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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Beyond the stomach: An updated view of *Helicobacter pylori* pathogenesis, diagnosis, and treatment

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Abstract

Helicobacter pylori (*H. pylori*) is an extremely common, yet underappreciated, pathogen that is able to alter host physiology and subvert the host immune response, allowing it to persist for the life of the host. *H. pylori* is the primary cause of peptic ulcers and gastric cancer. In the United States, the annual cost associated with peptic ulcer disease is estimated to be $6 billion and gastric cancer kills over 700000 people per year globally. The prevalence of *H. pylori* infection remains high (> 50%) in much of the world, although the infection rates are dropping in some developed nations. The drop in *H. pylori* prevalence could be a double-edged sword, reducing the incidence of gastric diseases while increasing the risk of allergies and esophageal diseases. The list of diseases potentially caused by *H. pylori* continues to grow; however, mechanistic explanations of how *H. pylori* could contribute to extragastric diseases lag far behind clinical studies. A number of host factors and *H. pylori* virulence factors act in concert to determine which individuals are at the highest risk of disease. These include bacterial cytotoxins and polymorphisms in host genes responsible for directing the immune response. This review discusses the latest advances in *H. pylori* pathogenesis, diagnosis, and treatment. Up-to-date information on correlations between *H. pylori* and extragastric diseases is also provided.

Key words: Enterohepatic; Pathogenesis; Diagnosis; Treatment; Extragastric; CagA; Cancer; Autoimmune; Inflammation; Virulence factor

Core tip: *Helicobacter pylori* (*H. pylori*) infection remains a common cause of morbidity and mortality. Evidence for additional *H. pylori*-mediated diseases, as well as potentially beneficial effects of *H. pylori* infection, complicates decisions regarding when testing for and treating of *H. pylori* infections is appropriate. In the meantime, eradication of *H. pylori* is becoming more difficult due to increasing antibiotic resistance. This review summarizes recent findings on *H. pylori* pathogenesis, testing, and treatment.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) has infected humans for more than 58000 years[1], yet it largely escaped notice until it was cultured by Marshall and Warren[2]. Research on *H. pylori* changed paradigms regarding disease causation. Physicians previously attributed ulcers to stress or anxiety and did not believe that bacteria could cause cancer.

H. pylori was the first bacterial species proven to cause cancer and is classified as a group I carcinogen by the International Agency for Research on Cancer. This is the same category as smoking, radiation, and asbestos. Many patients with *H. pylori*-associated MALT lymphoma can be cured by antibiotic treatment without the need for surgery or chemotherapy.

H. pylori-associated gastric cancer comprises about 5.5% of all cancers globally and accounts for 25% of all infection-associated cancers[3]. If *H. pylori* increases the risk of developing other diseases, the cost of *H. pylori*-associated morbidity could be much higher. An effective *H. pylori* vaccine is not yet on the horizon, so eradication must be accomplished using antibiotics. As with many other organisms, *H. pylori* antibiotic resistance is increasing[4,5].

Researchers continue to discover new associations between *H. pylori* and idiopathic diseases, as well as potential benefits of *H. pylori* infection. The systemic effects of gastric colonization can lead to extragastric pathology; however new sites of *H. pylori* colonization have also been identified. More research is needed to clarify which extragastric diseases are caused by *H. pylori* and whether the bacteria must be present at the disease site.

MAJOR VIRULENCE FACTORS AND PATHOGENESIS MECHANISMS

General properties of H. pylori

Unlike most bacterial pathogens, *H. pylori* typically colonizes the host for life unless specific treatment is given. *H. pylori* has co-evolved with humans for approximately 58000 years, and strain types that predominate within certain regions of the world correlate with human migration patterns[1,6]. Most infected individuals do not develop overt disease, leading to the hypothesis that some *H. pylori* strains are harmless or even beneficial[7]; however, the list of diseases potentially caused or worsened by *H. pylori* has been growing in recent years, making it premature to conclude that any strain is commensal.

Several unique properties contribute to *H. pylori* persistence. All *H. pylori* clinical isolates express urease. Urease converts urea to ammonia plus carbon dioxide, raising the pH of the surrounding area. This provides temporary protection against gastric acid, but *H. pylori* is not an acidophile. It requires the near-neutral pH found in the mucus layer directly adjacent to the gastric surface epithelium. The helical shape of *H. pylori* makes it easier for its polar flagella to propel *H. pylori* through viscous mucus. Chemotaxis systems direct *H. pylori* towards some amino acids, bicarbonate, and cholesterol, while acidic pH serves as a repellent[8]. This system keeps the organisms in the favorable milieu close to the surface epithelium.

The outer surface of *H. pylori* also has unique properties. *H. pylori* glycosylates host cholesterol and inserts it into its outer membrane. The function of glycosylated cholesterol is not entirely known, but *H. pylori* lacking cholesterol are extremely sensitive to environmental stress[9,10]. Lack of glucosylated cholesterol reduces CagA-mediated activities and interactions with T calls[10,11]. Another interesting membrane feature is the relatively non-toxic lipopolysaccharide (LPS) found in *H. pylori*, which may contribute to persistence by limiting the host inflammatory response. Unlike LPS from other species, *H. pylori* LPS is recognized by TLR-2 rather than TLR-4[12]. In some strains, side chains on the LPS O antigen mimic the Lewis blood group antigens Le^x and Le^y. The membrane extends to form a sheath covering the flagella. The combination of sheathed flagella, hypoinflammatory LPS, and molecular mimicry reduce the host response, allowing the organism to persist with minimal pathology. Furthermore, *H. pylori* forms outer membrane blebs that pinch off from the surface of the bacterium. These outer membrane vesicles contain both membrane-associated and cytoplasmic components, including CagA and other virulence factors[13]. In addition to being an alternative virulence factor-delivery mechanism, outer membrane vesicles may serve as "dummy targets" for the immune system, thus facilitating immune evasion.

CagA

H. pylori has a number of virulence factors which influence colonization and disease severity (Figure 1). CagA, encoded by cytotoxin-associated gene A (*cagA*) is the most important and best-studied virulence factor; however, it does not function in isolation. CagA-positive *H. pylori* strains are associated with greater inflammation and increased risk of ulcers and cancer in both humans and animals[14]. The *cagA* gene is part of a pathogenicity island that also encodes components of a type Ⅳ secretion apparatus. The secretion apparatus is a syringe-like structure that was once thought to have little importance other than its ability to inject CagA; however, recent studies suggest CagA-independent functions. For example, the structural protein CagL mimics fibronectin[15] and peptidoglycan is injected into host cells along with CagA[16]. Finally, it is important to note that the presence of *cagA* usually coincides with the presence of other virulence factors, including *vacA*, *babA* and *oipA*[17]. Thus, *H. pylori* pathogenesis is multifactorial and cannot be boiled down to one gene.

