Esophagus (2019) 16:52–62
https://doi.org/10.1007/s10388-018-0637-5

REVIEW ARTICLE

Interactions between *Helicobacter pylori* and gastroesophageal reflux disease

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Received: 22 May 2018 / Accepted: 17 August 2018 / Published online: 27 August 2018

Abstract

Interactions between *Helicobacter Pylori* (HP) and gastroesophageal reflux disease (GERD) are a complex issue. Several pathophysiological factors influence the development and the course of GERD, HP infection might be only one of these. Many studies emphasize the co-existence of these diseases. HP infection could contribute to GERD through both a protective and an aggressive role. Gastric acid secretion is a key factor in the pathophysiology of reflux esophagitis. Depending on the type of gastritis related to HP, acid secretion may either increase or decrease. Gastritis in corpus leads to hypoacidity, while antrum gastritis leads to hyperacidity. In cases of antral gastritis and duodenal ulcers which have hyperacidity, the expectation is an improvement in pre-existing reflux esophagitis after eradication of HP. In adults, HP infection is often associated with atrophic gastritis in the corpus. Atrophic gastritis may protect against GERD. Pangastritis which leads to gastric atrophy is commonly associated with CagA strains of HP and it causes more severe gastric inflammation. In case of HP-positive corpus gastritis in the stomach, pangastritis, and atrophic gastritis, reflux esophagitis occurs frequently after eradication of HP. Nonetheless, as a predisposing disease of gastric cancer, HP should be treated. In conclusion, as the determinative factors affecting GERD involving in HP, detailed data on the location of gastric inflammation and CagA positivity should be obtained by the studies at future.

Keywords CagA · Children · Gastritis · Gastroesophageal reflux · *Helicobacter pylori*

Introduction

Helicobacter pylori (HP) infection and Gastroesophageal Reflux Disease (GERD) are common diseases worldwide. HP infection is most likely acquired in childhood [1]. While the prevalence of HP infection is decreasing all over the world due to better living conditions, better hygiene and frequent use of antibiotics in childhood, GERD is increasing. The protective role of HP infection for GERD was first reported by Labenz in 1997 [2]. Thereafter, some authors have pointed out the interaction which involves gastric acid secretion between these diseases. HP infection could contribute to GERD through different mechanisms. It may have both a protective [3–12] and an aggressive role in GERD incidence and severity. Many studies emphasize the co-existence of these diseases [13–15].This review aimed to understand and clarify the interactions between HP and GERD in both children and adults.

Pathogenesis

In the pathogenesis of GERD, the esophagus, LES and stomach work as a single functional unit controlled by neurohormonal factors. Parasympathetic dysfunction adversely affects the motor activity of this area by increasing the transient LES relaxation number and impairing LES pressure, esophageal acid clearance and motility of the proximal stomach. Recently, numerous investigations have been performed to elucidate the role of HP infection in GERD pathogenesis with the most concern given to its potency to increase gastric acid secretion.

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The effect of HP on GERD

HP infection implicates in the development of gastritis, and duodenal and gastric ulcers. Depending on the type of gastritis, acid secretion may either increase or decrease. Genetic factors change the immune and inflammatory response to HP infection. The distribution of gastritis (antrum, corpus or pangastritis) is also important in the development of reflux esophagitis. Gastritis in the corpus leads to hypoacidity, while antrum gastritis causes hyperacidity. The positive effects of HP eradication are most likely due to antral predominant gastritis which is the most common type in childhood. However, corpus-predominant gastritis is more common in adults [15–18].

Antrum-predominant gastritis is characterized by hypergastrinemia and more acidity. The risk of either peptic ulceration or GERD increases in patients with antral gastritis [19]. After eradication of HP, acid secretion will return at least to normal in antrum-predominant gastritis. The expectation is that, in these patients, HP eradication should improve or not affect reflux esophagitis [19–23].

The region secreting gastric acid is the corpus of the stomach which is full of parietal cells. As a result of prolonged inflammation of the corpus, in cases with atrophic gastritis or severe corpus gastritis, there is an association with decreased gastric acid production. This process is considered to be the main mechanism by which HP infection inhibits the onset of GERD [1]. HP eradication may result in increased acid secretion and cause reflux esophagitis or aggravation of GERD symptoms [5, 7, 19, 20, 23].

