Chapter 15
Helicobacter pylori and Nonmalignant Diseases

Doron Boltin and Yaron Niv

Abstract Infection with *Helicobacter pylori* initially leads to superficial gastritis and usually progresses to chronic active gastritis. Although the vast majority of chronically infected subjects remain asymptomatic, somewhere between 10 % and 15 % develop peptic ulcer disease. Most commonly, *H. pylori* infection is located in the gastric antrum, where it acts to inhibit somatostatin release and thus stimulate acid secretion, causing duodenal ulceration. Patients with pangastritis are predisposed to developing gastric ulceration. Although population-based studies show that patients with gastroesophageal reflux disease have a lower likelihood of *H. pylori* infection, there is no robust evidence suggesting that eradication of *H. pylori* leads to erosive esophagitis. Patients who lack endoscopic evidence of disease such as peptic ulceration (i.e., functional dyspepsia) experience a greater reduction in their dyspeptic symptoms following eradication of *H. pylori* as compared to placebo. The pathophysiology of *H. pylori*-mediated dyspepsia in these patients probably involves increased acid, decreased ghrelin, and altered gastric emptying. Eradication of *H. pylori* in patients with functional dyspepsia has the added benefit of preventing future peptic ulcer disease, especially in Asian populations. *H. pylori* has been weakly linked to various nonmalignant conditions ranging from halitosis to coronary heart disease. However, evidence in support of actively seeking and treating *H. pylori* exists only for idiopathic thrombocytopenic purpura and iron deficiency anemia. In epidemiological studies, *H. pylori* infection has been shown to be inversely associated with Crohn's disease and asthma.

Keywords *Helicobacter pylori* • Peptic ulcer • Gastroesophageal reflux • Dyspepsia

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15.1 Introduction

Helicobacter pylori has been implicated as a precipitating factor, a perpetuating factor, or a protective factor, in various nonmalignant diseases. *H. pylori* may exert its effect via direct toxicity or via indirect paracrine, endocrine, neurocrine, or immune pathways. Foremost, *H. pylori* is associated with the formation, complication, and recurrence of peptic ulcer disease, both as a solitary factor and in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs). Testing for *H. pylori* and subsequent eradication is therefore essential in patients with a history of ulcer bleeding or prior to commencing long-term NSAID therapy. On the other hand, evidence of a role for *H. pylori* in causing functional dyspepsia is less robust, and the likelihood of symptomatic improvement following eradication varies greatly across geographic region. *H. pylori* infection offers theoretical protection against gastroesophageal reflux disease (GERD), owing to the hypochlorhydria typically manifest in the setting of pangastritis. Indeed, the prevalence of infection observed in subjects with both erosive and nonerosive GERD is reduced. Nevertheless, there is no evidence that GERD may develop following *H. pylori* eradication nor is there evidence that preexisting GERD or Barrett's esophagus may worsen. Epidemiological studies have found an inverse relationship between *H. pylori* infection and atopic disease and Crohn's disease, and various candidate immune mechanisms have been explored. As yet, no causal relationship has been established.

15.2 Peptic Ulcer Disease

15.2.1 Pathophysiology

Peptic ulcer disease (PUD) occurs when mucosal defense mechanisms are overwhelmed by the destructive effects of acid and pepsin and most commonly result from *H. pylori* infection or NSAIDs (Table 15.1). Although acute infection with *H. pylori* causes hypochlorhydria, chronic *H. pylori* infection may cause either hypo- or hyperchlorhydria. Whether *H. pylori* ultimately increases or decreases gastric acid secretion depends upon the severity and distribution of gastritis (Schubert and Peura 2008). Pangastritis usually results in decreased acid secretion. This is probably mediated by inflammatory cytokines and bacterial toxins including the vacuolating cytotoxin (VacA) gene product and cytotoxin-associated gene A (CagA) product (Fig. 15.1). This pattern of gastritis is seen in approximately 85 % of subjects with chronic *H. pylori* infection and predisposes to gastric ulceration. Conversely, 15 % of subjects with chronic *H. pylori* infection may develop antral predominant gastritis, which is characterized by reduced antral secretion of somatostatin. This in turn results in elevated basal and stimulated

Table 15.1 Etiology of peptic ulcer disease

Common
H. pylori infection
NSAIDs/aspirin
Uncommon
Hypersecretion
Zollinger–Ellison syndrome
Systemic mastocytosis
Medications (usually in combination with NSAIDs)
Bisphosphonates
Corticosteroids
Potassium chloride
5-Fluorouracil
Sirolimus
Mycophenolate mofetil
Infiltrative disease
Carcinoma/lymphoma
Sarcoidosis
Crohn's disease
Infections
Helicobacter heilmannii
Herpes simplex virus
Cytomegalovirus
Tuberculosis
Syphilis
Ischemia
Atherosclerosis/embolic disease
Cameron ulcer
Cocaine
Severe systemic disease

gastrin secretion and increased corporal acid production. This pattern of gastritis predisposes to duodenal ulceration.

