How *Helicobacter pylori* Changed the Life of Surgeons

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Key Words

Helicobacter pylori eradication · Gastroduodenal disease · Surgery

Abstract

Helicobacter pylori infection has been identified as a pathogenic factor in a number of gastroduodenal diseases, most importantly in gastric and duodenal ulcer disease. This association and the development of *H. pylori* eradication therapies has had a tremendous influence on the surgical therapy for these disorders. Decades ago, surgery was the therapy of choice for gastric and duodenal ulcers. Now, however, the first line of therapy includes treatment of *H. pylori* infection, suppression of gastric acid secretion, and protection of gastric mucosal barriers combined with a range of endoscopic procedures. These developments have had a major impact on the indications for surgery in benign gastroduodenal diseases. In addition, advances in our understanding of the pathogenetic mechanisms of *H. pylori* infection have also changed our views of gastric mucosa-associated lymphoid tissue lymphoma, gastric cancer, and gastroesophageal reflux disease.

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Introduction

The discovery of *Helicobacter pylori* and its identification as a pathogen in chronic active gastritis in 1983 [1] have dramatically changed the treatment approach for gastroduodenal diseases in the last two decades. *H. pylori* has subsequently been implicated in several benign and malignant gastroduodenal diseases. Due to advances in the medical therapy of *H. pylori* infection with the development of potent eradication regimens, it has become possible to treat a number of these diseases conservatively without surgical procedures. Due to the high prevalence of *H. pylori*-associated diseases, recognition of this pathogen has changed the lives of gastrointestinal surgeons in terms of surgical decision-making and definitive treatment options. In this review, we briefly summarize the pathophysiology and prevalence of *H. pylori* infection and its impact on various gastroduodenal diseases, with special emphasis on surgical decision-making.

Prevalence of *H. pylori* Infection

It is estimated that approximately 50% of the world population is infected with *H. pylori* [2]. The prevalence of *H. pylori* infection varies widely by geographic area,

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age, race, ethnicity, and socioeconomic status. Rates appear to be higher in developing than in developed countries, with most of the infections occurring during childhood, and they seem to decrease with improved hygiene [3]. The highest infection rates are observed in populations with low socioeconomic status, overcrowding, and poor sanitary conditions. Epidemiological data indicate that in Western countries approximately 35–62% of the general population are infected with *H. pylori* [4]. There is no difference in prevalence of infection between men and women. Subjects with higher education have considerably lower levels of infection (34.1%) compared to subjects with a lower education level (46.9%) or those with primary education only (61.6%) [4]. In developing countries, *H. pylori* infection is usually acquired in childhood, with infection rates ranging from 13.4 to 24%, and increases with age [5, 6]. Children living in crowded conditions are at the greatest risk for *H. pylori* acquisition, and an inverse correlation is seen between the mother's education and *H. pylori* positivity in children [6]. In contrast, in developed countries, *H. pylori* infection is usually acquired in adulthood [7].

Pathophysiology of *H. pylori* Infection

H. pylori is a gram-negative microaerophilic bacillus. It was first identified and cultured in vitro by Marshal and Warren [1] in 1983. Although *H. pylori* has been linked with many benign and malignant diseases of the gastroesophageal system [8], the mechanisms by which *H. pylori* causes diseases are only partially understood [9]. The primary feature of *H. pylori* infection is progressive damage to the structure and function of the gastric mucosa, which may result in hypochlorhydria or achlorhydria. Low or absent acid secretion increases the risk for gastric ulcer, enteric infection, and gastric malignancy [10]. In addition, *H. pylori* can cause duodenal ulceration by the combined effects of antral gastritis with increased acid secretion, subsequent gastric metaplasia in the duodenum, which can be colonized by *H. pylori*, duodenitis, reduced duodenal bicarbonate secretion, and mucosal damage [11]. *H. pylori* resides in the surface of the stomach within the mucus, attached to mucous cells, as well as within epithelial cells. Various features of *H. pylori* have been investigated to determine which factors influence its virulence, including urease, flagella, and adhesins [12]. Urease and flagella enable viability and mobility in the acidic and viscous gastric mucus [12], and adhesins interact with receptors on the gastric epithelium to enable the attachment