In the adult patient with pangastritis, there is an irreversible reduction in gastric acid secretion in contrast to those with duodenal ulcer. In case of pangastritis, gastric acid production decreases [5] and HP infection prevents reflux esophagitis by decreasing gastric acid secretion. In cases with HP-positive gastritis and gastric ulcers, reflux esophagitis occurs frequently after eradication [5, 23]. PPIs are effective for curing reflux esophagitis after eradication. On the other hand, in cases of duodenal ulcers which have hyperacidity, there was an improvement in pre-existing reflux esophagitis after eradication of HP [20, 24]. Some adult studies supported the claim that HP eradication results in decreased symptoms of GERD [10, 23, 25]; however, others reported no impact on GER symptoms [26, 27] (Tables 1, 2) [28–31]. Unfortunately, lots of the studies do not emphasize the location of gastric inflammation while evaluating the effect on GERD of HP infection.

Also, the importance of an anti-reflux barrier should be kept in mind. In terms of developing reflux esophagitis, patients with impairment of the barrier, such as a hiatal hernia, will be affected more by HP eradication [23, 32]. Koike [5] reported that reflux esophagitis developed after HP eradication in patients with a hiatal hernia.

The effects of geographic differentiation

The reported prevalence of GERD in patients of all ages worldwide is increasing. Host racial differences affecting HP-related gastritis may have an influence on symptoms and severity of GERD between Asian and Western countries. Epidemiological studies show that the prevalence of GERD ranges from 20 to 40% in Western countries and from 5 to 17% in Asian countries [33, 34]; however, the prevalence is increasing in Asian populations [35]. According to previous Asian population-based studies, the prevalence of GERD is reported to have a lower prevalence in patients with HP infection [23, 36–41]. In the populations in which there is significant involvement of corpus gastritis, the eradication of HP leads to an increase in esophageal acid exposure and a worsening of the symptoms. Population-based studies have shown that reflux disorders are less common in Eastern Asia than in Europe and North America [42, 43]. The reason is that in East-Asian patients, HP-related gastritis is primarily located in the corpus [17, 44]. However, in the Far East, European and North America populations, patients with HP infection experience the complications due to antrum-predominant gastritis [45]. HP infection does not lead to a major change in gastric acid secretion because of the antral involvement. However, gastric acid secretion associated with HP infection decreases in the majority of cases in Asian countries [23, 46]. In adult studies, increased severity of GERD after eradication of HP has been reported especially among Asians compared to North Americans and Europeans [1, 5, 47–50] (Fig. 1a, b). Twenty-eight studies of the prevalence of GERD reported a prevalence of 18.1–27.8% in North America, 8.8–25.9% in Europe, 2.5–7.8% in East Asia, 8.7–33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America [51, 52]. African-Americans and Asians also appear to be at lower risk for the development of GERD-related complications, including Barrett's esophagus (BE) [51].

The effects on children

During childhood, HP is associated with antral predominant gastritis and duodenal ulcers [44, 53, 54]. Determining the prevalence of HP is also difficult because of frequent use of antibiotics in childhood. Some authors pointed out that antibiotics such as Amoxicillin and Clarithromycin could eradicate HP in 10–50% of patients [18, 55, 56]. Almost all of the children with chronic active gastritis colonized with HP can be diagnosed using endoscopy/biopsy [57–60]. However,

Table 1 The studies, after HP eradication, of the prevalence of persistent or *de novo* GERD