CagA is responsible for myriad signaling alterations, which profoundly influence host cell physiology. When *H. pylori* makes contact with host cells, CagA is directly injected into the host cell cytoplasm where it becomes phosphorylated and binds the SH2 domain of host SHP-2[18]. SHP-2 is a phosphatase involved in transduction of signaling from receptor tyrosine kinases[19]. Mutations in SHP-2 are found in some human tumors, providing a mechanistic link between CagA activity and tumor development. CagA also interacts with other proteins involved in signal transduction, such as c-Met[19]. CagA colocalizes with tight junction proteins, causing decreased cell-cell adhesion and loss of cell polarity (Figure 2)[20]. This, along with cytoskeletal rearrangements, contributes to increased invasiveness of host cells through the

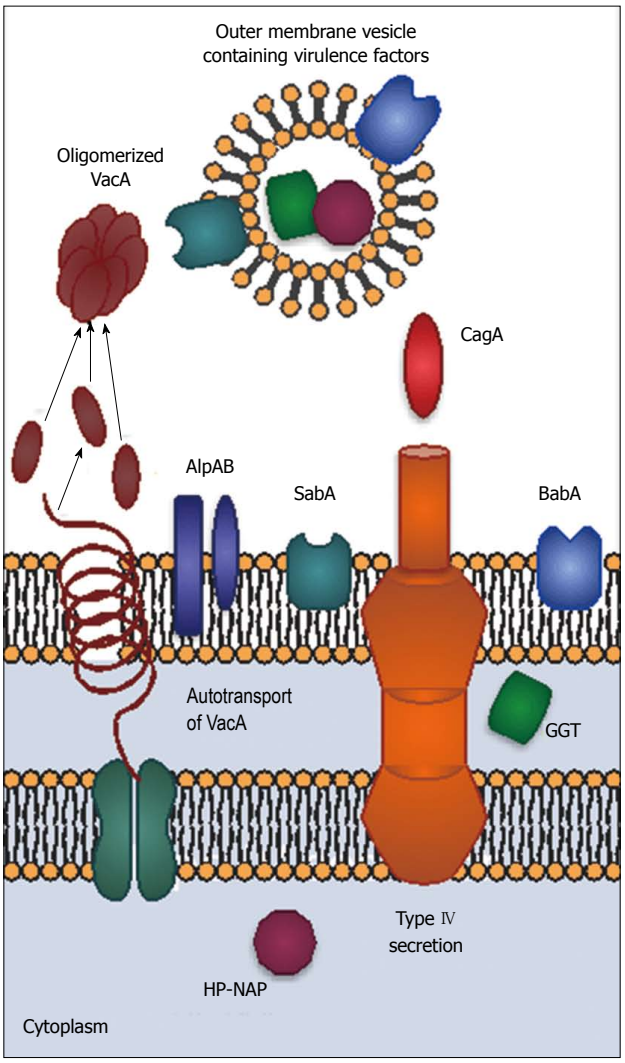

Figure 1 Major virulence factors of *Helicobacter pylori*. Type Ⅳ secretion system-mediated transport of CagA and autotransport of VacA monomers are depicted. Outer membrane vesicles can contain membrane-associated and soluble virulence factors. Representative outer membrane adhesins are shown. GGT: γ-Glutamyl transpeptidase.

extracellular matrix. CagA also drives the transition from an epithelial to a mesenchymal cell phenotype[12]. All of these phenotypes are associated with carcinogenesis[21]. CagA positive strains are often associated with increased IL-8 production; however *H. pylori* induces IL-8 secretion through multiple mechanisms, some of which are CagA-independent[22]. CagA induces genes encoding defensin 2 and other antimicrobial peptides, which could explain why CagA positive strains appear to be easier to eradicate than CagA negative strains[23]. Dendritic cells intoxicated by CagA display impaired activation, leading to decreased inflammatory cytokine production and decreased stimulation of a Th-1 response[24].

Not all CagA proteins are created equal; some *cagA* alleles encode additional SH2 binding sites, further suppressing the function of SHP-2[18]. A five amino acid motif (EPIYA motif) in the carboxy-terminal portion of CagA is the phosphorylation site, and clinical isolates differ in the number of EPIYA motifs present[25]. EPIYA motifs are of particular interest because certain EPIYA polymorphisms are more strongly associated with cancer than others[26]. CagA lacking the EPIYA motif is not phosphorylated and activates the STAT3 pathway instead of the MAPK/ERK pathway, which is induced by SHP-2 binding[27]. STAT3 activation leads to increased cell migration, while MAPK/ERK activation leads to cell growth inhibition and morphological changes.Oddly, CagA reduces the cellular effects of VacA and *vice versa*. CagA reduces vacuolization and apoptosis caused by VacA and VacA reduces the cytoskeletal rearrangements caused by CagA[28]. These findings once again highlight the influence of *H. pylori*'s genetic variability and interactions between virulence factors on pathogenesis.

VacA

Vacuolating toxin A (VacA) was named for its ability to induce numerous large vacuoles in host cells. Unlike CagA, VacA forms an autotransporter structure to secrete itself without the need for host cell contact. VacA proteins oligomerize to form pore-like structures. VacA binds to receptor-like protein tyrosine phosphatases (RPTPα and RPTPβ) and other glycosylated transmembrane proteins on the host cell surface[29]. VacA is then endocytosed and forms anion-selective channels in vacuole membranes. The channels allow accumulation of chloride anions and weak bases, resulting in osmotic swelling[30]. VacA also inserts into mitochondrial membranes, causing mitochondrial dysfunction and subsequent apoptotic death of the cell[31]. Vacuolation is not the only effect of VacA intoxication. VacA disrupts the barrier function of epithelial cells, allowing leakage of crucial nutrients such as iron, nickel, and amino acids. This likely improves *H. pylori* growth[32]. *In vitro*, VacA inhibits antigen presentation and T cell activation, but it is not clear whether these activities occur *in vivo*[21].

All *H. pylori* strains contain *vacA* genes, but not all strains produce functional VacA. This is due to polymorphisms within the VacA gene, particularly at the amino terminus (s region), in the middle of the gene (m region), and in an intermediate region (i region). The s2 polymorphism yields an inactive toxin[28]. Thus, strains with the s2 allele are often termed "VacA negative". The i region polymorphisms were discovered more recently and influence vacuolating activity; *vacA* containing the i1 allele produces the most active toxin[33]. Strains harboring the s1m1 allele have been more commonly associated with ulcers and gastric cancer, but it now appears that the i1 allele is more strongly associated with ulcers and cancer than the presence of the s1m1 genotype[28]. In spite of the dramatic effects of VacA on epithelial cells, it is unclear whether VacA plays a causative role in these diseases. More likely, VacA facilitates nutrient acquisition, improving the ability of *H. pylori* to colonize the gastric epithelium[34].