despite peristalsis and continuous turnover of gastric epithelium and mucus [12]. Other possible factors of virulence include the cytotoxic-associated gene (*cag*), the signal sequence-1 genotype of vacuolating cytotoxin A (*vacAs1*) and others [12, 13]. Most importantly, factors that are responsible for different responses to *H. pylori* appear to be environmental and host-related, such as dietary factors [13], immunological factors [14], and antigens of the Lewis blood group [15]. It is important to emphasize that there is a wide spectrum of host responses to infection ranging from very little, to profound inflammation, mucosal atrophy and their sequelae. These differences represent variable interactions between the host and bacterial virulence factors mentioned.

H. pylori-induced chronic active gastritis is the starting point for the clinical sequelae, such as peptic ulcer disease, gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and others. *H. pylori* is responsible for approximately 80–90% of all forms of gastritis [16, 17]. Chemical gastritis, or C-gastritis, which is caused most often by the intake of nonsteroidal anti-inflammatory drugs (NSAIDs) or bile reflux, is the second most common type of gastritis [18]. Autoimmune gastritis, or A-gastritis, is caused by parietal cell antibodies or antibodies against the intrinsic factor, and accounts for 3–6% of all types of gastritis.

Gastric Ulcer and Duodenal Ulcer

Historical Background

Throughout the major part of the last century, ulcers were believed to be caused by stress and dietary factors, and therefore treatment was focused on hospitalization, bed rest, and dietary modifications. Later, gastric acid was blamed for ulcer diseases and subsequently antacids and acid inhibitors became the standard of therapy. In 1983 Warren and Marshall [1] first identified the link between *H. pylori* and ulcers, concluding that the bacterium, and not stress or diet, caused ulcers. It is now well established that in most instances peptic ulcers occur as a complication of *H. pylori* infection [19]. To begin with, *H. pylori* can be isolated from approximately 70–80% of patients with gastric ulcers and from 90–95% of patients with duodenal ulcers [9, 20, 21]. Secondly, *H. pylori* eradication significantly lowers the recurrence rate of peptic ulcers. Thus, patients with duodenal ulcers who are treated with a single course of H₂-receptor antagonists alone have recurrence rates of 85–95%/year. Those receiving long-term treatment with H₂-receptor antagonists

have recurrence rates of 30%/year. In contrast, the recurrence rate within 1 year after *H. pylori* eradication therapy is less than 20%, which has been shown in a number of studies, including a meta-analysis of double-blinded, randomized trials of duodenal ulcer patients with *H. pylori* [22]. Similar trials show that *H. pylori* eradication reduces the recurrence rate for gastric ulcers [23]. In addition, it has been postulated that while *H. pylori* eradication actually reduces ulcer recurrence, continuous treatment with acid suppression therapy only delays it.

Since the relationship between *H. pylori* infection and peptic ulcer diseases has been firmly established and since effective treatment strategies for *H. pylori* eradication are available [10, 24–26], the role of surgery has changed. Thus, the first line of treatment for uncomplicated peptic ulcer disease in *H. pylori*-positive patients is now eradication therapy. The current eradication strategies usually involve a combination of two antibiotics with either a proton-pump inhibitor or a bismuth compound, although a number of different regimes have been tested and are at the center of ongoing clinical trials. In addition, alternative strategies (e.g. lactobacilli, flavonoids and others) have been suggested and tested in clinical trials [27], and new strategies for the prevention and eradication of *H. pylori*, including vaccination, have evolved [28]. These new treatment forms might not only have prophylactic, but also therapeutic applications and perhaps hold more promise for the long term, especially in developing countries.

Surgery may only be indicated in situations where multiple eradication attempts have failed or with recurrent *H. pylori*-negative ulcers [29]. Therefore the role of the surgeon in the treatment of uncomplicated peptic ulcer has declined in recent decades to almost zero, beginning first with the development of potent acid-suppression drugs [30], and then further reduced by the identification and treatment of *H. pylori*.

How Has H. pylori Changed Surgery?