Authors	Countries	The number of cases (N.)	Follow-up (mean)	After HP eradication, the prevalence of GERD	*de novo* GERD risk
Minatsuki [28]	Japan	N. 10,837 healthy N. 733 (cases with RE)		From 2.3 to 8.8%	
*Kawanishi [99]	Japan	N. 326 (cases with HP)	5 years	22.7%	RR 2.43
*Take [100]	Japan	N. 1195, cases with HP/peptic ulcer	10 years	27.9%	
Hamada [32]	Japan	N. 286 (cases with HP), N. 286 control	3 years	From 0.3 to 18%	RR 36
Koike [5]	Japan	N. 105 (cases with HP, no RE), Control:105	7 months	10.5%	
*Inoue [101]	Japan	N. 148	5 years	From 3.8 to 20.5%	
Miyamoto [50]	Japan	N. 322	6 years	16.5%	
Lee [29]	Taiwan	N. 813 (cases with HP)	From 13.7 to 27.3%		
*Nam [102]	Korea (N. 4007)	N. 10,102 OR 2.34	2 years	From 4.3 to 10.0%	RR 3.39
*Kim [103]	Korea	N. 81	26 months	RR 2.01	
*Kim [104]	Korea	N. 1489 (cases without RE)	2 years	7.3%	
*Wu [105]	Australia	N. 236	12 months	RR 8.67	
Vaira [27]	Italy	N. 169	8.5 years	OR 0.57	RR 1.32
*Vakil [106]	USA	N. 693	12 months	RR 7.34	
Labenz [2]	USA	N. 244	17 months		13% RR 4.05
*Malfertheiner [107]	Germany	N. 1497	6 months		2% RR 1.07
*Bytzer [108]	Denmark	N. 99	24 months		RR 1.43
*Harvey [109]	UK	N. 10,537 (20–59 years of age) N. 1636 (cases with HP)	24 months	18.9% (OR 1.05) 17.6% (placebo)	RR 1.07
*Ott [110]	USA	N. 157	12 months	9%	RR 0.94
Befrits [111]	Sweden	N. 145	18 months		9% RR 1.34
*Moayyedi [112]	Canada	N. 190	12 months		RR 1.09

RE reflux esophagitis, *RR* risk ratio, *OR* odds ratio

*The articles signed are based on the meta-analysis of Xie et al. and the review of Raghunath et al. [36, 41]

endoscopy is not a widespread application for diagnosis of GERD in childhood.

Children and adolescents who have HP infection are more likely to have antral gastritis predominantly [57–61] with prevalence ranging from 1.9 to 71.0 (median 4.6 years) [62]. In a previous study [63], children from the lower risk populations (USA) were compared with children from a higher risk population (Colombia) which exhibited more severe inflammation and HP colonization density. In both populations, the inflammatory lesions were seen predominantly in the antrum. Carvalho [60] also pointed out that HP density in the antrum was higher than in the corpus in children. In the studies by Langner [58] from Brazil, among children and adolescents, HP-related gastritis was present in the antrum for 27.3% and in the corpus for 4.5% (mean 10.5 years). The study by Carvalho [60] found pangastritis in 61.9% of cases, followed by antrum- (32.1%) and corpus-predominant gastritis (5.9%) (mean 9.5 years). Another study showed that 83% of Chilean children had antrum-predominant gastritis [59]. Hoepler's [57] study showed that in Austrian children, pangastritis was present in 46% of children who had HP infection, with 50% antrum predominant (mean 10.5 years). In Moon's [15] study including patients with HP infection, children between 1–10 years and older than 10 years had odds ratios of 7.00 and 5.99, respectively, of having reflux esophagitis compared to patients less than 1 year (mean 8.2 years).

Some studies showed that eradication therapy did not influence the presence of GER [18, 20, 64]. Xinias [17] showed that HP-positive patients with antral gastritis had no clinical improvement after eradication in spite of increasing the mean lower esophageal sphincter pressure and decreasing the "Reflux Index". Pollet [65] reported that HP eradication did not provoke or worsen

Table 2 Meta-analysis studies

Authors	After HP eradication, the risk of GERD	Risk Ratio; Odds ratio
Raghunath et al. [36]	NO relationship	OR 0.87 (0.66–1.14)
*Saad et al. [113]	NO relationship	
Tan et al. [30] (16 cohort studies)	NO relationship	
*Cremoni et al. [114]	YES	OR 3.25 (2.09–5.33) (de novo GERD) OR 2.39 [1, 34] (GERD aggravation)
*Yaghoobi et al. [115]	YES	RR 2.0 [1–3, 9]
Xie et al. [41]	YES (in Asia)	RR 2.0 [1–3]
*Asian studies		RR 4.5 [1, 7–12] (min/max: 1.07–7.34)
*Western studies		RR 1.2 (0.9–1.6) (min/max: 2.01–36.0)
Wang [31] China (1978–2015) (20 RCTs; N. 6575)	YES in patients with peptic ulcer: Eradicated group: 7.25% Control group: 4.20%	OR 1.62 [1, 19]
	NO in patients with reflux esophagitis: Eradicated group: 25.2% Control group: 24.6%	OR 1.03 (0.87–1.21)

*The articles signed are based on the meta-analysis by Xie et al. [41]

GERD in neurologically-impaired children. According to these results, HP may aggravate GERD symptoms in children and eradication of HP does not play a major role in GERD symptoms even among neurologically-handicapped children.