BabA and SabA

H. pylori encodes two variably expressed sialic acid-binding adhesins, BabA and SabA. BabA, encoded by *babA2*,

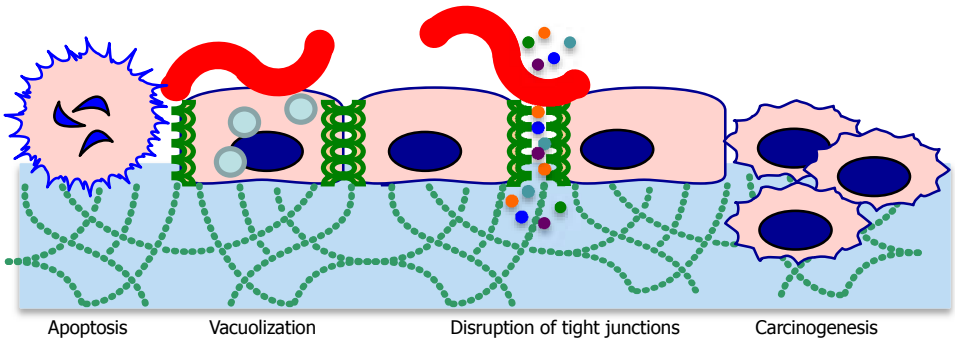

Figure 2 Effects of *Helicobacter pylori* on host cells. *Helicobacter pylori* virulence factors can lead to apoptosis, vacuolization, disruption of barrier function (leading to nutrient leakage), de-differentiation, and carcinogenesis.

binds to the Lewis b ABO blood group antigen (Le^b) and is present on red blood cells and certain epithelial cells. Expression of *babA2* is variable, and can be turned "on" and "off" by slipped-strand mispairing mutations. BabA binding activity is most often present in CagA positive strains[34]. BabA-mediated binding to Le^b contributes to formation of double stranded DNA breaks in host cell lines and may promote cancer-associated gene mutations[35]. Adherence *via* BabA also enhances the ability of the type Ⅳ secretion apparatus to contact host cells, leading to a stronger inflammatory response[36]. These data suggest that BabA may indirectly influence pathology by improving adherence to host cells.

SabA is a sialic acid-binding adhesin that recognizes the sialyl-Lewis A antigens sLe^x and sLe^a[37,38]. SabA increases colonization density in patients lacking Leb, indicating its importance as an adhesin. Sialylated Lewis antigens are more prevalent on inflamed or cancerous gastric tissue, leading to the hypothesis that SabA is involved in carcinogenesis; however, not all studies demonstrate correlations between the presence of SabA and cancer[39].

Other outer membrane proteins

H. pylori has about 30 other outer membrane proteins which may serve as adhesins, but only a few have known functions. AlpA and AlpB are now known to bind host laminin. Their presence modulates the inflammatory response in gerbils through unknown mechanisms[40]. It is not known whether variability in *alpAB* gene sequence or expression influence human disease. OipA (Outer Inflammatory Protein; a.k.a HopH) is an outer membrane protein that functions as an adhesin[41]. The gene can be turned on and off *via* slipped strand mispairing. Interestingly, most *cagA* positive strains possess an expressed form of *oipA*, making it more difficult to separate the clinical effects of *oipA* from those of *cagA*[17]. *In vitro* and *in vivo* animal experiments clearly show that OipA is associated with increased IL-8 production and carcinogenicity[42]. Inactivating *oipA* in a carcinogenic *H. pylori* strain eliminated tumorigenesis in gerbils[43]. This may be partially explained by the decreased nuclear translocation of beta-catenin induced by mutant strains lacking OipA. Beta-catenin is an important player in the gastric carcinogenesis process[44].

HP-NAP

The neutrophil-activating protein (HP-NAP), encoded by *napA*, was first isolated from water extracts of *H. pylori*[45]. Although it is cytoplasmic, HP-NAP escapes *via* autolysis. Amino acid sequencing led to the *napA* gene, which is homologous to other bacterioferritins. Bacterioferritins are similar to mammalian ferritins in that they form multimeric, hollow structures that store iron and bind DNA. These proteins protect prevent iron-mediated chemical reactions from forming reactive oxygen species[46]. Further studies revealed that HP-NAP does not behave like other bacterioferritins. HP-NAP crosses both the epithelium and the endothelium, where it recruits neutrophils and stimulates both neutrophils and monocytes to produce IL-12 and IL-23[47,48]. These cytokines induce T cells to secrete interferon-γ and mediates the shift to a Th1 response[48]. HP-NAP binds to TLR-2, which typically recognizes bacterial cell wall components. Unlike other TLR-2 agonists, HP-NAP induces substantial IL-12 production[48]. HP-NAP also promotes clot formation and inhibits fibrin degradation by monocytes[49].

HP-NAP has been suggested as a tumor-fighting agent and an allergy modulator. Intratumoral injection of HP-NAP into mouse neuroendocrine or bladder tumors led to tumor regression and a shift towards cytotoxic T cells[50,51]. Since allergies are associated with a Th2-skewed immune response, inducing a shift towards a Th1 response could be beneficial[52]. Proof-of-principle has been demonstrated in a mouse model of ovalbumin-induced asthma. Injection of HP-NAP reduced eosinophilia and IgE concentrations in sensitized animals[53]. Enthusiasm for HP-NAP-based treatments is tempered by concerns regarding the potential for autoimmune reactions induced by homology between HP-NAP and human aquaporin in neural tissues[54].

Gamma-glutamyl transpeptidase

The discovery that *H. pylori* gamma-glutamyl transpeptidase (GGT) functions as a virulence factor was surprising, since it hadn't been identified as a virulence factor in other bacteria[55]. Moreover, it appears to be periplasmic rather than surface-associated or secreted. Its presence in outer membrane vesicles[13] could facilitate interactions

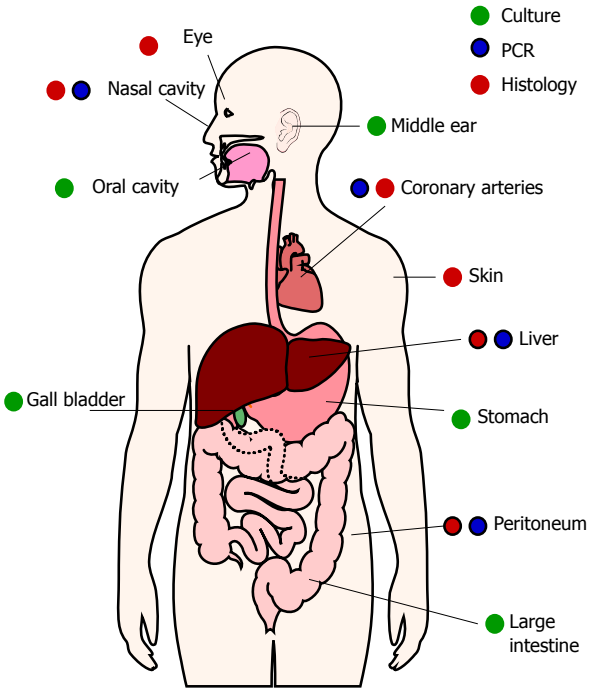

Figure 3 Detection of *Helicobacter pylori*. Evidence of *Helicobacter pylori* (*H. pylori*) has been found in numerous sites throughout the body. Colored dots indicate the method of detection used. In cases where *H. pylori* has been directly cultured, other detection methods are not listed.

with host cells. GGT increases IL-8 secretion and hydrogen peroxide production in epithelial cells and is associated with peptic ulcer development[56]. It also contributes to colonization, persistence, and tolerization of dendritic cells[57]. GGT-mediated degradation of glutathione produces pro-oxidant compounds that facilitate formation of reactive oxygen species. This mechanism could be responsible for host tissue damage[58].