15.2.2 Epidemiology

The population-based prevalence of peptic ulcer disease depends greatly on ethnic, geographic, and socioeconomic factors, as well as the method of data collection. A recent meta-analysis with pooled data from the USA, Europe, and Israel found an annual PUD incidence of 0.03–0.19 % and a 1-year prevalence of 0.1–1.5 % (Sung et al. 2009). The occurrence of PUD has been decreasing over the past few decades in most Western populations. The prevalence of *H. pylori* infection in duodenal ulcers was reported to be 84 % in studies published from 1999 to 2003 (Fig. 15.2),

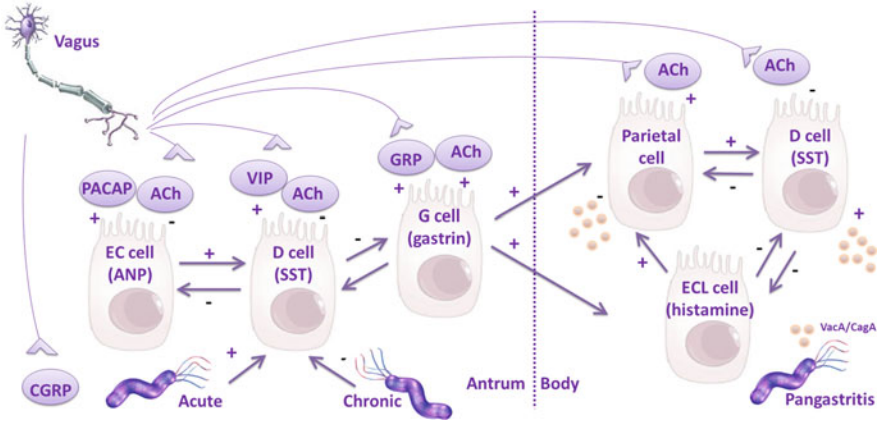

Fig. 15.1 Regulation of gastric acid secretion. Acute infection with *H. pylori* activates CGRP neurons to stimulate SST and thus inhibit gastrin secretion. In duodenal ulcer patients with chronic antral *H. pylori* infection, the organism or cytokines released from the inflammatory infiltrate inhibit SST and thus stimulate gastrin and hence acid secretion. When *H. pylori* colonizes the gastric body, bacterial toxins such as VacA and CagA act to decrease acid secretion; however, the precise mechanism is unknown

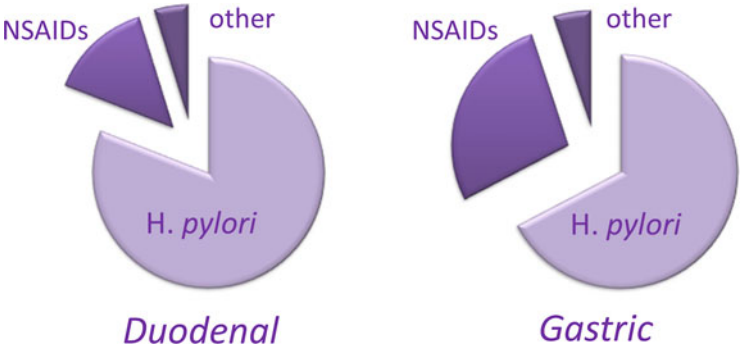

Fig. 15.2 Pie charts depicting the etiology of peptic ulcer disease. The percentages shown are based on studies conducted in Western populations. Such a representation is clearly simplistic, as *H. pylori* and NSAID use often coexist. Similarly, the relative proportion of each factor varies according to age, ethnicity, and socioeconomic status

whereas in studies published from 2004 to 2008, the prevalence of *H. pylori* was 77 % (Gisbert and Calvet 2009). However, this trend might not be apparent in some Asian populations, where the incidence of *H. pylori* gastric ulcer could be increasing (Jang et al. 2008).

The declining incidence of PUD has occurred in parallel to a decline in *H. pylori* infection rates. In areas of high *H. pylori* prevalence (e.g., in Asia), *H. pylori* causes almost all uncomplicated duodenal ulcers and more than 80 % of gastric ulcers, especially if the previous use of NSAIDs has been excluded (Gisbert et al. 1999). In

low-prevalence areas such as the USA, *H. pylori* accounts for a smaller proportion of PUD (Table 15.2). However, evidence supporting this is derived from retrospective cohorts, which do not fully consider NSAID and proton pump inhibitor (PPI) use (Jyotheeswaran et al. 1998; Ciociola et al. 1999).

15.2.3 Treatment of PUD

Eradication of *H. pylori* infection undoubtedly alters the natural history of PUD. Several studies have shown that ulcer recurrence is very low or nonexistent 1 year following eradication. This is in stark comparison with the natural recurrence rate of over 70 % (Marshall et al. 1988). Following failure of *H. pylori* eradication, ulcer recurrence may exceed 50 % (Fiocca et al. 1991). The details of medical treatment for *H. pylori* infection are covered in Chap. 20.