Gastric and duodenal ulcers in children

The prevalence of HP-positive ulcers in children differed between countries. In a European multicenter study, in children, one quarter of cases with ulcers (10.6%) had HP infection [66]. In another study from "the pediatric European register for treatment of HP" (PERTH), the ulcer was determined in 12.3% of children with HP-associated gastritis (2001–2002) [67].

In children, the prevalence of HP with duodenal ulcer (83%) was higher than those with gastric ulcer [61, 62]. The prevalence of peptic ulcer was 6.7% in European children, 35% in Russian children [67], and 6.9% in Chinese children where HP positivity was 56.8% in duodenal ulcer and 33.3% in gastric ulcer [68]. Daugule [69] from Latvia determined that 82% of symptomatic children aged 8–18 years had antral gastritis and 7% had a duodenal ulcer. Finally, HP infection is associated with antral gastritis and duodenal ulcer in childhood. Pollet [65] did not determine ulcers or atrophic gastritis in neurologically-impaired children with HP infection (mean 13 years). In the study by Arent [70], duodenal and gastric ulcers among children aged 10–16 years were mostly linked to HP infection, but not ≤ 9 years.

Atrophic gastritis

Long-term HP infection causes inflammatory sequelae such as atrophic gastritis and intestinal metaplasia in the stomach. Moreover, apart from the distinction between infection of the fundus and of the antrum with consequent hypoacidity and hyperacidity, it should be remembered that the final consequence of HP infection is atrophic gastritis, even in the antrum, with a reduced acid production. In adults, HP infection often is associated with atrophic gastritis which leads to hypochlorhydria and hypergastrinemia [71, 72]. That is, hypochlorhydria and atrophic gastritis may protect against GERD [4–6, 9, 73]. Furthermore, atrophic gastritis predisposes individuals to gastric cancer.

Little is known about the prevalence of atrophic gastritis in childhood. Studies in children showed that atrophy and metaplasia were highly rare in childhood [20, 57–60, 71, 74–78]. In studies which focused on HP-positive children, the prevalence was reported as from 0 to 4% [74]. In the study by Hoepler [57] from Austria, one case was determined to have severe pangastritis and atrophy; a girl of 15 years old. In a study from Tunisia, the prevalence of pangastritis was 9.3 or 34.6% for moderate or severe atrophy (Grade 2–3) [79]. HP-induced gastric inflammation can cause atrophy in Japanese children, predominantly in the antrum [71]. The prevalence of grade 2 or 3 atrophy in the antrum was 10.7% and in the corpus 4.3% (mean 12.1 years). Furthermore, none of the children from two studies presented intestinal metaplasia. The prevalence of gastric atrophy and intestinal metaplasia varies according to the geographic/genetic origins as well as environmental