In addition to *H. pylori* variability, several host factors also influence disease outcome. IL-1β is induced rapidly following infection. Polymorphisms in genes encoding IL-1β or its receptor antagonist increase the risk of gastric cancer in many populations; however this may not hold true for some Asian and white populations[21]. Polymorphisms in genes encoding TNFα, IL-10, and HLA are also implicated[21]. Reduced IL-10 expression results in a more inflammatory Th1-polarized host response. Smoking and a diet high in salty foods exacerbate the effects of *H. pylori*. All of these things could explain why some studies show clear correlations between *H. pylori* and a particular disease, while others do not.

H. PYLORI COLONIZES MULTIPLE SITES WITHIN THE BODY

H. pylori primarily colonizes the stomach, but evidence suggests occasional or persistent colonization of other sites (Figure 3). Growth properties of *H. pylori* hamper detection of low-density colonization. Relatively slow growth and complex growth requirements have been barriers to identifying *H. pylori* colonization. *H. pylori* will not grow in many commonly-used solid or liquid media. *H. pylori* grows best with 1%-5% serum, but higher serum concentrations can be inhibitory[59,60]. *H. pylori* is also microaerophilic and is killed by atmospheric oxygen. Exposure of samples to ambient oxygen, as well as complement and phagocytic cells from blood, will kill some of the bacteria before they can be cultured. Even under ideal conditions, *H. pylori* requires about 5 d to form visible colonies on solid media. By that time, any other bacteria or fungi present in the sample can overtake the culture.

Culture remains the gold standard for establishing the presence of viable *H. pylori*, but molecular methods have proven more sensitive in identifying alternative colonization sites. PCR is a sensitive method for detecting *H. pylori* in many locations, but does not prove whether the bacteria are alive or dead. *In situ* hybridization using probes that only bind mRNA can demonstrate viability. This method has been used to detect live *H. pylori* in the peritoneal cavities of pseudomyxoma peritonei cancer patients[61].

H. pylori DNA has been amplified from atherosclerotic plaques and the oral cavity for years, but the significance of *H. pylori* in these locations is still debated[62]. Many have reasonably questioned whether *H. pylori* truly colonizes those sites. For example, macrophages might have phagocytized *H. pylori* in the stomach and later traveled to atherosclerotic plaques. Similarly, oral *H. pylori* might be due to gastric reflux. Additional testing has been performed in laboratories worldwide, using a variety of techniques. *H. pylori* has been cultured from root canal samples, and occasionally from plaque[63,64], but is most often identified by PCR. The presence of *H. pylori* in the oral cavity correlates with its presence in the stomach[65-67], but oral *H. pylori* does not correlate with poor oral hygiene[68,69]. On the other hand, several studies suggest that untreated periodontal disease increases the risk of becoming re-infected after *H. pylori* eradication[70]. Similarly, reducing the number of oral *H. pylori* using antiseptic mouthwash and/or periodontal treatment improves the eradication rate following antibiotic therapy[71]. It is therefore possible that *H. pylori* gains a toehold in the mouth before colonizing the stomach and that the stomach can be reinfected by oral *H. pylori*.

Evidence of *H. pylori* colonization has also been found in the gallbladder, ears, nose, skin, and even eyes[72-75]. Aside from the gallbladder, *H. pylori* has only been found in the above locations when inflammatory or hyperproliferative pathology is present. These diseases will be discussed in more detail below.

There is ample evidence of other *Helicobacter species* in the stomach, intestine, and biliary tract. "*H. heilmannii*", which is now known to comprise several species including *H. bizzozeronii* and *H. salmonis*, is occasionally present in the stomach and appears to cause the same diseases as *H. pylori*[76,77]. Other species that infect humans include *H. cinaedi*, *H. pullorum*, *H. canis*, *H. canadensis*, *H. fennelliae*, *H. rappini*, *H. bilis*, *H. hepaticus*, and *H. suis*[72,73]. Most of the aforementioned species are likely acquired from pets and livestock. *H. cinaedi*, and occasionally other species, can

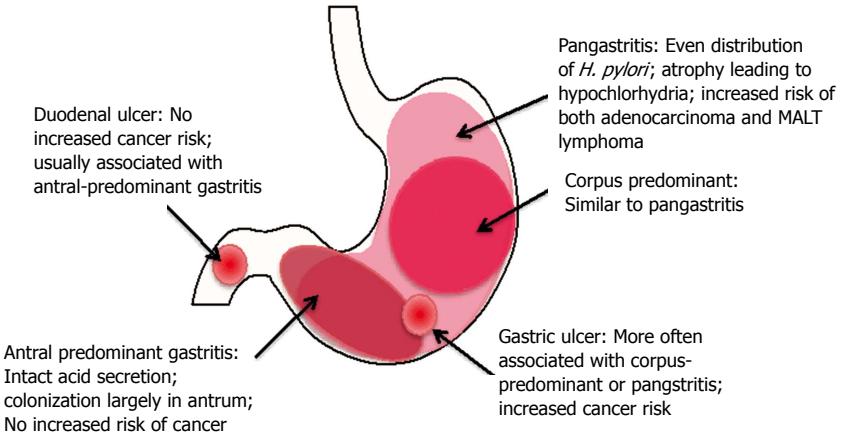

Figure 4 Typical *Helicobacter pylori*-associated pathology. Gastritis may be antral-predominant, corpus-predominant, or diffuse. The risk of developing adenocarcinoma or MALT lymphoma varies depending on the type of pathology present.

cause enterocolitis, cellulitis, and sepsis[77]. Some *Helicobacter* species have been postulated to cause inflammatory bowel disease[78,79], but non-*pylori* species have not been adequately studied and routine tests for those species do not exist.

CLASSIC *H. PYLORI*-ASSOCIATED DISEASES

Dyspepsia

Functional dyspepsia is defined as pain associated with the stomach or upper abdomen. Ulcers are one cause of dyspepsia, but many patients have no evidence of gastric damage. The role of *H. pylori* in non-ulcer dyspepsia has been somewhat controversial. The preponderance of evidence suggests that *H. pylori* infection contributes to some cases of dyspepsia. A randomized clinical trial involving 585 dyspepsia patients found that *H. pylori* eradication led to greater benefit in patients with epigastric pain syndrome than in postprandial distress syndrome[80]. These and other results suggest that the "test and treat" strategy is reasonable for non-ulcer dyspepsia patients[81], particularly those with epigastric pain. Dyspepsia symptoms do not always resolve following eradication therapy, but the risk of future ulcer and gastric cancer development are reduced.

Gastritis

Gastritis is universally present in *H. pylori* infected patients and is reproduced in various animal models. Acute gastritis, sometimes associated with dyspepsia or nausea, develops soon after initial infection. Acute gastritis affects the entire stomach and is accompanied by loss of acid secretion[82,83]. Neutrophils are recruited to the lamina propria and epithelium and damage results from reactive oxygen species and other neutrophil products. The acute phase gives way to chronic gastritis as lymphocytes replace neutrophils.