15.2.4 Complications of PUD

15.2.4.1 Bleeding

Complications of PUD develop in 20–25 % of patients and include hemorrhage, perforation, penetration, and obstruction. Bleeding is the most frequent complication and accounts for approximately 70 % of complicated PUD. Bleeding is the major cause of PUD-associated morbidity and mortality. *H. pylori*-associated ulcers are thought to confer a lower risk of bleeding compared to NSAID or idiopathic ulcers (Vaira et al. 1997; Boltin et al. 2012). Gisbert and coworkers reviewed 32 studies and found *H. pylori* in 80 % of bleeding peptic ulcers which was lower than the positivity rate in non-bleeding ulcers (Gisbert and Abraira 2006). However, when delayed detection techniques are employed to determine *H. pylori* infection, sensitivity is greatly improved, and the prevalence of *H. pylori* in bleeding ulcers approaches that of non-bleeding ulcers. This was shown in an analysis of 71 studies including 8496 subjects, where *H. pylori* was found to increase the risk of ulcer bleeding by a factor of 1.79 (Sánchez-Delgado et al. 2011). CagA-positive strains of *H. pylori* confer an even higher risk of ulcer bleeding (Stack et al. 2002).

Prospective long-term data indicate that the risk of rebleeding is virtually eliminated following *H. pylori* eradication (Gisbert et al. 2012). Persistence of H. *pylori* appears to be one of the most important factors causing rebleeding in patients with ulcer bleeding. For this reason, PPI treatment is recommended until the documented healing of a gastric ulcer, or until *H. pylori* eradication for duodenal ulcers, but not beyond (Malfertheiner et al. 2012).

Table 15.2 Large studies ($N \geq 100$) performed in Western countries evaluating *Helicobacter pylori* prevalence in patients with duodenal ulcer (1999–2013)

Author	Year	Country	Number of patients	Prevalence of *H. pylori* (%)
Ciociola et al.	1999	The USA	2394	73
Gisbert et al.	1999	Spain	774	95
Higuchi et al.	1999	Japan	330	96
Tsuji et al.	1999	Japan	120	96
Aoyama et al.	2000	Japan	111	98
Arakawa et al.	2000	Japan	368	96
Meucci et al.	2000	Italy	317	92
Nishikawa et al.	2000	Japan	152	99
Bytzer et al.	2001	Denmark	276	88
Lutgen et al.	2001	France	152	79
Spaziani et al.	2001	Italy	240	75
Sugiyama et al.	2001	Japan	151	99
Xia et al.	2001	Hong Kong	599	79
Palli et al.	2002	The UK	275	90
Kamada et al.	2003	Japan	464	97
Arents et al.	2004	The Netherlands	254	89
Arroyo et al.	2004	Spain	472	96
Kato et al.	2004	Japan	100	83
Chu et al.	2005	Hong Kong	1343	70
Xia et al.	2005	Hong Kong	271	90
Ong et al.	2006	The UK	288	69
Pietroiusti et al.	2008	Italy	608	93
Chen et al.	2010	Taiwan	626	88.7
Ortega et al.	2010	Chile	5664	86.6
Li et al.	2010	China	1030	92.6
Musumba et al.	2012	The UK	386	66
Cekin et al.	2012	Turkey	222	84.9
Buzás et al.	2013	Hungary	4647	59.1

15.2.4.2 Perforation

H. pylori eradication is similarly beneficial following perforation of a peptic ulcer. A large meta-analysis found that *H. pylori* eradication combined with operative management resulted in a lower rate of ulcer recurrence at 1 year, compared to surgery followed by PPI therapy alone (5.2 % vs. 35.2 %) (Tomtitchong et al. 2012). Therefore, after surgical management of perforated peptic ulcer, *H. pylori* eradication is recommended in all infected patients in order to prevent ulcer relapse.

15.2.4.3 Gastric Outlet Obstruction

In a shift from the traditional approach of managing obstructing duodenal ulcers surgically, most current guidelines recommended conservative treatment with *H. pylori* eradication. A nonsurgical approach may also combine enteral nutritional support and endoscopic dilatation. Surgery should be reserved for salvage treatment in patients unresponsive to medical therapy (Gisbert and Pajares 2002).

15.2.5 H. pylori, *Aspirin, and NSAIDs*

Both *H. pylori* and NSAIDs are established risk factors for PUD and ulcer-related bleeding. When these two factors are simultaneously present, the potential for complications is compounded, even though it is impossible to know precisely the individual contribution of each factor (Huang et al. 2002). *H. pylori* increases the risk of NSAID-related mucosal injury (Lanza et al. 2009). So too, patients with complicated PUD who continue to receive NSAIDs/aspirin following *H. pylori* eradication have an increased incidence of rebleeding.