Eradication therapy for *H. pylori* has been available for more than a decade. However, the impact on the incidence of ulcer-related complications and the prevalence of surgical procedures performed for complicated and uncomplicated peptic ulcers is difficult to estimate. This is partly because of the efficacy of H₂-receptor antagonists and proton pump inhibitors (PPIs) as well as advanced endoscopic procedures on one hand, and the rise in *H. pylori*-negative NSAID-induced ulcers and subsequent complications on the other [31, 32]. It is a known fact that H₂-receptor antagonists and PPIs have significantly re-

duced the need for elective peptic ulcer surgery. For example, McConnell et al. [33] examined the changes in surgical treatment of peptic ulcer disease within a veterans hospital in the 1970s and 1980s. In the 1970s, 47% (n = 49) of patients were operated for chronic symptoms, whereas 53% (n = 55) of patients were operated for acute complications of peptic ulcer disease. In the 1980s this relationship changed to 18% of patients with elective surgery versus 82% of patients with emergency peptic ulcer surgery [33]. Thus, it was clearly apparent that already as a result of effective H₂-receptor antagonists and PPI treatment, elective peptic ulcer surgery had been virtually abandoned. Janik and Chwirot [34] analyzed the changes in the surgical management of patients with peptic ulcer disease during two time periods (1977–1981 and 1992–1996) to demonstrate the effects of acid-suppressing drugs and *H. pylori* eradication on the indications for and the type of surgery. There was a decrease in the number of patients operated by almost 1/3 between the two time periods. Regarding the indications, there was a several-fold decline in the number of patients undergoing surgery for recurrent peptic ulcer disease. The number of patients operated on for gastric outlet obstruction decreased by half. The decrease in the number of patients operated on for bleeding ulcers was proportional to the general decrease, and the number of patients operated for perforated ulcers increased slightly. Furthermore, the percentage of women who underwent surgery increased, possibly because of the use of NSAIDs in this patient group [34]. However, these data reflect changes in surgery which cannot be solely attributed to *H. pylori* treatment, but rather to the combined effects of acid-blocker and *H. pylori* treatment. To more accurately delineate the changes in the pattern of ulcer surgery associated with *H. pylori*, we utilized the US national hospital discharge surveys of 1993 [35] and 1998 [36], a time period in which *H. pylori* eradication was established as the standard treatment for peptic ulcers in *H. pylori*-positive patients. These databases represent estimates of all diagnosed conditions and surgical procedures in US hospitals. In this time period, there was a 16% decrease in diagnosed gastric ulcers and a 29% decrease in duodenal ulcers in the hospital patient population (fig. 1) [35, 36]. This decrease was observed for both genders, and in all age groups. Regarding the role of elective ulcer surgery, there was a further 63% decline in vagotomies between 1993 and 1998 (fig. 2). Thus, only 7,000 vagotomies were performed in US hospitals in 1998 out of 41,500,000 overall surgical procedures [36]. In contrast, however, in the same time period the total number of gastric or duodenal ulcer operations increased by 24%

Fig. 1. Gastric and duodenal ulcers in US hospitals in 1993 (out of 112,793,000 diagnosed conditions) and 1998 (out of 131,768,000 diagnosed conditions) utilizing the US national hospital discharge surveys of 1993 and 1998. These databases represent estimates of all diagnosed conditions in US hospitals. Data are presented as percentage $\times 1,000$.

Fig. 2. Vagotomies and peptic ulcer operations in US hospitals in 1993 (out of 41,608,000 surgical procedures) and 1998 (out of 41,500,000 surgical procedures) utilizing the US national hospital discharge surveys of 1993 and 1998. These databases represent estimates of all surgical procedures in US hospitals. Data are presented as percentage $\times 1,000$. The absolute number of vagotomies are indicated in the bar graph (left panel).

(fig. 2). Although the utilized databases do not differentiate between elective and emergency operations, it appears appropriate to assume that the vast majority of those represent emergency ulcer operations.

Complications of Peptic Ulcer Disease

Since nowadays uncomplicated peptic ulcers rarely require surgery, the focus has shifted to the typical complications of peptic ulcer disease: bleeding, perforation, and gastric outlet obstruction.