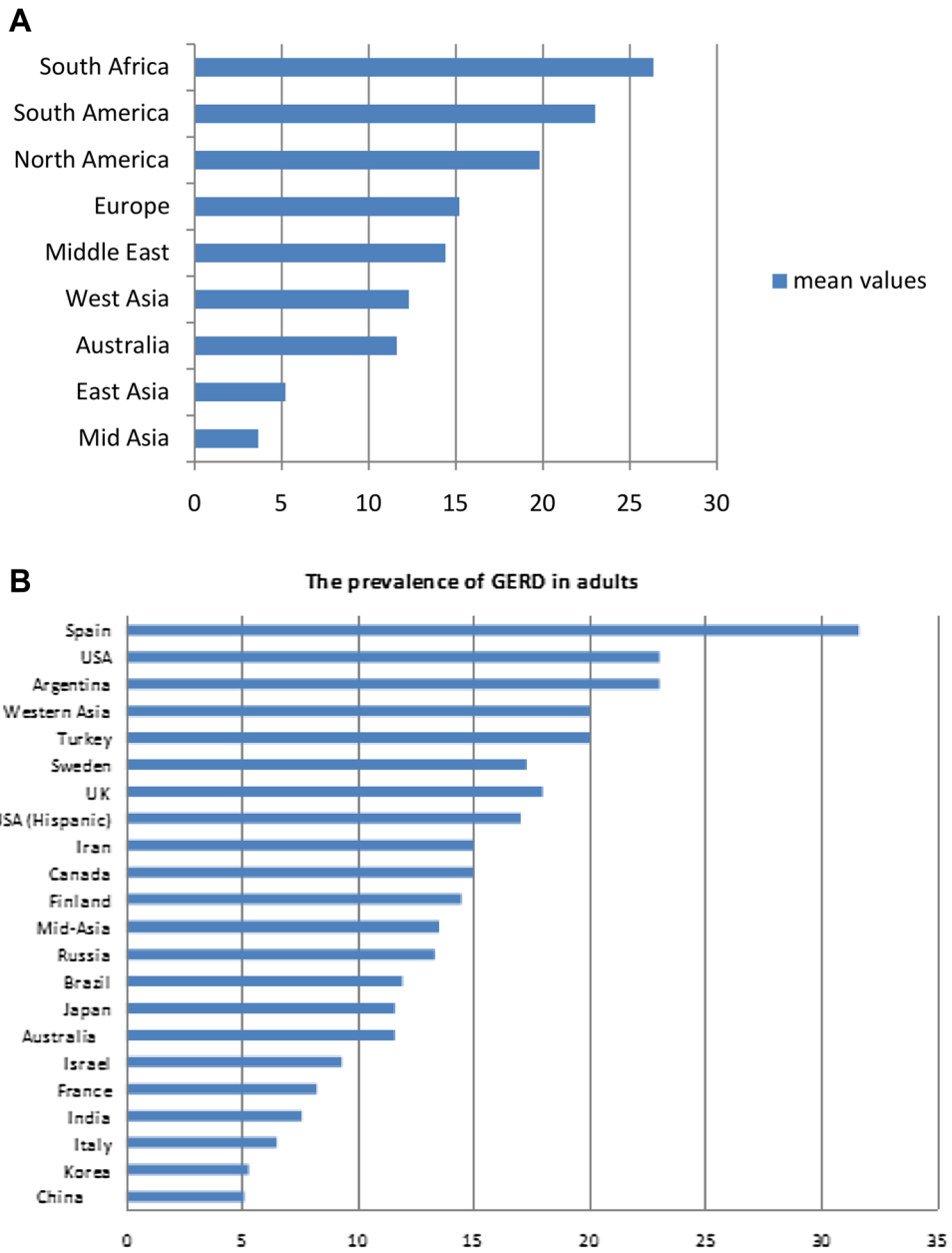

Fig. 1 **a** The prevalence of GERD in the world and **b** The prevalence of GERD in adults

factors [80]. Unfortunately, there is no pediatric study which compared the prevalence of gastric atrophy according to geographic, genetic or environmental factors.

The effects on severity of HP infection

HP infection was present in 27% of children in 19 centers from 14 European countries. The frequency of ulcers and/or erosions in children was 8.1%, occurring mainly in the second decade of life [66]. Probably, high-level histological scores may be a problem mainly among patients older than 20 years old. Keep in mind that the patients who had impairment of the barrier, such as a hiatal hernia, are a high-risk group in terms of developing severe histological scores as a complication of reflux esophagitis.

Little is known about the exact histological features of reflux and its contributions to esophageal and gastric mucosal lesions in children with HP-related gastritis. The studies which examined and scored the histological characteristics of the mucosa showed that in the presence HP, esophagitis was less severe according to the Los Angeles classification system (grade A) [12, 18]. Higher histological scores were determined in antrum-predominant gastritis in children, as expected [57–60].

Malignancy

Gastric cancer is most common cancer in Korean and Japanese men. Despite the high prevalence of HP infection in Bangladesh, Thailand, and India; however, the incidence of gastric cancer is extremely low in these countries in contrast to Japan. Antrum-predominant gastritis is more common in Bangladesh among all age groups with HP infection. In the Japanese, antrum-predominant gastritis is common in those younger than 59 years and corpus-predominant gastritis in cases older than 60 years [81]. Atrophy and metaplasia are the complications of pangastritis or corpus-predominant gastritis.