Naïve patients, without prior PUD, who are set to commence long-term therapy with NSAIDs/aspirin clearly benefit from *H. pylori* eradication. This is based on large, well-designed randomized controlled trials (Chan et al. 1997). In subjects already receiving long-term NSAIDs/aspirin, there is no obvious benefit in treating *H. pylori*. A meta-analysis concluded that long-term PPI is more effective than *H. pylori* eradication for the prevention of ulcer bleeding in patients already receiving NSAIDS (Vergara et al. 2005). In this study, 2.6 % of subjects developed PUD following eradication, whereas none of the patients receiving PPI developed an ulcer, despite persistent *H. pylori* infection.

Patients receiving low-dose aspirin are at minimal risk of PUD and ulcer-related bleeding. A prospective 10-year cohort study including 904 subjects receiving low-dose aspirin compared three patient groups: *H. pylori*-positive patients with bleeding ulcers who resumed aspirin following eradication, *H. pylori*-negative patients with bleeding ulcers who resumed aspirin following ulcer healing, and new users of aspirin without a history of ulcers (average risk) (Chan et al. 2013). None of the patients received PPI treatment. The rate of ulcer bleeding in patients with previous ulcer bleeding following eradication was similar to the average-risk group (0.97 % and 0.66 %, respectively). Recurrent ulcer bleeding was highest in aspirin users without prior *H. pylori* infection (5.22 %). In keeping with these findings, the Maastricht IV/Florence Consensus Report recommends that patients with a history of PUD should be tested for *H. pylori* and following eradication these patients do not require long-term PPI (Malfertheiner et al. 2012). *H. pylori*-negative patients should receive adequate antisecretory therapy if they have a history of ulcer bleeding, since they are prone to ulcer bleeding with aspirin use.

15.3 Gastroesophageal Reflux Disease

15.3.1 Pathophysiology

The most commonly cited cause for GERD is transient relaxation of the lower esophageal sphincter. Additional causes include a hypotensive sphincter, hiatal hernia, and acid hypersecretion. Chronic *H. pylori* infection is commonly associated with hypochlorhydria, and therefore patients harboring *H. pylori* are theoretically protected from GERD and may even exhibit an augmented response to proton pump inhibitors. Following eradication of *H. pylori*, acid hypersecretion may occur for up to 8 weeks due to increased parietal and ECL cell masses; however, these changes are short-lived and GERD does not generally ensue (Gillen et al. 1999).

15.3.2 Epidemiology

GERD affects 25–40 % of the population. Population-based studies have consistently found a lower prevalence of *H. pylori* infection among patients with GERD, especially CagA-positive strains. A systematic review including 20 studies and 4134 patients found a lower prevalence of *H. pylori* in GERD subjects compared to controls (OR 0.60, 95 % confidence interval, 0.47–0.78) (Raghunath 2003). This disparity was most profound in Asian populations where subjects with GERD had an even lower prevalence of *H. pylori* compared to their Western counterparts, despite their higher background prevalence. Data from 1611 African American patients with endoscopic evidence of esophagitis found that the prevalence of *H. pylori* was 4 %. After adjusting for age and gender, the odds ratio of *H. pylori* infection in erosive esophagitis was 0.06 (95 % confidence interval, 0.01–0.59; $p = 0.01$) (Ashktorab et al. 2012).

An association between *H. pylori* eradication and the subsequent development GERD remains unsubstantiated (Table 15.3). A meta-analysis of ten randomized controlled trials, comparing patients who received either *H. pylori* eradication or placebo, found no significant difference in the incidence of reflux symptoms (17 % vs. 23 %) or erosive esophagitis (5 % vs. 5.1 %) following treatment. In fact, a sub-analysis found a significantly lower incidence of reflux symptoms in the eradicated versus the placebo group (14 % vs. 25 %) (Saad et al. 2012). These findings are consistent with current recommendation not to refrain from treating helicobacter in patients with GERD (Malfertheiner et al. 2012).

Table 15.3 Randomized controlled trials comparing *Helicobacter pylori* treatment with no treatment in symptomatic adults with gastroesophageal reflux disease (GERD)

Author	Year	Country	Number of patients	GERD symptoms following *H. pylori* eradication, n (%)	
				Treatment group	Placebo
Befrits et al.	2000	Sweden	145	22/79 (27.8)	29/66 (43.9)
Bytzer et al.	2000	Denmark	276	7/83 (8.4)	5/85 (5.9)
Hamada et al.	2000	Japan	572	36/286 (12.6)	1/286 (0.3)
Vakil et al.	2000	The USA	242	41/178 (23.0)	12/64 (18.8)
Kim et al.	2001	Korea	452	26/233 (11.2)	8/144 (5.6)
Moayyedi et al.	2001	The UK	178	15/85 (17.6)	15/93 (16.1)
Schwizer et al.	2001	Switzerland	29	7/13 (53.8)	15/16 (93.8)
Laine et al.	2002	The USA	1165	33/361 (9.1)	27/172 (15.7)
Malfertheiner et al.	2002	Germany	1362	121/993 (12.2)	88/369 (23.8)
Harvey et al.	2004	The UK	1558	169/787 (21.5)	170/771 (22.0)
Kuipers et al.	2004	The Netherlands	231	30/111 (27.0)	27/120 (22.5)
Wu et al.	2004	Hong Kong	104	15/53 (28.3)	8/51 (15.7)
Ott et al.	2005	Brazil	157	8/73 (11.0)	7/60 (11.7)
Pilotto et al.	2006	Italy	61	6/31 (19.4)	6/30 (20.0)
Jonaitis et al.	2010	Lithuania	181	17/119 (14.3)	2/31 (6.4)
Nam et al.	2010	Korea	10,102	25/548 (4.6)	22/1635 (1.3)
Rodrigues et al.	2012	Brazil	32	7/9 (77.8)	12/13 (92.3)