Bleeding. Bleeding is one of the most common complications of peptic ulcer disease. Its incidence is approximately 1/1,000 adults per year, with a mortality rate of 8–14% [37]. Endoscopic treatment is the first line of treatment in active bleeding peptic ulcers. Surgery is mandatory if the bleeding cannot be controlled endoscopically, and should be considered if re-bleeding occurs or in ulcers with a high rate of recurrence (Forrest Ia and IIa on the posterior wall of the duodenum and on the lesser curvature of the stomach) [38]. Whilst it is undisputed that

bleeding peptic ulcers that cannot be controlled endoscopically are a clear indication for surgery, controversy exists over whether and when surgery should be considered as the first-line therapy for bleeding peptic ulcers and following endoscopic therapy for ulcers that run a high risk of re-bleeding [39]. Nonetheless, there is a clear indication for *H. pylori* eradication following endoscopic or surgical hemostasis in *H. pylori*-positive patients, since recurrent bleeding can be prevented by *H. pylori* eradication [40], and since there is persistent *H. pylori* infection in patients undergoing surgery for peptic ulceration [41].

Perforation. The second most common complication of peptic ulcer disease is perforation. This comprises open perforation into the abdominal cavity as well as penetration into adjacent viscera. The treatment of perforated ulcers has changed during the last centuries, which began with the first report of ulcer excision and suture by Mikulicz in 1885. In the 1970s and 1980s, ulcer perforation was treated by ulcer excision, suture and various vagotomy procedures (e.g., truncal vagotomy, proximal gastric vagotomy, highly selective vagotomy) [42, 43]. Nowadays, as a result of the identification of *H. pylori*, the standard treatment has changed to simple ulcer excision and suture and subsequent *H. pylori* eradication [44]. While perforated peptic ulcers are generally considered an indication for surgery [45, 46], conservative treatment has been suggested under special circumstances (e.g., a prohibitive anesthesiological risk or the absence of peritoneal signs) [47]. An alternative method has recently been proposed by Pescatore et al. [48], who treated patients with anterior ulcer perforations with concomitant laparoscopy and endoluminal endoscopy with closure of the perforation by an omental plug. Regardless of the method used to treat perforated peptic ulcer disease, it is essential to eradicate *H. pylori* in positive patients, since it has been shown that eradication of *H. pylori* after simple closure of a perforated peptic ulcer reduces the incidence of residual and recurrent ulcers [49]. It should be noted, however, that while there seems to be a clear reduction in the incidence of peptic ulcer perforations since the introduction of H₂-receptor antagonists and PPIs [50], the discovery and treatment of *H. pylori* has not led to a further decline in the incidence of ulcer perforation [44].

Gastric Outlet Obstruction. Gastric outlet obstruction is another complication of peptic ulcer disease. This complication can be treated surgically or endoscopically [39, 51]. Although only scattered evidence exists in the current literature, it has been suggested that gastric outlet obstruction can be successfully treated with *H. pylori* eradication in positive patients [52, 53]. It should be kept in mind that

eradication therapy is indicated in all *H. pylori*-positive patients undergoing surgical or endoscopic therapy for gastric outlet obstruction.

How Is H. pylori Changing the Life of the Surgeon with Respect to Peptic Ulcer Surgery?

Although H₂-receptor antagonists and PPIs have had a major impact on surgical indications and decision-making in gastroduodenal disease, *H. pylori* has further changed gastroduodenal surgery. Nowadays, surgery for uncomplicated peptic ulcer disease is extremely rare [54], but operations for complications of peptic ulcer disease such as bleeding, perforation and gastric outlet obstruction are still frequently performed by gastrointestinal surgeons. This is in part due to the continuous use of NSAIDs in the patient population at risk. While there is a clear association between consumption of NSAIDs and peptic ulcers, is it currently not known whether the ratio of NSAID-induced emergency ulcer operations has changed with the introduction of *H. pylori* eradication. However, it is clear that NSAID use represent a major risk factor for complicated peptic ulcer disease, responsible for the majority of emergency ulcer operations in some series [55–57].

