining the rationale for the decision not to treat (or treat). What is not clear at present is, how long and how often the children in whom decision is made not to treat, should be followed up.[16] In part, this would be dependent on the background risk of gastric cancer in the population, but further longitudinal studies are needed to address this. For now, however, when you next encounter a child with *H. pylori* infection/gastritis but no PUD, let it not trigger an automatic eradication treatment prescription but rather consider leaving *H. pylori* alone, taking into account the probable beneficial effects of *H. pylori* as discussed above and the low-frequency complications in children.

Conclusion

The decision to treat *H. pylori* infection in children should be based on providing true benefit and do no harm. No doubt, eradication treatment needs to be undertaken in children with PUD but not in every child in whom *H. pylori* is detected. The aim of this review is not to dispute the fact that *H. pylori* is a class 1 human carcinogen and is etiologically related to gastric and duodenal ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma but to draw reader's attention to possible beneficial effects *H. pylori* may confer against asthma, allergies, EoE, and IBD especially in childhood. There appears to be increasing evidence base for these beneficial effects of *H. pylori*. Various molecular mechanisms have been elucidated to explain these beneficial effects; detailed description of these is beyond the scope of this review.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

M Ravikumara: Conceptualization; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The author declares that there is no conflict of interest.

Availability of data and materials

Not applicable.

ORCID iD
M. Ravikumara https://orcid.org/0000-0001-5422-7284

References

1. Hooi JKY, Lai WY, Ng WK, *et al.* Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology* 2017; 153: 420–429.
2. Yuan C, Adeloye D, Luk TT, *et al.* The global prevalence of and factors associated with Helicobacter pylori infection in children: a systematic review and meta-analysis. *Lancet* 2022; 6: 185–194.
3. Salama NR, Hartung ML and Müller A. Life in the human stomach: persistence strategies of the bacterial pathogen Helicobacter pylori. *Nat Rev Microbiol* 2013; 11: 385–399.
4. Warren JR and Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; 1: 1273–1275.
5. Ford AC, Gurusamy KS, Delaney B, *et al.* Eradication therapy for peptic ulcer disease in Helicobacter pylori-positive people. *Cochrane Database Syst Rev* 2016; 4: CD003840.
6. 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. e3.
7. Yuan W, Li YUMIN, Yang KEHU, *et al.* Iron deficiency anemia in Helicobacter pylori infection: meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2010; 45: 665–676.
8. 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.
9. Huang X, Qu X, Yan W, *et al.* Iron deficiency anaemia can be improved after eradication of Helicobacter pylori. *Postgrad Med J* 2010; 86: 272–278.
10. Franchini M, Cruciani M, Mengoli C, *et al.* Effect of Helicobacter pylori eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007; 60: 237–246.
11. Ražuka-Ebela D, Giupponi B and Franceschi F. Helicobacter pylori and extragastric diseases. *Helicobacter* 2018; 23 Suppl 1: e12520.
12. He J, Liu Y, Ouyang Q, *et al.* Helicobacter pylori and unignorable extragastric diseases: mechanism and implications. *Front Microbiol* 2022; 13: 972777.
13. Chey WD, Leontiadis GI, Howden CW, *et al.* ACG clinical guideline: Treatment of Helicobacter pylori infection. *Am J Gastroenterol* 2017; 112: 212–239.
14. Sugano K, Tack J, Kuipers EJ, *et al.* Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015; 64: 1353–1367.
15. Malfertheiner P, Megraud F, O'Morain CA, *et al.* Management of Helicobacter pylori infection-the maastricht V/Florence Consensus Report. *Gut* 2017; 66: 6–30.
16. Hojsak I and Kolacek S. Is Helicobacter pylori always a "bad guy"? *Curr Pharm Des* 2014; 20: 4517–4520.
17. Nasri P, Saneian H, Famouri F, *et al.* Helicobacter pylori infection in pediatrics with gastrointestinal complaints. *Int J Physiol Pathophysiol Pharmacol* 2022; 14: 118–123.
18. Spee LA, Madderom MB, Pijpers M, *et al.* Association between helicobacter pylori and gastrointestinal symptoms in children. *Pediatrics* 2010; 125: e651–e669.
19. Dore MP, Fanciulli G, Tomasi PA, *et al.* Gastrointestinal symptoms and Helicobacter pylori infection in school-age children residing in Porto Torres, Sardinia, Italy. *Helicobacter* 2012; 17: 369–373.
20. Chobot A, Porębska J, Krzywicka A, *et al.* No association between *Helicobacter pylori* infection and gastrointestinal complaints in a large cohort of symptomatic children. *Acta Paediatr* 2019; 108: 1535–1540.
21. Jaime F, Villagrán A, Hernández C, *et al.* Functional gastrointestinal disorders in children from low socio-economic status and Helicobacter pylori infection. *Child Care Health Dev* 2018; 44: 319–325.
22. Hojsak I, Kos T, Dumančić J, *et al.* Antibiotic resistance of Helicobacter pylori in pediatric patients – 10 years' experience. *Eur J Pediatr* 2012; 171: 1325–1330.
23. Koletzko S, Richy F, Bontems P, *et al.* Prospective multicentre study on antibiotic resistance of Helicobacter pylori strains obtained from children living in Europe. *Gut* 2006; 55: 1711–1716.
24. Jansson L and Agardh D. Prevalence of clarithromycin-resistant Helicobacter pylori in children living in south of Sweden: a 12-year