15.3.3 Proton Pump Inhibitors

Patients with chronic *H. pylori* infection typically exhibit low basal and stimulated acid output compared to noninfected subjects (Fig. 15.1). Holtmann and coworkers demonstrated that patients with *H. pylori* infection have accelerated healing of erosive esophagitis when treated with PPIs, compared to uninfected patients. After 4 weeks of treatment, complete healing of esophageal erosions was seen in 86.6 % of H. *pylori*-positive patients and 76.3 % of *H. pylori*-negative patients, $p < 0.01$ (Holtmann et al. 1999). The mechanism, via which *H. pylori* augments healing of esophagitis in the presence of PPI, has not been explored. There is currently no evidence that lower PPI doses are required in *H. pylori*-infected GERD patients in order to induce or maintain remission of erosive esophageal disease (Schenk et al. 1999).

Long-term acid suppression with proton pump inhibition, commonly prescribed for GERD, causes the progressive loss of parietal glands. Patients with *H. pylori* infection who are treated with PPIs may develop a corpus predominant atrophic gastritis. This pattern of inflammation is distinct from the pangastritis typically seen in infected patients who are not receiving PPIs (Moayyedi et al. 2000b; Kuipers et al. 1996). In *H. pylori*-infected animal models, PPIs have been shown to

accelerate the progression of gastric cancer, although data in humans are lacking. The Maastricht IV/Florence Consensus Report recommends eradication of *H. pylori* in patients receiving chronic PPIs in order to heal gastritis and prevent atrophic changes (Malfertheiner et al. 2012).

15.3.4 Complications of GERD

15.3.4.1 Barrett's Esophagus

Barrett's esophagus is a premalignant lesion of the distal esophagus, related to chronic acid exposure. Histologically, Barrett's esophagus is characterized by metaplastic columnar epithelium which replaces the stratified squamous epithelium which normally lines the distal esophagus. Seven studies including 1621 patients with Barrett's esophagus found a significantly lower prevalence of *H. pylori* (49.1 %) compared to matched controls (57.7 %). The pooled odds ratio for *H. pylori* infection in Barrett's esophagus was 0.64 (95 % CI, 0.43–0.94; $p = 0.03$) (Rokkas et al. 2007). A negative correlation between *H. pylori* infection and Barrett's esophagus is similarly observed for CagA-positive strains (35.6 % vs. 51.5 %; OR, 0.39; 95 % CI, 0.21–0.76; $p < 0.01$). Nevertheless, there is no evidence to support withholding eradication of *H. pylori* in patients with Barrett's esophagus.

15.3.4.2 Esophageal Adenocarcinoma

It is tempting to attribute the recent increase in esophageal adenocarcinoma (EAC) in Western countries to the declining prevalence of *H. pylori*. A review of 10 studies, including 737 patients with EAC, found that the prevalence of *H. pylori* in these patients was lower compared to controls (34.3 % vs. 50.1 %; OR, 0.52; 95 % CI, 0.37–0.73; $p < 0.01$) (Rokkas et al. 2007). A negative correlation between *H. pylori* infection and EAC is similarly observed for CagA-positive strains (26 % vs. 40 % CagA positivity in EAC and controls, respectively; OR, 0.51; 95 % CI, 0.31–0.82; $p < 0.01$). There is no evidence to support withholding eradication of *H. pylori* in patients following resection of EAC.

15.4 Functional Dyspepsia

15.4.1 Classification

The Rome III committee defines functional dyspepsia (FD) as "the presence of one or more dyspepsia symptoms that are considered to originate from the

gastroduodenal region, in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms" (Drossman 2006). Dyspeptic symptoms can be broadly characterized into two subgroups: the postprandial distress syndrome or the epigastric pain syndrome. According to the Rome III consensus, *H. pylori* infection does not preclude a diagnosis of FD, despite the fact that *H. pylori* is an undisputed cause of mucosal inflammation. This has prompted a debate whether it is really appropriate that *H. pylori*-associated dyspepsia be considered a functional disease (Sugano 2011). Adding fuel to this debate, emerging endoscopic technologies enable the reliable diagnosis of *H. pylori*-associated chronic gastritis at the time of endoscopy.