Chronic gastritis can be antrum-predominant, corpus-predominant, or diffuse (pangastritis or multifocal gastritis) (Figure 4). In antrum-predominant gastritis, acid secretion usually remains intact and *H. pylori* colonization is limited to the antrum[83]. Antral gastritis favors development of duodenal ulcers, while corpus-predominant gastritis favors gastric ulcer formation, sometimes progressing to metaplasia and adenocarcinoma[82,84]. Patients with diffuse gastritis typically have severely impaired acid secretion, which allows *H. pylori* to colonize the corpus. Chronic acid suppression mediated by proton pump inhibitors can lead to a switch from antral predominant to pangastritis[83]. Interestingly antrum-predominant gastritis and duodenal ulcers do not increase the risk of cancer development[85,86].

Historically, *H. pylori* has been responsible for 70%-85% of gastric ulcers and 90%-95% of duodenal ulcers[82,87]. The percentage of ulcers not associated with *H. pylori* is rising due to increased use of NSAIDs and decreasing prevalence of *H. pylori* infection; however *H. pylori* eradication is partially protective against ulcer development in NSAID users[87,88]. Also, the hypothesis that ulcers are caused by stress is reemerging. Several studies show that anxiety disorders and physical or emotional trauma correlate with ulcer development (reviewed in[89]). Studies testing the interaction between *H. pylori* and stress are lacking, so it is not clear whether those factors operate independently or whether there is an additive effect of infection and stress on ulcer formation.

Gastric cancer

H. pylori is an accepted cause of gastric adenocarcinoma and MALT lymphoma (official name: extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue). Gastric adenocarcinoma is divided into intestinal subtype and diffuse subtype. Intestinal type adenocarcinoma is more common and has been well studied. The sequence of pathological changes leading to intestinal type cancer starts with gastritis, followed by gastric atrophy (loss of glandular structure) and progressing to intestinal metaplasia, dysplasia, and finally carcinoma[14]. This progression occurs over many years; consequently, most patients are middle aged or older. Environmental factors,

such as smoking and diet, increase the risk of developing gastric adenocarcinoma. *H. pylori*-associated adenocarcinoma most often occurs in the distal (non-cardia) stomach. *H. pylori*-mediated adenocarcinoma has been replicated in animal models, particularly in gerbils[85,90]. The presence of *cagA*, *vacA*s1m1, *babA2*, and *oipA* increase the risk of cancer[91-94]. Cancer risk is further elevated by the presence of certain EPIYA motifs in CagA[26,95]. A number of good reviews discuss the molecular mechanisms in detail[85,96,97].

Diffuse type adenocarcinoma is characterized by scattered tumor cells and lack of glandular organization. Diffuse-type gastric cancer tends to occur in younger individuals and may have a strong genetic component, although *H. pylori* also plays a role[98]. Environmental factors contribute little to this type of cancer. Pangastritis and rugal hyperplasia confer higher risks of diffuse-type adenocarcinoma[99,100]. The mechanisms underlying development of diffuse-type cancer are poorly understood, but abnormal DNA methylation is likely involved. *H. pylori* induces hypermethylation of the gene encoding E-cadherin, which is implicated in hereditary diffuse-type cancer[99,101].

The association between MALT lymphoma and *H. pylori* was first published in 1991[102] and has since been corroborated by numerous studies. *H. pylori* is responsible for 92%-98% of gastric MALT lymphoma[3]. The formation of lymphoid follicles is necessary, but not sufficient for development of MALT lymphoma. CagA and other virulence factors contribute little to the risk of developing MALT lymphoma[103]; however the presence of CagA within tumor-associated B cells correlated with earlier remission following *H. pylori* eradication compared with patients whose tumors did not contain CagA[104]. Most gastric MALT lymphomas are low grade when discovered and are dependent upon continued antigen stimulation. Lymphocytes are prone to developing genetic mutations, and prolonged antigen-driven proliferation of B lymphocytes eventually leads to a population that is antigen independent[105]. Interestingly, the tumor-associated B cells do not recognize *H. pylori*. Some have suggested that B cells recognize autoantigens, but an in-depth study of antigen specificity did not uphold previous results[105,106]. Thus it is not clear whether antigen specificity plays a role in MALT lymphoma development.

The first line of treatment for *H. pylori*-positive MALT lymphoma is eradication therapy. *H. pylori* eradication leads to lasting remission in about 80% of patients[107]. Some *H. pylori*-negative MALT lymphomas, including a recurrent parotid lymphoma, have also responded to eradication therapy, suggesting that these were either false negatives or perhaps caused by another *Helicobacter* species[108,109].

OTHER CANCERS POTENTIALLY CAUSED BY *H. PYLORI*

Colorectal cancer

Gastric adenocarcinoma and MALT lymphoma were the first cancers associated with *H. pylori*, but they may not be the last. Several other cancers have been recently associated with *H. pylori*, though the evidence is not ironclad. The most common extragastric cancer potentially influenced by *H. pylori* is colorectal adenocarcinoma. Gastric *H. pylori* routinely passes through the intestinal tract, so it is not unreasonable to suspect that *H. pylori* could influence development of colorectal cancer. Several studies support this hypothesis. Three recent meta-analyses found a significantly increased risk of both colon polyps and colon cancer in *H. pylori*-infected patients[110-112]. One study examined the prevalence of gastric pathology in patients with hyperplastic polyps, colon adenoma, advanced adenoma, and colon cancer[113]. All patient groups had higher prevalences of *H. pylori*-positive gastritis and intestinal metaplasia. The odds ratios were largest in patients with colon cancer. Those patients had significantly increased risks of gastritis, intestinal metaplasia, gastric adenoma, gastric cancer, and gastric lymphoma. Grouping patients according to whether or not the cancer was advanced revealed that the infection rate was higher in advanced cases (86%) than on non-advanced cases (51%). Forty eight percent of control patients were infected[114]. Oddly, *cagA* positive strains were not more prevalent in cancer patients. In summary, it appears that *H. pylori* could contribute to the risk or aggressiveness of colorectal cancer, but much additional research is needed to confirm the association and determine the underlying mechanism.

Pseudomyxoma peritonei (PMP) is a rare peritoneal cancer that most often originates in the appendix[115]. Appendiceal rupture allows the cancer to invade the peritoneal cavity. Bacteria are able to enter the peritoneum at the time of rupture, but the viscous mucus prevents leakage of fecal material into the peritoneum and peritonitis does not ensue. Instead, a subset of bacteria present within the mucus persistently colonizes the peritoneal cavity. The appendiceal rupture site heals, trapping the tumor, mucus, and bacteria within the peritoneal cavity. Subsequent mucin accumulates in the peritoneal cavity causing compression of abdominal organs. Pseudomyxoma peritonei originating from the appendix is essentially similar to the mucinous subtype of colorectal adenocarcinoma. In fact, mucinous colonic polyps sometimes cause PMP[116]. Live *H. pylori* have been found within tumor and mucinous material[117]. Patients who were treated with standard *H. pylori* eradication therapy prior to surgery had reduced nuclear β-catenin, indicating cellular normalization, and tended to survive longer than patients given only standard care[61,118].