follow-up. *Scand J Gastroenterol* 2019; 54: 838–842.

25. 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.
26. Bonilla S, Mitchell PD and Mansuri I. Low adherence to society guidelines for the management of Helicobacter pylori among pediatric gastroenterologists. *J Pediatr Gastroenterol Nutr* 2021; 73: 178–183.
27. Hansen TE, Evjenth B and Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985-2008. *Acta Paediatr* 2013; 102: 47–52.
28. Serebrisky D and Wiznia A. Pediatric Asthma: A Global Epidemic. *Ann Global Health* 2019; 85: 6, 1–6.
29. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *New Engl J Med* 2002; 347: 911–920.
30. Kalach N, Bontems P and Raymond J. Helicobacter pylori infection in children. *Helicobacter* 2017; 22(Suppl. 1): e12414.
31. Rowland M. The continuing decline in the prevalence of Helicobacter pylori infection. *Lancet Child Adolesc Health* 2022; 6: 139–140.
32. Leja M, Grinberga-Derica I, Bilgilier C, *et al*. Review: Epidemiology of Helicobacter pylori infection. *Helicobacter* 2019; 24(Suppl. 1): e12635.
33. Chen Y and Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; 198: 553–560.
34. Chen Y, Zhan X and Wang D. Association between Helicobacter pylori and risk of childhood asthma: a meta-analysis of 18 observational studies. *J Asthma* 2022; 59: 890–900.
35. Elias N, Nasrallah E, Khoury C, *et al*. Associations of Helicobacter pylori seropositivity and gastric inflammation with pediatric asthma. *Pediatr Pulmonol* 2020; 55: 2236–2245.
36. Zevit N, Balicer RD, Cohen HA, *et al*. Inverse association between Helicobacter pylori and pediatric asthma in a high-prevalence population. *Helicobacter* 2012; 17: 30–35.
37. Wang D, Chen Y, Ding Y, *et al*. Inverse association between Helicobacter pylori infection and childhood asthma in a physical examination population: a cross-sectional study in Chongqing, China. *BMC Pediatr* 2022; 22: 615.
38. Fouda EM, Kamel TB, Nabih ES, *et al*. Helicobacter pylori seropositivity protects against childhood asthma and inversely correlates to its clinical and functional severity. *Allergol Immunopathol* 2018; 46: 76–81.
39. Chen C, Xun P, Tsinovoi C, *et al*. Accumulated evidence on Helicobacter pylori infection and the risk of asthma: a meta-analysis. *Ann Allergy Asthma Immunol* 2017; 119: 137–145.e2. e2.
40. Amberbir A, Medhin G, Abegaz WE, *et al*. Exposure to Helicobacter pylori infection in early childhood and the risk of allergic disease and atopic sensitization: a longitudinal birth cohort study. *Clin Exp Allergy* 2014; 44: 563–571.
41. Lionetti E, Leonardi S, Lanzafame A, *et al*. Helicobacter pylori infection and atopic diseases: is there a relationship? A systematic review and meta-analysis. *World J Gastroenterol* 2014; 20: 17635–17647.
42. Taye B, Enquselassie F, Tsegaye A, *et al*. Is Helicobacter Pylori infection inversely associated with atopy? A systematic review and meta-analysis. *Clin Exp Allergy* 2015; 45: 882–890.
43. Pedullà M, Fierro V, Del Tufo E, *et al*. Helicobacter pylori immunization and atopic dermatitis in South Italian children. *United Eur Gastroenterol J* 2014; 2: 263–267.
44. Arnold IC, Dehzad N, Reuter S, *et al*. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J Clin Investig* 2011; 121: 3088–3093.
45. Oertli M and Müller A. Helicobacter pylori targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes* 2012; 3: 566–571.
46. Oertli M, Sundquist M, Hitzler I, *et al*. DC-derived IL-18 drives Treg differentiation, murine Helicobacter pylori-specific immune tolerance, and asthma protection. *J Clin Investig* 2012; 122: 1082–1096.
47. Miftahussurur M, Nusi IA, Graham DY, *et al*. Helicobacter, hygiene, atopy, and asthma. *Front Microbiol* 2017; 8: 1034.
48. Dowling PJ, Neuhaus H and Polk BI. The role of the environment in Eosinophilic Esophagitis. *Clin Rev Allergy Immunol* 2019; 57: 330–339.
49. Furuta K, Adachi K, Aimi M, *et al*. Case-control study of association of eosinophilic