In conclusion, a combination of H₂-receptor antagonists, PPIs, and *H. pylori* therapy have virtually 'eradicated' elective ulcer surgery. However, regarding emergency peptic ulcer surgery, the available data do not suggest a decline in the procedures performed only as a result of *H. pylori* treatment.

***H. pylori* after Gastric Surgery**

An important clinical topic is whether *H. pylori* plays an important role in recurrent ulcers after gastric surgery. In one of the first studies touching on this topic by Friess et al. [58], 24 *H. pylori*-positive patients with chronic ulcer disease were analyzed following proximal gastric vagotomy. In 13 patients treated additionally with single-shot antibiotics perioperatively, there was a significant reduction in *H. pylori* infection, the degree of inflammation and the frequency of metaplasia 3 months postoperatively [58]. In contrast, in 11 patients not receiving perioperative antibiotics there was only a reduction in gastric metaplasia in the duodenum [58].

A more thorough analysis was conducted by Schilling et al. [59] on 50 patients with partial gastric resection for peptic ulcer disease and 50 matched control patients. The prevalence of *H. pylori* infection was 38% in the resected

group and significantly higher (60%) in the control group. Furthermore, the association of *H. pylori* infection and endoscopic findings was significant in the control group, but not in the resected group [59]. Since the prevalence of *H. pylori* infection in patients with partial gastric resection was significantly lower than in matched controls, it was concluded that *H. pylori* does not play a significant role in recurrent ulcers after partial gastric resection [59]. Similar results were obtained by Lee et al. [60], who examined 93 patients with previous vagotomy or partial gastrectomy presenting with dyspepsia or ulcer bleeding. Of the 36 patients in the gastrectomy group, 42% were *H. pylori*-positive, and of the 12 patients in the vagotomy group 67% were infected with *H. pylori* [60]. Since the prevalence of *H. pylori* infection did not differ between patients with or without ulcer recurrence, it was concluded that *H. pylori* infection cannot account for ulcer recurrence after peptic ulcer surgery [60]. A different conclusion was drawn by Danesh et al. [41] who reviewed 36 studies published before January 1997 dealing with this topic. Overall, the prevalence of *H. pylori* infection was 83% after vagotomy procedures, and 50% following partial gastric resection. In view of the persistently high prevalence of *H. pylori* infection postoperatively, the authors argued in favor of eradicating *H. pylori* in those patients.

Further studies are necessary to better define whether *H. pylori* plays a role in the pathophysiology of recurrent ulcers after gastric resection and whether eradication is indicated in asymptomatic patients following gastric resection for peptic ulcer disease.

Gastric Cancer

The association of *H. pylori* infection and the development of gastric cancer has gained much attention in the last years [61, 62]. There is ample evidence that *H. pylori* infection is a risk factor for gastric cancer [4, 63–65]. Individuals who acquired *H. pylori* at a young age have a 13-fold increased risk compared to the uninfected population [66]. In addition, certain genetic polymorphisms, such as of the interleukin-1 gene, increase the risk of gastric cancer additionally [67]. The best estimate for the overall risk of gastric cancer associated with *H. pylori* infection is a 5.9-fold increased risk [68]. The association between gastric cancer and *H. pylori* infection seems to be restricted to cancers of the gastric corpus and antrum, while cancer of the cardia does not show a significant association [68–70]. In addition, there is direct experimental evidence in animals that *H. pylori* infection can induce gastric adenocar-

cinoma [71]. These findings have not had a significant impact on the decision-making and recommendation of surgical therapy for gastric cancer. However, identification of populations at risk of gastric cancer has major implications for screening and patient management.