Lymphomas

H. pylori could increase the risk of other lymphoma types. Diffuse large B cell lymphoma (DLBCL) is an aggressive cancer that can occur in the stomach and elsewhere. It is considered separate from gastric MALT lymphoma, although the former can sometimes transform into the latter[119]. This type of cancer is currently not believed to be *H. pylori*-associated; however, there have been a number of case reports in which *H. pylori* eradication alone led to

complete remission[120]. Inaba *et al*[121] found that primary gastric diffuse large B cell lymphoma increases the risk of developing gastric adenocarcinoma, often within 5 years of treatment. The author proposes that chemotherapy and radiation may hasten the development of gastric adenocarcinoma in *H. pylori*-positive patients. Testing DLBCL patients for *H. pylori* may therefore be prudent.

As yet, there is only scant evidence that *H. pylori* influences extragastric lymphomas. One patient with rectal MALT lymphoma had a complete response to *H. pylori* eradication therapy and remained disease-free after 34 mo[122]. Ocular adnexal lymphoma (OAL) is a most often a MALT lymphoma presenting on the orbit or conjunctiva[123]. A comparison of patients suffering from ocular adnexal lymphoma, extragastric lymphoma in other body sites, and controls found that OAL patients were 32% more likely to be infected with *H. pylori* than controls. Furthermore, patients with lymphoma at other sites were 13% more likely to be infected. Both of these findings were highly significant[124]. *H. pylori* DNA has been found in one OAL tumor out of 6 tested[125]. To date, there are no reports of *H. pylori* eradication therapy being tested in OAL patients.

Laryngeal/pharyngeal cancer

A number of studies report that *H. pylori* infection protects against Barrett's esophagus and subsequent laryngeal adenocarcinoma development (see section on laryngeal disease); however, some studies suggest a positive association with laryngeal squamous cell carcinoma[126-128]. Burdick[129] examined 75 patients with laryngeal squamous cell cancer. All samples were positive for *ureA*, and 47%-49% of *ureA* positive samples were also *cagA* positive. The *cagA* gene was much more prevalent in lymph node positive tumors than in lympth node negative tumors. Additionally, *cagA* was far more prevalent in supraglottic tumors than in glottic or subglottic tumors. The survival rate was also lower in *cagA* positive patients. Guilemany *et al*[130] found a significant correlation between hypopharyngeal squamous cell carcinoma and *H. pylori* infection ($P < 0.001$). It should be noted that not all studies have found a positive correlation[131,132].

EXTRAGASTRIC DISEASES ASSOCIATED WITH *H. PYLORI*

H. pylori is increasingly being associated with extragastric diseases. *H. pylori* is widely accepted as a cause of iron deficiency anemia and idiopathic thrombocytopenia, but the jury is still out on other diseases. In most cases, *H. pylori* is believed to be one of several causes, meaning that *H. pylori* eradication will only benefit a subset of patients. This section summarizes current epidemiological, clinical, and experimental evidence supporting a role for *H. pylori* in causing or exacerbating a range of diseases.

Iron deficiency anemia

The association between *H. pylori* infection and iron deficiency anemia (IDA) is well established[133,134], but the mechanisms underlying this association are unclear. The most obvious mechanism for *H. pylori* to cause IDA is through competition for dietary iron. *H. pylori* requires higher concentrations of inorganic iron and zinc for in vitro growth than other pathogens[59], yet there is no evidence that *H. pylori* has more iron- or zinc-dependent enzymes than other bacteria. *H. pylori* may have less efficient iron acquisition symptoms than other organisms, but this would suggest that *H. pylori* competes poorly for dietary iron. *H. pylori* is able to acquire iron from host transferrin and lactoferrin, yet it binds the iron-free forms of these proteins more avidly than the iron-loaded proteins[60]. All of this points towards an evolutionary advantage for *H. pylori* strains that do not overly tax the host iron supply. Nonetheless, *H. pylori* genomes vary considerably from strain to strain, as do virulence properties. Yokota *et al*[135] found that certain polymorphisms within the *H. pylori* neutrophil-activating protein were more prevalent in strains from IDA patients than from non-IDA patients. Moreover, IDA strains harboring these polymorphisms internalized iron more rapidly than other strains. Inorganic iron dissolves best in highly acidic conditions. Loss of gastric acid secretion due to *H. pylori* infection could therefore reduce bioavailability of dietary iron. Excess lactoferrin in gastric tissue could impair iron uptake, since transferrin is the normal route of host iron uptake[136]. In male patients with refractory IDA, *H. pylori* infection was associated with higher serum TNFα levels, particularly in those infected with $CagA^+$ *H. pylori*[137]. This is relevant because TNFα and other pro-inflammatory cytokines can induce anemia.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is characterized by autoimmune destruction of platelets, which leads to bruising. Significant evidence points to *H. pylori* as a causative agent in some cases of ITP. For example, *H. pylori* eradication therapy increases platelet counts only in those who were infected with *H. pylori*, not those who were uninfected ruling out an off-target effect of antibiotics[138]. Among ITP patients treated for *H. pylori* infection, patients who had a lower serum pepsinogen Ⅰ / Ⅱ ratio responded better (*i.e.*, greater improvement in platelet counts) than those with higher pepsinogen Ⅰ / Ⅱ ratios. This correlated with more severe atrophic gastritis in responders than in non-responders[139]. Host factors likely play a role as well. *H. pylori*-infected patients who lack a particular single nucleotide polymorphism in IL-β, the IL-β (-511) T allele, were more likely to develop ITP before age 50 years than uninfected ITP patients[140].

Skin diseases

H. pylori appears contribute to several inflammatory skin diseases. Rosacea is the most common skin disease potentially associated with *H. pylori*. In one study, *H. pylori* was present in 81% of rosacea patients who also had gastric complaints, and almost all of those patients har-

bored *cagA*+ strains[141]. A similar Egyptian study found that both *cagA* and the s1m1 allele of *vacA* were more prevalent in papular rosacea patients. The papular rosacea patients responded better to eradication therapy than the erythematous rosacea patients[142]. A limited study of ocular rosacea patients reports that the seven ocular rosacea patients responded better to *H. pylori* eradication therapy than did rosacea patients without ocular symptoms[143].

Chronic prurigo consists of intensely itchy nodules. There are several variants, including prurigo pigmentosa and prurigo chronica multiformis. These disease are most common in young women of Japanese or Turkish descent[144]. Limited studies suggest higher prevalence of *H. pylori* or clinical improvement following *H. pylori* eradication therapy[145]. *H. pylori*-associated gastric diseases are also more prevalent in these patients[145-147]. Immunohistochemical evidence of *H. pylori* in a prurigo pigmentosa patient strengthens the case for a link and suggests that *H. pylori* acts directly within the skin, rather than indirectly through inflammatory mediators[148]. These mechanisms are not mutually exclusive, but much more research is needed to clarify etiology and pathogenic mechanisms related to *H. pylori*.

Chronic idiopathic urticaria consists of itchy wheals that are present on most days with no known cause. A meta-analysis of 10 chronic urticaria studies completed prior to 2003 found that the overall remission rate following *H. pylori* eradication was 30.9%. This was statistically significant with an odds ratio of 2.9[149]. Chiu *et al*[150] found no difference in the *H. pylori* infection rates in chronic spontaneous urticaria (CSU) patients, but 63.6% of patients had complete remission after *H. pylori* eradication. Likewise, Campanati *et al*[151] found no difference in *H. pylori* prevalence, but found significant improvement following *H. pylori* eradication therapy. In the same study, the authors found an unusually high rate of small intestinal bacterial overgrowth in CSU patients. Those patients were treated with the recommended antibiotic, but their CSU symptoms did not improve. Yoshimasu and Furukawa[152] grouped patients according to anti-*H. pylori* titer. None of the patients with high titers was cured with antihistamine treatment alone. Eradication therapy raised the cure rate to 56%. Patients with low or absent anti-*H. pylori* titers were more likely to respond to antihistamine treatment alone. These studies point to the conclusion that *H. pylori* is one of several causes of CSU.