gastrointestinal disorders with Helicobacter pylori infection in Japan. *J Clin Biochem Nutr* 2013; 53: 60–62.

50. O'Shea KM, Aceves SS, Dellon ES, *et al.* Pathophysiology of eosinophilic esophagitis. *Gastroenterology* 2018; 154: 333–345.

51. Elitsur Y, Alrazzak BA, Preston D, *et al.* Does Helicobacter pylori protect against eosinophilic esophagitis in children? *Helicobacter* 2014; 19: 367–371.

52. Shah SC, Tepler A, Peek Rm Jr, *et al.* Association between Helicobacter pylori exposure and decreased odds of eosinophilic Esophagitis-A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2019; 17: 2185–2198.e3.

53. Arnold IC, Hitzler I and Müller A. The immunomodulatory properties of Helicobacter pylori confer protection against allergic and chronic inflammatory disorders. *Front Cell Infect Microbiol* 2012; 2: 10.

54. Zuo ZT, Ma Y, Sun Y, *et al.* The protective effects of Helicobacter pylori infection on allergic asthma. *Int Arch Allergy Immunol* 2021; 182: 53–64.

55. Vercelli D. Mechanisms of the hygiene hypothesis – molecular and otherwise. *Curr Opin Immunol* 2006; 18: 733–737.

56. Kuenzig ME, Fung SG, Marderfeld L, *et al.* Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. *Gastroenterology* 2022; 162: 1147–1159.e4. e4.

57. Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; 390: 2769–2778.

58. Thia KT, Loftus Ev Jr., Sandborn WJ, *et al.* An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008; 103: 3167–3182.

59. Luther J, Dave M, Higgins PD, *et al.* Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. *Inflamm Bowel Dis* 2010; 16: 1077–1084.

60. Sonnenberg A and Genta RM. Low prevalence of Helicobacter pylori infection among patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; 35: 469–476.

61. Rokkas T, Gisbert JP, Niv Y, *et al.* The association between Helicobacter pylori infection and inflammatory bowel disease based on meta-analysis. *United Eur Gastroenterol J* 2015; 3: 539–550.

62. Wu XW, Ji HZ, Yang MF, *et al.* Helicobacter pylori infection and inflammatory bowel disease in Asians: a meta-analysis. *World J Gastroenterol* 2015; 21: 4750–4756.