15.4.2 Pathophysiology

The precise mechanism via which *H. pylori* may cause postprandial distress or epigastric pain is unknown; however, several pathways have been suggested:

1. Increased acid secretion. Patients with isolated antral *H. pylori* gastritis manifest increased gastric acid secretion. This is probably mediated by a reduction in somatostatin, a negative regulator of gastrin release. *H. pylori*-infected subjects with FD manifest greater acid secretion in response to gastrin-releasing peptide, compared to those without FD (el-Omar et al. 1993).
2. Decreased ghrelin secretion. Ghrelin is a peptide hormone produced by the P/D1 cells of the gastric fundus and is involved in hunger sensation, acid secretion, and motility. Both gastric expression and serum levels of ghrelin are significantly lower in *H. pylori*-positive subjects (Boltin and Niv 2012). Activation of ghrelin receptors leads to increased levels of neuropeptide Y (NPY) and agouti-related peptide which promote appetite. Low levels of ghrelin, as seen in *H. pylori* infection, possibly mediate symptoms of early satiety and postprandial fullness.
3. Altered gastric emptying. Chronic *H. pylori* infection leads to downregulation of muscle-specific miRNA expression. In murine models this causes hyperplasia of the muscularis mucosa leading to reduced gastric accommodation and accelerated gastric emptying (Saito et al. 2011).
4. Mast cells. Increased numbers of antral mast cells have been noted in *H. pylori*-infected subjects with FD. Although this may be involved in the pathogenesis of FD, mast cell proliferation is unlikely to be mediated by *H. pylori*, as an increased number of mast cells is also observed in FD patients without *H. pylori* (Hall et al. 2003).

15.4.3 Epidemiology

About 20–30 % of the population reports persistent dyspepsia each year. Only a minority of these patients is fully investigated; however, an organic cause is not usually identified. Therefore, the remainder can be considered to have FD. The incidence of FD is estimated at 1/100 person-years (Agréus et al. 1995).

15.4.4 Treatment

A recent systematic review identified 21 randomized controlled trials which have examined the efficacy of *H. pylori* eradication for the treatment of FD. Overall, *H. pylori* eradication is associated with a relative risk reduction of 10 %, for dyspeptic symptoms, compared to placebo. The number needed to treat to cure one case of dyspepsia is 14 (Moayyedi et al. 2011). Nevertheless, studies performed in Western populations have inconsistent results, with eradication having a variable impact on dyspeptic symptoms (Table 15.4) (Mazzoleni et al. 2011; Talley et al. 1999; Hsu et al. 2001). Eradication may, however, be beneficial in preventing the subsequent development of PUD in patients with epigastric pain. Studies in Asian populations are more likely to show a benefit for H. *pylori* treatment in FD (Gwee et al. 2009; Des Bruley Varannes et al. 2001; Lan et al. 2011). The cost-effectiveness of eradication in FD depends upon the background prevalence of H. *pylori*, the cost of treatment, as well as other factors. Therefore, although eradication may be cost-effective in Asia and Europe, this is not necessarily true in the USA (Moayyedi et al. 2000a).

15.5 Other Gastrointestinal Disease

15.5.1 Inflammatory Bowel Disease

Patients with Crohn's disease (CD) have a disproportionately low prevalence of *H. pylori* (Luther et al. 2010). The estimated relative risk of *H. pylori* infection in CD is 0.64 (95 % CI, 0.54–0.75). Over the past few decades, the declining rates of H. *pylori* carriage have mirrored the increasing prevalence of inflammatory bowel disease. This cannot be fully explained by socioeconomic or other environmental factors, since a similar relationship is not observed with ulcerative colitis or other chronic diseases which feature immune dysfunction. Subjects with *H. pylori* infection exhibit a blunted T_{h1}/T_{h17} immune response and have low tissue and serum levels of proinflammatory cytokines such as interferon-γ (IFN-γ) (Fig. 15.3) (Luther et al. 2011). On the other hand, patients with CD have an exaggerated T_{h1}/T_{h17} immune response. The factors involved in defining the nature of an

Table 15.4 Randomized controlled trials comparing *Helicobacter pylori* treatment with no treatment in adults with functional dyspepsia

Author	Year	Country	Number of patients	Duration of follow-up	Outcome measure	Results		
						Treatment group n (%)	Control n (%)	*p*
Talley et al.	1999	Australasia and Europe	278	12 months	Near-total relief of epigastric pain	32/133 (24)	31/142 (22)	ns
Hsu et al.	2001	Taiwan	161	12 months	Symptom resolution	47/81 (58.0)	44/80 (55.0)	ns
Des Bruley Varannes et al.	2001	France	253	12 months	Symptom resolution	55/129 (43)	38/124 (31)	0.048
Gwee et al.	2009	Singapore	82	12 months	Symptom resolution	10/41 (24.4)	3/41 (7.3)	0.02
Lan et al.	2011	China	195	3 months	Reduction rate (pretreatment–posttreatment scores)/pretreatment score × 100	36/98 (36.7)	19/97 (19.6)	<0.05
Mazzoleni et al.	2011	Brazil	404	12 months	50 % symptom reduction	94/192 (49.0)	72/197 (36.5)	0.01