In a community-based study by Corley et al. [82], the prevalences of HP infection were 11.7%, 9.6%, and 22.7% in the BE cases, GERD patients, and controls, respectively. Persons with BE have a substantially increased risk of EAC. The decreasing prevalence of *H. pylori* infection in many countries correlates with the recent marked increases in EAC incidence, and the prevalence of HP infection is lower in demographic groups at higher risk of EAC. In the case of *H. pylori* infection protecting against GERD in corpus-predominant gastritis, the development of BE and EAC will decrease. In contrast, eradication of HP infection will increase the risk of BE and EAC. The prevalence of HP infection in EAC patients and distal gastric cancer has been compared by Inomata in Japan [83]. EAC was observed in 9.4% of the 852 cases. The rate of HP infection was lower in patients with EAC than gastric cancer (73.8 vs. 94.1%). The prevalence of corporal gastritis was lower in patients with EAC than gastric cancer also (80.7 vs. 94.6%). Concurrent HP infection and corporal gastritis were not observed in patients with BE.

Pediatric cohort studies pointed out that acute inflammation may be less intense in children, but that chronic inflammation may increase in intensity. In the study by Carvalho [60], the histological scores for esophagitis in Brazilian children and adolescents were higher in the non-infected group than in the HP-infected group and, among HP-positive children, neither intestinal metaplasia nor gastric atrophy was determined. In a study from a high-risk population (58 Korean and 115 Colombian; mean 15 years), the atrophic mucosa was present in 16% of children (31% intestinal metaplasia; 63% pseudopyloric metaplasia; 6% both) [84]. In case of atrophic gastritis or gastric cancer, HP infection prevents reflux esophagitis by decreasing gastric acid secretion. Atrophic gastritis is a risk factor for progression of malignancy even in children. Furthermore, children are less prone to develop HP-related malignancy which is only sporadically reported because of the time required for this development; it may take longer from childhood to adulthood [85].

Cytotoxin-associated gene A (CagA)

Host genetic factors and CagA strains of HP interact to determine HP and GERD. Therefore, the degree and extent of gastritis are affected by these factors [23]. A high prevalence of Cag A-positive strains has been reported in Asian populations and in some developing countries [86] and ranged between 90 and 97% in Korea, Japan, Malaysia, Southeast Asia, and China. It ranged between 80 and 89% in German, Estonia, and Brazil, ranged between 70 and 79% in Iraq, Iranian, and Turkey [87–89], between 60 and 69% in the United States, and between 40 and 49% in the Netherlands, and Sri Lanka. The prevalence ratios were reported differently from South- and East-Asian countries. Middle East countries had a similar range to that reported from European and North American countries between 60 and 70%.

Pangastritis which leads to gastric atrophy is associated with CagA strains [86, 90]. HP infection with CagA strains is associated with less severe reflux esophagitis due to pangastritis leading to hypochlorhydria. In adult studies, the protective effect of cagA-positive strains of HP against GERD has also been shown in Hong Kong, Iran, and Malaysia [45, 91]. A meta-analysis showed that eradication of Cag A-positive HP was also related to a higher risk of developing GERD [41]. Eradication of Cag A-positive HP leads to recovery of acid secretion capacity and corpus gastritis which might be the cause of the higher incidence of GERD in Asian populations [46]. Thus, it was claimed that HP CagA-positive strains may protect against the development of GERD. The genetic variability of HP strains is dependent on the geographical and ethnic status of human hosts.

Information about the HP strains in children is limited. Geographical location of the studies due to differences in the prevalence of *H. Pylori* globally is the reason for this heterogeneity [92]. Among children and adolescents with HP infection, the rate of cagA-positive strains was 41.5% in Italy, 58% in Latvia and 46% in Estonia [69, 93]. Sökücü [94] determined that esophageal lesions were less common in Turkish children infected with CagA-positive strains. In the study by Gold [44], gastric inflammation was more severe among children infected with CagA-positive strains. Eradication of HP has resulted in resolution of both esophageal and gastric diseases at 6-month follow-up. Analysis of pediatric HP strains continues to suggest that CagA-positive strains are less prevalent than in adult isolates, but gastric inflammation is more severe [95].

Inflammatory cytokines

CagA protein can induce IL-8 and IL-1β production. Thus, patients infected with CagA-positive strains develop more pronounced inflammation. The outer membrane in

inflammatory proteins of HP can also stimulate IL-8 secretion. HP-related corpus-predominant gastritis may have reduced gastric acid probably mediated by cytokines such as interleukin 1. Furthermore, vacuolating cytotoxin A (VacA), especially the virulent form s1m1, inhibits gastric acid secretion by disrupting the gastric parietal cells. This may reduce acid exposure in the esophagus causing less GER symptoms [7, 14, 86].