63. Kayali S, Gaiani F, Manfredi M, *et al.* Inverse association between Helicobacter pylori and inflammatory bowel disease: myth or fact? *Acta Biomed* 2018; 89: 81–86.

64. Tepler A, Narula N, Peek RM Jr, *et al.* Systematic review with meta-analysis: association between Helicobacter pylori CagA seropositivity and odds of inflammatory bowel disease. *Aliment Pharmacol Ther* 2019; 50: 121–131.

65. Shirzad-Aski H, Besharat S, Kienesberger S, *et al.* Association between Helicobacter pylori colonization and inflammatory bowel disease: a systematic review and meta-analysis. *J Clin Gastroenterol* 2021; 55: 380–392.

66. Zhong Y, Zhang Z, Lin Y, *et al.* The relationship between Helicobacter pylori and inflammatory bowel disease. *Arch Iran Med* 2021; 24: 317–325.

67. Imawana RA, Smith DR and Goodson ML. The relationship between inflammatory bowel disease and Helicobacter pylori across East Asian, European and Mediterranean countries: a meta-analysis. *Ann Gastroenterol* 2020; 33: 485–494.

68. Roka K, Roubani A, Stefanaki K, *et al.* The prevalence of Helicobacter pylori gastritis in newly diagnosed children with inflammatory bowel disease. *Helicobacter* 2014; 19: 400–405.

69. Fialho A, Fialho A, Nassri A, *et al.* Helicobacter pylori is associated with less fistulizing, stricturing, and active colitis in Crohn's disease patients. *Cureus* 2019; 11: e6226.

70. Lin KD, Chiu GF, Waljee AK, *et al.* Effects of anti–Helicobacter pylori therapy on incidence of autoimmune diseases, including inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019; 17: 1991–1999.

71. Tanner S, Katz J, Cominelli F, *et al.* Inflammatory bowel disease and Helicobacter pylori: protective or present? *Inflamm Bowel Dis*. Epub ahead of print 28 September 2022. DOI: 10.1093/ibd/izac202.

72. Castaño-Rodríguez N, Kaakoush NO, Lee WS, *et al.* Dual role of Helicobacter and

Campylobacter species in IBD: a systematic review and meta-analysis. *Gut* 2017; 66: 235–249.

73. Axelrad JE, Cadwell KH, Colombel JF, *et al.* Systematic review: gastrointestinal infection and incident inflammatory bowel disease. *Aliment Pharmacol Ther* 2020; 51: 1222–1232.

74. Higgins PD, Johnson LA, Luther J, *et al.* Prior Helicobacter pylori infection ameliorates Salmonella typhimurium-induced colitis: mucosal crosstalk between stomach and distal intestine. *Inflamm Bowel Dis* 2011; 17: 1398–1408.

75. Luther J, Owyang SY, Takeuchi T, *et al.* Helicobacter pylori DNA decreases pro-inflammatory cytokine production by dendritic cells and attenuates dextran sodium sulphate-induced colitis. *Gut* 2011; 60: 1479–1486.

76. Yu Y, Zhu S, Li P, *et al.* Helicobacter pylori infection and inflammatory bowel disease: a crosstalk between upper and lower digestive tract. *Cell Death Dis* 2018; 9: 961.

77. Papamichael K, Konstantopoulos P and Mantzaris GJ. Helicobacter pylori infection and inflammatory bowel disease: is there a link? *World J Gastroenterol* 2014; 20: 6374–6385.

78. Arnold IC and Müller A. Helicobacter pylori: does gastritis prevent colitis? *Inflamm Intest Dis* 2016; 1: 102–112.

79. Raghunath A, Hungin AP, Wooff D, *et al.* Prevalence of Helicobacter pylori in patients with gastro-oesophageal reflux disease: systematic review. *BMJ* 2003; 326: 737.

80. Scida S, Russo M, Miraglia C, *et al.* Relationship between Helicobacter pylori infection and GERD. *Acta Biomed* 2018; 89: 40–43.

81. Wang Z, Shaheen NJ, Whiteman DC, *et al.* Helicobacter pylori infection is associated with reduced risk of Barrett's Esophagus: An Analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. *Am J Gastroenterol* 2018; 113: 1148–1155.