Case reports suggested an association between psoriasis and *H. pylori*[153,154], providing impetus for a larger study by Onsun *et al*[155]. Stratifying a group of 300 plaque psoriasis patients by symptom score revealed that 100% of patients with moderate or severe psoriasis were *H. pylori* positive, while only 37% of mild psoriasis patients were infected. *H. pylori* positive patients were treated with acitretin alone, *H. pylori* eradication therapy alone, or both. All treatment groups showed improvement after 8 wk, but improvement was more rapid when *H. pylori* eradication was included. *H. pylori* treatment alone was just as effective as both eradication therapy and acitretin[155].

Diseases of pregnancy

H. pylori may contribute to diseases of pregnancy. Hyperemesis gravidarum consists of severe and prolonged vomiting that goes far beyond typical "morning sickness". A meta-analysis of clinical studies found that the majority support the hypothesis that *H. pylori* contributes to hyperemesis gravidarum, although further studies are needed[156]. One study found that 80% of hyperemesis gravidarum patients were *H. pylori*-positive compared with 35% of controls[157]. Mansour and Nashaat[158] report improvements in *H. pylori*-positive hyperemesis gravidarum patients following eradication therapy[158].

A study comparing women with normal pregnancies to those with pre-eclampsia (PE) yielded striking results[159]. The correlation between *H. pylori* seropositivity and PE was highly significant, with an odds ratio of 9.22. The relationship was even stronger for pregnancies with both PE and fetal growth retardation (OR = 35.56). $CagA^+$ strains were overrepresented in both PE and PE with fetal growth retardation, yielding odds ratios of 17.66 (PE) and 54.97 (PE with fetal growth retardation). In contrast, pregnancies with only fetal growth retardation were not associated with greater than expected *H. pylori* seropositivity. A more recent study found that antibodies against CagA cross-react with beta-actin of cytotrophoblast cells[160]. This may impair placental invasion.

Diseases of the ears, nose, and throat

Since *H. pylori* is frequently present in the oral cavity, perhaps it is not surprising that it is occasionally found in the ear, nose and throat. Aside from gastroesophageal reflux disease, too few studies have been done to determine whether *H. pylori* causes disease in those locations. Nonetheless, some of the data are tantalizing. In one study, *H. pylori* was cultured from 40% of adults with otitis media with effusion[161]. Other studies have used the *Campylobacter*-like organism test (CLO test) to identify *H. pylori* infections in the middle ears of patients with otitis medium or tympanosclerosis[162,163]. Melake *et al*[164] compared children undergoing myringotomy for chronic otitis media with children who were undergoing tonsillectomy/adenoidectomy, but did not have a history of otitis media. The study group was roughly three times more likely to have evidence of *H. pylori* in the stomach, adenoids, or tonsils than the control group. Almost all of the study patients with evidence of gastric *H. pylori* were also either culture- or PCR-positive for *H. pylori* in middle ear fluid. Interestingly, another study found that 48 of 49 biopsies taken from 37 children with adenotonsillar hypertrophy contained *H. pylori*[165], raising the possibility that the association between *H. pylori* and chronic otitis media could be stronger than it appeared to be in the Melake study. *H. pylori* worsened inflammation in a rabbit model of histamine-induced otitis media with effusion[166]. This suggests that *H. pylori* may not be the initial cause of otitis media, but these bacteria may exacerbate pre-existing infections.

Several studies have demonstrated the presence of *H. pylori* in nasal polyps[167-169]. One study failed to find a difference in gastric colonization between patients with nasal polyps *vs* patients with concha bullosa, but *H. pylori* was only found in nasal biopsies from nasal polyposis patients[170]. In a study of nasal polyps *vs* benign laryngeal disease, *H. pylori* was detected in all 60 patients with either nasal polyps or benign laryngeal disease. Interestingly, *cagA*-positive *H. pylori* was detected in 23.3% of patients with laryngeal disease, but in none of the nasal polyps[171]. CagA is often associated with more severe gastric disease, but this toxin may put *H. pylori* at a disadvantage in certain anatomical sites.

The relationship between *H. pylori* infection and esophageal diseases has been a controversial topic for years. According to the dogma, eradicating *H. pylori* increases gastric acid output. This leads to exacerbation of gastroesophageal acid reflux disease (GERD) and an increased risk for developing Barrett's esophagus and esophageal adenocarcinoma. The decreasing prevalence of *H. pylori* infection is therefore predicted to increase the prevalence of esophageal diseases. Indeed, there has been an increase in the incidence of esophageal adenocarcinoma[172]. Some studies and meta-analyses have concluded that *H. pylori* eradication worsens gastroesophageal reflux disease, while others report no effect[173-176]. There is also an inverse correlation between *H. pylori* infection and Barrett's esophagus[177-179]. A recent meta-analysis confirms the inverse correlation between *H. pylori* infection and esophageal adenocarcinoma in Eastern and Western populations. The analysis also revealed a significantly reduced risk of esophageal squamous cell carcinoma in Eastern populations, but not Western populations[173].

On the other hand, some studies suggest a more complex relationship between the incidence of esophageal disease and the prevalence of *H. pylori*. Studies of gastric pH and manometric values have not found a difference between *H. pylori* infected and uninfected patients or in patients before and after *H. pylori* eradication[175,180]. McColl reports that *H. pylori*-induced gastric atrophy reduces the risk of esophageal adenocarcinoma, but antral-predominant gastritis with increased acid production increases the risk[181]. In contrast, Derakshan *et al*[182] report that atrophy does not impact the risk of adenocarcinoma. While univariate analysis showed a protective effect of *H. pylori* infection on esophageal adenocarcinoma, this effect was lost upon multivariate analysis and only smoking and GERD symptoms > 2 times per week remained significant[182]. Obesity is one of the strongest risk factors for esophageal adenocarcinoma, and the worsening obesity epidemic could be partially responsible for the rise in esophageal adenocarcinoma cases[179].

If the dogma holds true, one would expect that regions of the world with lower *H. pylori* prevalence should have higher rates of esophageal adenocarcinoma and squamous cell carcinoma. Ethnic Malays in the Northeastern peninsular region of Malaysia have only a 4%-5% rate of *H. pylori* infection. The rates of esophageal adenocarcinoma and Barrett's esophagus in this population were lower than in populations with greater *H. pylori* prevalence[183]. Therefore, lack of *H. pylori* alone does not explain the increasing prevalence of esophageal disease.