Children infected with HP have increased gastric concentrations of IL-1β and/or TNF-α, both potent inhibitors of gastric acid secretion [86]. Kutukculer [96] determined that TNF-alpha levels in gastric juice and in gastric biopsy were found to be significantly higher in patients with HP-positive gastritis than those in children without it. Increased levels of inflammatory cytokines may contribute to the pathogenesis of HP-associated gastritis in childhood.

Discussion

The prevalence of GERD has increased during the past 2 decades in the general population. While decreasing the rate of HP infection, GERD has been increasing. If this trend continues, in the future, HP infection rate will be extremely low in some countries in Asia. However, the incidence of GERD-associated severe complications, such as BE or EAC will also increase as a common health problem. Approximately 20–40% of patients with GERD have erosive esophagitis, and 65–70% of them have more severe complications at follow-up, such as stricture, BE, or EAC. For this reason, GERD with or without HP infection should be treated. Identifying the mechanism of abnormalities helps effective causative therapy. The role of HP infection in GERD have been related to gastric acid output, on the other hand, the evidence from pathophysiological studies show that TLESRs are the predominant mechanism of reflux in both children and adults with GERD without HP infection. The presence of HP, especially cagA-positive strains, tends to be protective against erosive esophagitis and BE by gastric atrophy and decreasing acid production which leads to decreased esophageal exposure to acid. Gastric acid secretion in patients with BE and BE-related EAC do not differ from those of appropriately matched controls with esophagitis alone.

The results of HP eradication depend on the type and location of gastritis in the patients with GERD. In the populations in which there is significant involvement of corpus gastritis, the eradication of HP leads to an increase in esophageal acid exposure and a worsening of the symptoms. Atrophic gastritis seems to be protective against GERD. In these patients, after the eradication of HP, GERD symptoms aggravate and reflux esophagitis occurs frequently. Studies in different geographic regions or populations may result in entirely different outcomes. The geographical location and genetic predisposition may involve factors that influence the pattern of gastritis. Studies should be evaluated based on geographic and ethnic characteristics. In a meta-analysis, subgroup analyses were carried out separately on studies from Asian (N. 3236; 4 RCTs) and western countries (N. 2922; 8 RCTs) and showed a significantly higher risk for the development of GERD in patients with eradication therapy compared with controls in Asian studies (RR 4.53); however, this risk was not observed in the subgroup analysis of western studies (RR 1.22). The protective effect may exist only in Asian populations [41].

The Maastricht IV/Florence consensus report describes that eradication of HP in populations of infected patients, on average, neither causes nor exacerbates GERD. Therefore, the presence of GERD should not dissuade practitioners from HP eradication treatment where indicated. In most populations, the changes in acid production after HP treatment have no proven clinical relevance and should not be used as an argument to treat or not to treat HP [97]. According to the guidelines for the management of HP infection in Japan in 2009, when long-term observation of patients with reflux esophagitis is performed following HP eradication, most of them remain in grade A or B of the Los Angeles Classification and their symptoms may not become more severe. The Maastricht IV/Florence consensus report describes that long-term treatment with PPIs in HP-positive patients is associated with the development of corpus-predominant gastritis. This accelerates the process of loss of specialized glands, leading to atrophic gastritis. Eradication of HP in patients receiving long-term PPIs heals gastritis and prevents the progression to atrophic gastritis. Therefore, in HP-infected patients with reflux esophagitis, eradication therapy is recommended prior to the long-term use of PPIs [98].

In conclusion, the determinative factors affecting GERD involving in HP are the location of gastric inflammation and CagA positivity in both children and adults. The reason why HP affects the corpus or antrum of the stomach in different populations may be due to genetic differentiation and CagA-positive strains of HP which is associated with pangastritis leading to hypochlorhydria and less severe GERD. We hope that this article puts into perspective to understand this complex relationship. Data on the location of gastric inflammation and CagA positivity should be obtained by further studies.

Limitation

First, only children who underwent upper gastrointestinal endoscopy were enrolled in the studies. Second, lots of the studies do not emphasize the location of gastric inflammation while evaluating the effect on GERD of HP infection.

Funding None.

Compliance with ethical standards

Ethical Statement This article does not contain any studies with human or animal subjects performed by any author.

Conflict of interest The author declares no conflict of interest.

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