It should be kept in mind that although epidemiological studies have shown an association between *H. pylori* and gastric cancer, clinical trials have not proven that eradication therapy prevents gastric cancer [72]. Furthermore, it is doubtful whether eradication therapy after gastric resection prevents subsequent gastric cancer [73]. It is hoped that future studies and analysis will clarify the role of *H. pylori* eradication in the prevention of gastric cancer. In addition, the health economic costs of the potential gastric cancer prevention by eradication of *H. pylori* have not been estimated, due to the methodologically difficult analysis and the lack of properly designed clinical trials [74]. It can be speculated that on one hand *H. pylori* eradication might lower the incidence of gastric cancer and subsequent related costs. On the other hand, *H. pylori* eradication might lead to more frequently encountered antibiotic resistance and potentially an increase in the incidence of gastroesophageal reflux disease (GERD), Barrett's esophagus and esophageal cancer (see below) with increased health care costs. Careful cost analysis, as has already been performed for duodenal ulcer [75], is necessary to answer these important questions.

Low-Grade B-Cell Lymphomas of Mucosa-Associated Lymphoid Tissue

Low-grade B-cell lymphomas of MALT are thought to arise within organized lymphoid tissue in the gastric mucosa, which is most frequently acquired in response to *H. pylori* infection [76]. Thus, over 92% of patients with gastric MALT lymphoma have active *H. pylori* infection [77]. There is general agreement that apart from localized disease (stage I), gastric MALT lymphoma should be treated by surgery [29, 78] if the tumor is potentially resectable. The extent of resection (subtotal or total gastrectomy) depends on the extent of the disease. Advanced disease may be treated by chemo- and/or radiotherapy. It has been strongly suggested to perform *H. pylori* eradication following surgery for gastric MALT lymphoma at all stages to prevent recurrence [29]. The appropriate treatment for localized (stage I) gastric MALT lymphoma is still controversial since high remission rates for these lymphomas have been observed following *H. pylori* eradication [79, 80]. Neubauer et al. [79] examined 50 patients

with stage-I gastric MALT lymphomas in whom *H. pylori* infections had been eradicated. *H. pylori* infections were cured in all 50 patients, and after a median follow-up of 24 months there was no recurrence of the gastric MALT lymphomas, although most patients displayed evidence of monoclonal B cells [79]. In a more recent study, Montalban et al. [80] investigated 19 consecutive patients with stage-I gastric low-grade MALT lymphoma. 18 of the 19 patients (94.7%) achieved histologic regression of the MALT lymphoma and there was no relapse after a mean follow-up of 37 months [80]. It thus appears that in most cases of gastric low-grade MALT lymphoma in stage I, eradication of *H. pylori* can produce histologic regression of the lymphoma and this regression can be maintained for years. However, persistent B-cell monoclonality is detected in most cases. These findings indicate that in cases of localized gastric low-grade MALT lymphoma associated with *H. pylori*, the initial treatment step should be eradication of *H. pylori*. It has to be kept in mind, however, that a close and long follow-up is essential to determine the ultimate outcome of these patients. Whether these patients are truly cured of their lymphomas remains uncertain.

Ménétrier's Disease

Hypertrophic gastropathy (Ménétrier's disease) is a special and rare form of gastritis possibly leading to severe complications such as protein loss and subsequent hypogammaglobulinemia and increased cancer risk.

Although it has been suggested that eradication of *H. pylori* in patients with Ménétrier's disease results in a return to normal mucosal histology and in the normalization of serum protein concentrations [81–83], no definite conclusions and recommendations can be drawn from the above-mentioned studies, due to the low frequency of this disease. Since the chance of gastric carcinoma developing in these patients is appreciable and the reported long-term results of operative therapy appear favorable, it has been argued previously that patients with persistent and sufficiently distressing symptoms should be considered for gastric resection [84]. However, therapeutic eradication regimens in patients with Ménétrier's disease and *H. pylori* infection may represent an effective alternative to surgical intervention in these patients, and could be considered as the first line of treatment. Further research on the role of *H. pylori* in the pathophysiology of Ménétrier's disease and further clinical observations and trials will help answer questions regarding the optimal treatment strategy for patients with this uncommon disease.