This table includes principal studies performed and is not intended to be exhaustive

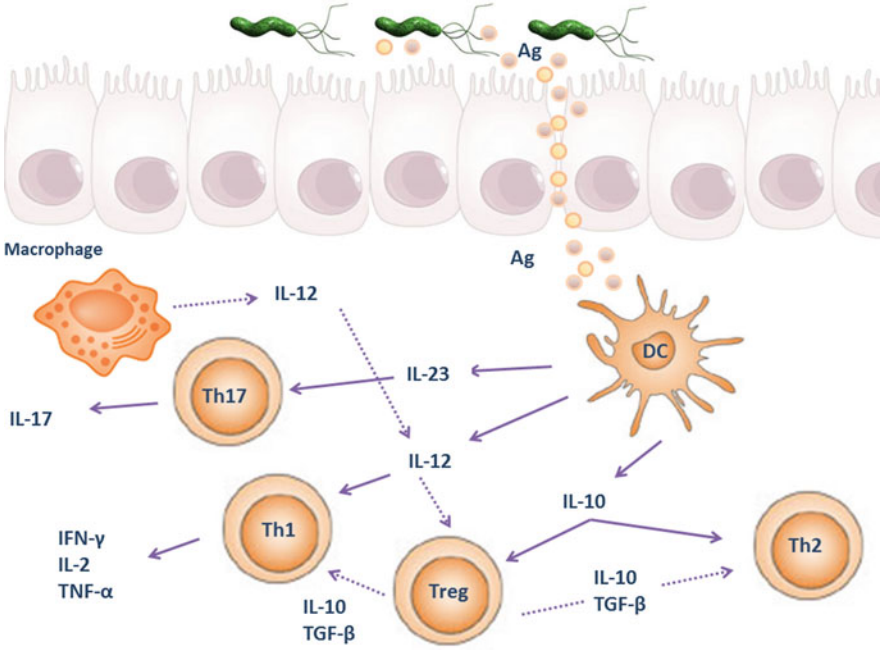

Fig. 15.3 A proposed model of *H. pylori*'s effect on host immune regulation. Dendritic cells (DCs) sample *H. pylori* antigens directly. DCs, in turn, secrete cytokines such as IL-10 to upregulate Foxp3-positive regulatory T cells (Tregs). This upregulation skews the host immunologic tone away from the IL-12 and IL-23-mediated inflammatory Th1/Th17 responses and leads to decreased production of proinflammatory cytokines. This may theoretically confer protection from the development of CD

individual's T_{h1}/T_{h17} immune response remain elusive. An individual's particular immune response might be modified by H. *pylori* at the time of infection, or it might be an inherited trait which predisposes to either to chronic gastritis (following exposure to *H. pylori*) or to future CD, at the two ends of the spectrum. Animal models suggest the former – mice colonized with *H. pylori* are protected from developing dextran sodium sulfate (DSS) – colitis, indicating that *H. pylori* modulates immune function. As more data becomes available on the immunoregulatory function of *H. pylori*, we may find additional evidence to advocate postponing eradication of *H. pylori* in children, with the added benefit of decreasing the incidence of CD.

15.5.2 Halitosis

In the vast majority of cases (>90 %), halitosis is attributable to oral or nasopharyngeal pathology. A connection between halitosis and either upper gastrointestinal

symptoms or endoscopic findings has not been conclusively proven (Tas et al. 2011). Nevertheless, a theoretical basis exists, as well as abundant empirical data, linking *H. pylori* to halitosis. Following Marshall's historic ingestion of *H. pylori* in his quest to prove Koch's postulate, oral malodor was noted by his colleagues (Marshall et al. 1985). Volatile sulfur compounds including hydrogen sulfide (H_2S) and methyl mercaptan (CH_3SH), which are produced by certain strains of *H. pylori*, are also the major components of oral malodor (Lee et al. 2006). Katsinelos et al. reported that *H. pylori* eradication in FD led to a sustained resolution of halitosis during long-term follow-up (Katsinelos et al. 2007). Nevertheless, in the absence of robust data, *H. pylori* cannot be considered a treatable cause of halitosis.