82. Du YL, Duan RQ and Duan LP. Helicobacter pylori infection is associated with reduced risk of Barrett's esophagus: a meta-analysis and systematic review. *BMC Gastroenterol* 2021; 21: 459.

83. Ma S, Guo X, Wang C, *et al.* Association of Barrett's esophagus with Helicobacter pylori infection: a meta-analysis. *Ther Adv Chronic Dis* 2022; 13: 20406223221117971.

84. Moon A, Solomon A, Beneck D, *et al.* Positive association between Helicobacter pylori and gastroesophageal reflux disease in children. *J Pediatr Gastroenterol Nutr* 2009; 49: 283–288.

85. Daugule I, Rumba I, Alksnis J, *et al.* Helicobacter pylori infection among children with gastrointestinal symptoms: a high prevalence of infection among patients with reflux oesophagitis. *Acta Paediatr* 2007; 96: 1047–1049.

86. Gold BD. Outcomes of pediatric gastroesophageal reflux disease: in the first year of life, in childhood, and in adults. . .oh, and should we really leave Helicobacter pylori alone? *J Pediatr Gastroenterol Nutr* 2003; 37(Suppl 1): S33–S39.

87. Abdollahi A, Morteza A, Khalilzadeh O, *et al.* The role of Helicobacter pylori infection in gastro-oesophageal reflux in Iranian children. *Ann Trop Paediatr* 2011; 31: 53–57.

88. Yucel O. Interactions between Helicobacter pylori and gastroesophageal reflux disease. *Esophagus* 2019; 16: 52–62.

89. Vo HD, Goli S, Gill R, *et al.* Inverse Correlation Between *Helicobacter pylori* Colonization and obesity in a cohort of inner city children. *Helicobacter* 2015; 20: 64–68.

90. Moran-Lev H, Lubetzky R, Mandel D, *et al.* Inverse correlation between Helicobacter pylori colonization and pediatric overweight: a preliminary study. *Child Obes* 2017; 13: 267–271.

91. Lender N, Talley NJ, Enck P, *et al.* Review article: associations between *Helicobacter pylori* and obesity – an ecological study. *Aliment Pharmacol Ther* 2014; 40: 24–31.

92. Tatsuguchi A, Miyake K, Gudis K, *et al.* Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa. *Am J Gastroenterol* 2004; 99: 2121–2127.

93. Pacifico L, Anania C, Osborn JF, *et al.* Long-term effects of Helicobacter pylori eradication on circulating ghrelin and leptin concentrations and body composition in prepubertal children. *Eur J Endocrinol* 2008; 158: 323–332.

94. Dooley CP, Cohen H, Fitzgibbons PL, *et al.* Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons. *New Engl J Med* 1989; 321: 1562–1566.

95. Cover TL and Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; 136: 1863–1873.

96. McColl KE. Clinical practice: Helicobacter pylori infection. *New Engl J Med* 2010; 362: 1597–1604.

97. Reshetnyak VI, Burmistrov AI and Maev IV. Helicobacter pylori: commensal, symbiont or pathogen? *World J Gastroenterol* 2021; 27: 545–560.

98. Sitkin S, Lazebnik L, Avalueva E, *et al*. Gastrointestinal microbiome and Helicobacter pylori: eradicate, leave it as it is, or take a personalized benefit-risk approach? *World J Gastroenterol* 2022; 28: 766–774.

99. Blaser MJ. Helicobacter pylori and gastric diseases. *BMJ* 1998; 316: 1507–1510.

100. Blaser MJ. Helicobacters are indigenous to the human stomach: duodenal ulceration is due to changes in gastric microecology in the modern era. *Gut* 1998; 43: 721–727.

101. Schubert JP, Rayner CK, Costello SP, *et al*. Helicobacter pylori: have potential benefits been overlooked? *JGH Open* 2022; 6: 735–737.

102. Desai T, Edhi AI and Hakim S. Eradicating H. pylori. *Am J Gastroenterol* 2019; 114: 1827–1828.