Gastroesophageal Reflux Disease

The role of *H. pylori* in GERD has gained increasing attention in recent years. It has been noticed that patients with reflux esophagitis and *H. pylori* infection who are treated with PPIs or H₂-receptor antagonists are at increased risk of atrophic gastritis [85–87], which is of concern regarding the eventual consequences of the increase in severity of *H. pylori*-induced gastritis [10]. However, most importantly, there have been concerns regarding the development of GERD after successful eradication of *H. pylori* infection. Thus, the presence of GERD and its complications, e.g. Barrett's esophagus and adenocarcinoma of the esophagus, is higher in the population without *H. pylori* infection than in those with *H. pylori* infection [88, 89]. Warburton-Timms et al. [90] investigated 1,485 patients undergoing routine upper gastrointestinal tract endoscopy. While 45% of all patients were *H. pylori*-positive, only 38% of the patients with esophagitis were *H. pylori*-positive. More striking, there was a significant decrease in anti-CagA antibodies in patients with a normal esophagus (81%) compared to patients with severe esophagitis (46%) [90]. Since the risk of severe esophagitis significantly decreased in patients infected with cagA+ *H. pylori*, it was concluded that infection with this *H. pylori* strain may be protective for esophageal disease [90]. In addition, Yamaji et al. [91] examined 5,732 consecutive Japanese subjects during a health screening. There was a decreased prevalence of GERD in conjunction with gastric atrophy induced by *H. pylori* infection [91]. The mechanisms whereby *H. pylori* infection protects against GERD include the induction of gastric hypoacidity and thereby decreased potency of the gastric refluxate, and possibly other indirect mechanisms via alterations in the gastric mucosa [92–94]. Nonetheless, it has been argued that the consequences in terms of morbidity and mortality of an untreated *H. pylori* infection outweigh by far the possible mortality of concomitant worsening of esophageal disease [95]. Whether this statement will stand the test of time remains to be seen. Interestingly, it has also recently been shown in a double-blind, randomized, placebo-controlled study in 70 patients with GERD that *H. pylori* infection positively affects the relapse rate of GERD [96]. In contrast to the above-mentioned studies, it has therefore been suggested to eradicate *H. pylori* to help to prolong disease-free intervals in GERD patients [96]. However, other studies failed to demonstrate that *H. pylori* eradication therapy influences relapse rates in GERD patients [97]. It seems that while *H. pylori* may protect some GERD patients from reflux and subsequent

diseases, other patients experience longer disease-free time periods as a result of *H. pylori* eradication [98]. Regarding surgery, so far there has been no major change in the surgical treatment strategy for GERD due to *H. pylori*. However, the surgeon should be aware of the complex interaction of *H. pylori*, gastritis, GERD and acid-suppression therapy.

***H. pylori* and Pancreatic Cancer**

A recently published epidemiological study about the risk of *H. pylori* infection and exocrine pancreatic cancer was conducted in 29,133 male Finnish smokers aged 50–69 years [99]. There were 226 control subjects matched to the 121 case subjects, and a 10-year follow-up period. This study demonstrated a significantly elevated risk of pancreatic cancer in *H. pylori*-positive patients with an OR of 1.87 (95% CI = 1.05 to 3.34). This increased risk was even more evident in the subgroup of CagA+ *H. pylori* strains, with an OR of 2.01 (95% CI = 1.09 to 3.70) [99]. The pathophysiological mechanisms leading to an increased incidence of pancreatic cancer in *H. pylori*-positive patients are completely unknown and pose a challenge for clinicians and researchers in the coming years.

Conclusion

H. pylori infection is a serious, chronic, and transmissible disease responsible for a large proportion of peptic ulcer cases, and at least partly involved in the pathophysiology of gastric cancer, gastric MALT lymphoma, GERD, and other less common gastroesophageal diseases. The indications for elective surgery have changed dramatically, especially for peptic ulcer disease, due the development of potent *H. pylori* eradication therapies. Surgeons must be aware of the basic pathophysiological mechanisms of *H. pylori*-associated diseases and must consider eradication therapy more aggressively.

For the surgeon, the frequency of elective ulcer surgery has decreased to almost zero, at least partly because of the identification and therapy of *H. pylori*, while the frequency of emergency ulcer surgery has remained more or less unchanged. It remains to be seen whether there is an increase in GERD-associated surgery in the coming years as a result of *H. pylori* eradication.

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