15.6 Non-gastrointestinal Disease

15.6.1 Asthma and Allergy

As described previously with respect to CD, *H. pylori* has the ability to influence the maturation and direction of host immune pathways. *H. pylori* infection can induce dendritic cells to generate regulatory T cells (Tregs) which subsequently protect against asthma (Fig. 15.3) (Oertli and Müller 2012). The *H. pylori* virulence factor, neutrophil-activating protein A (NapA), might protect against asthma by inhibiting polarization of T helper (T_h)-1 and inhibiting the allergic T_{h2} response. NapA and Tregs are under investigation as novel asthma treatments. A meta-analysis of case–control and cross-sectional studies by Zhou and coworkers, including over 28,000 subjects across three continents, found a slightly lower rate of *H. pylori* infection in subjects with asthma (OR, 0.84; 95 % CI, 0.73–0.96; $p = 0.01$) (Zhou et al. 2013). Subgroup analysis, however, found that a significant difference in *H. pylori* prevalence between asthmatic and non-asthmatic subjects exists only in the USA and not in Europe or Asia. Wang and coworkers published a similar meta-analysis but also included cohort studies (Wang et al. 2013). Pooled data from all studies revealed a significant inverse association between *H. pylori* infection and asthma for both adults (OR, 0.88; 95 % CI, 0.71–1.08; $p < 0.05$) and children (OR, 0.81; 95 % CI, 0.72–0.91; $p < 0.05$). In both meta-analyses, CagA-positive *H. pylori* strains seem to be even more protective against asthma than CagA-negative strains. For more details we refer to Chap. 12.

15.6.2 Idiopathic Thrombocytopenic Purpura

The mechanism through which *H. pylori* causes idiopathic thrombocytopenic purpura (ITP) probably involves cross mimicry between *H. pylori* and platelet

antigens. This may be specifically related to CagA strains of *H. Pylori*. It has been demonstrated that platelet-associated IgG in ITP patients recognizes the CagA antigen (Franchini and Veneri 2006). Another mechanism could involve the interaction between *H. pylori* and platelets through von Willebrand factor and IgG anti-*H. pylori* antibody, leading to chronic platelet consumption. In a review of 16 studies involving 1126 subjects with ITP, *H. pylori* prevalence was 64 %. Following successful eradication, a platelet response was seen in 53 %. However, the studies included were heterogeneous and included mainly uncontrolled and anecdotal data (Franchini and Veneri 2006). The Maastricht IV/Florence Consensus Report advocates seeking and treating *H. pylori* in the setting of ITP (Malfertheiner et al. 2012).

15.6.3 Iron Deficiency Anemia

Possible pathogenic mechanisms for *H. pylori* causing iron deficiency anemia include: occult blood loss secondary to erosive gastritis, decreased iron absorption secondary to *H. pylori*-induced hypochlorhydria, and increased iron uptake and utilization by *H. pylori* (Dubois and Kearney 2005). Although epidemiologic studies support an association between *H. pylori* infection and low ferritin, only a few small, uncontrolled case series and one small, randomized trial have shown improvement in anemia following *H. pylori* treatment (Choe et al. 1999). The available evidence suggests that *H. pylori* is most likely to be associated with anemia in patients who are anyway predisposed to iron deficiency, such as premenopausal women and children.

15.6.4 Others

H. pylori has been epidemiologically linked to a wide range of diseases including Alzheimer's disease, Parkinson's disease, Raynaud's phenomenon, scleroderma, idiopathic urticaria, acne rosacea, migraines, thyroiditis, Guillain–Barré syndrome, and coronary artery disease. The proposed mechanisms leading to these various conditions range from systemic immune reactions, cross-reactivity of bacterial and host proteins, and events secondary to gastric mucosal injury (Goodman et al. 2006). Of these associations, the strongest link is for ischemic heart disease. Specifically, CagA seropositivity has been significantly associated with acute coronary events (OR, 1.34; 95 % CI, 1.15–1.58; $p < 0.01$) (Franceschi et al. 2009). Nevertheless, the available evidence is still insufficient to make a clear causal or therapeutic link.

15.7 Conclusions and Outlook

There is a wealth of information regarding the epidemiology and pathophysiology of *H. pylori* in the setting of nonmalignant diseases. The future direction of study in the area of peptic ulcer disease is likely to involve emerging molecular technologies such as micro-RNAs. Such research may focus on RNA silencing and posttranslational regulation of the genes for proteins which mediate *H. pylori* virulence, evasion of gastric mucosal defense apparatus, and subsequent ulcer formation. Further study will also investigate the complex interaction between *H. pylori* and the host immune system. This may lead to the recognition of a host "immunophenotype" which predisposes to the development of peptic ulcer disease in the presence of *H. pylori* or asthma or Crohn's disease in its absence. Study of *H. pylori* virulence factors will continue, including their role in peptic ulcer formation. For example, the structure of the *H. pylori* proton-gated urea channel was recently described. Future research into this channel might investigate gene polymorphisms which affect function, interaction with host immunity, and even therapeutic targeting of the channel. Another rapidly developing field of research relates to the effect of *H. pylori* infection on the composition of the gastric microbiome and intestinal microbiome as a whole. The functional role of the gastric microbiome is entirely unclear, as is the effect of *H. pylori*-associated gastritis on the composition of the intestinal microbiome. A better understanding of the interaction between *H. pylori* and the intestinal microbiome may be particularly relevant in the setting of functional dyspepsia. In the area of GERD, future study may be directed at identifying patients with a high risk of esophageal adenocarcinoma, in whom *H. pylori* eradication might be withheld. Undeniably, *H. pylori* is relevant to all of the highly prevalent nonmalignant diseases discussed. For this reason, *H. pylori* in nonmalignant disease will continue to be the subject of research for many years to come.

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