Liver and gallbladder

A few studies have implicated *H. pylori* and other *Helicobacter* species human liver and gallbladder disease. *H. pylori* has been detected in livers from hepatocellular carcinoma patients by PCR and histology[184]. Chronic cholecystitis patients were tested for the presence of *H. pylori* in the gallbladder mucosa. Patients with *H. pylori* positive gallbladders had increased levels of inducible nitric oxide synthase and higher incidences of adenomyomatosis and metaplasia[74]. Following the discovery of *H. pylori*, *H. hepaticus* was found in many colonies of research mice. This infection causes chronic active hepatitis and laboratory rodents are now routinely tested for *Helicobacter* infections[185]. While *H. pylori* predominantly colonizes the intestines, other *Helicobacter* species, such as *H. hepaticus*, *H. bilis*, and *H. cinaedi* infect the intestines and biliary tract in humans. *H. bilis* appears to be highly prevalent in patients with pancreaticobiliary maljunction[186]. The non-*pylori* helicobacters have been largely overlooked and more studies are needed to determine their prevalence and capacity to cause disease.

Pulmonary disease

A handful of studies have linked *H. pylori* infection with bronchiectasis and chronic obstructive pulmonary disease (COPD)[187-189]. Tsang *et al*[188] compared the seroprevalence of *H. pylori* among bronchiectasis, tubercoulosis, and control groups. Bronchiectasis patients were 76.0% seropositive, while tuberculosis and control patients were 52.9% and 54.3% seropositive for *H. pylori*. Interestingly, one study aimed at determining whether *H. pylori* seroprevalence differs between inflammatory bowel disease patients and controls used COPD patients for comparison[190]. They reasoned that COPD patients would have similar degrees of antibiotic exposure to inflammatory bowel disease patients. Separate age-matched control groups were used for IBD and COPD patients because COPD patients tend to be older. Seroprevalence of *H. pylori* is clearly lower among IBD patients than among controls. On the other hand, *H. pylori* seroprevalence was higher in COPD patients than in that control group. They do not mention whether the difference reached statistical significance.

Conversely, one very large study failed to find an association between COPD risk and *H. pylori* infections in nonsmokers[191]. A small study of Turkish soldiers also failed to find a correlation between bronchiectasis and *H. pylori*[187]. Oddly, patients with a history of gastric or cardiovascular disease were excluded. Gastric and extragastric diseases related to *H. pylori* often coexist in patients and may indicate the presence of more virulent *H. pylori* strains and/or a genetic predisposition to disease. Thus, there is insufficient evidence to draw conclusions regard-

ing the role of *H. pylori* and lung disease.

Ocular diseases

Credible evidence suggests a link between *H. pylori* infection and certain eye diseases, particularly open angle glaucoma. Kountouras *et al*[192] have been the primary proponents of this association, but studies have thus far been small; no study has involved patient groups larger than 100 subjects. In one study, the rate of *H. pylori* infection in glaucoma patients was almost double that of a control group. When these patients were followed for two years, intraocular pressure and visual field parameters were improved in patients who had undergone successful *H. pylori* eradication therapy, but not in patients who were *H. pylori*-negative or whose eradication therapy failed. Histological evidence has been found in eye tissue from 5 out of 43 *H. pylori*-positive patients, but in none of the control patients[75]. Cresyl violet staining was used to detect *H. pylori*. This stain reacts with *Helicobacter* and *Campylobacter*, but few other bacterial species. Therefore, the strength of this evidence is stronger than histology using less specific stains, but not as strong as that obtained from immunohistochemistry. Two studies, one in Canada and one in Israel, have failed to find a higher prevalence of *H. pylori* infection in glaucoma patients[193,194]. More studies are clearly warranted.

Central serous retinopathy (CSR) results when the retinal pigment epithelial barrier breaks down, causing fluid to leak into the subretinal space; this leads to visual impairment[195]. Permanent damage can result if the fluid is not reabsorbed quickly. To date, only a handful of clinical trials have been performed to explore the potential relationship between CSR and *H. pylori;* however, the results of these studies have been impressive. No published study has failed to find a correlation between CSR and *H. pylori* evidence. Three studies have measured the effects of *H. pylori* eradication on the course of the disease[195-197]. All three found some evidence of improvement. In the study by Rahbani-Nobar *et al*[196] one group of *H. pylori*-infected patients received eradication therapy, while another group did not. Reabsorbtion was significantly more rapid in the eradicated group than in the non-eradicated group.

Neurodegenerative diseases

There is tantalizing, but far from conclusive, evidence suggesting a link between *H. pylori* infection and development of Alzheimer's and Parkinson's diseases. In Parkinson's disease, *H. pylori* clearly interacts with L-dopa. The bacteria can bind L-dopa and impact the absorption of L-dopa treatment[198-200]. Some studies indicate that *H. pylori* eradication reduces motor fluctuations, but one study found that motor fluctuations were lower in infected patients than in uninfected patients[199,201,202]. A large Danish study found an association between Parkinson's disease diagnosis and *H. pylori* eradication treatment 5 or more years prior to Parkinson's disease diagnosis[203]. This suggests that past *H. pylori* infection may be just as relevant to Parkinson's disease as current infection. A double-blind, placebo-controlled trial found improvements in stride length, but worsening of rigidity, following eradication therapy in anti-nuclear antibody-negative patients[204]. Anti-nuclear antibody-positive patients did not benefit from eradication. Alarmingly, patients who remained *H. pylori*-positive following treatment (eradication failure) experienced rapid declines in motor functions. One interesting study examined the prevalence of *H. suis*, which frequently infects livestock, in Parkinson's disease patients. *H. suis* colonization was found in 12% of patients, but only 0.6% of controls. Many of the *H. suis*-infected patients had previously undergone *H. pylori* eradication therapy[205]. They hypothesize that *H. suis* infection could explain the higher prevalence of Parkinson's disease among farmers. At present, treatment of *H. pylori* in Parkinson's disease patients is not recommended due to the potential for deterioration of motor function associated with eradication failure.

With respect to Alzheimer's disease or general cognitive function, some studies have found correlations with *H. pylori* infection and some have not[206-208]. A very large, cross sectional study using data from the National Health and Nutrition Examination Ⅲ, phase 1 found that *H. pylori* seropositivity was strongly associated with poorer cognition among adults aged 60-90 years[209]. A small study of Alzheimer's patients and age-matched controls found that *H. pylori* eradication significantly improved cognitive status, as measured two years after treatment[210]. The five-year survival rate was improved in *H. pylori*-eradicated Alzheimer's patients, but again, this was a small study[211]. An *H. pylori* histidine-rich, nickel binding protein, Hpn, forms amyloid structures *in vitro* and has been postulated to play a role in Alzheimer's disease[212], but *in vivo* data are lacking.

Insulin resistance, diabetes and complications of diabetes

The association between *H. pylori* infection and diabetes was only recently suggested[213], but the preponderance of studies have shown positive associations[214]. Metabolic syndrome consists of obesity, particularly central obesity combined with two or more other factors, such as insulin resistance, hypertension, dyslipidemia, or elevated fasting glucose. Metabolic syndrome is accepted as a precursor to diabetes[215]. A large, cross sectional study of Japanese patients revealed a significant relationship between *H. pylori* infection and metabolic syndrome (OR = 1.39, $P < 0.001$)[216]. Microalbinuria, neuropathy, and heart disease are common complications of diabetes. Patients infected with *H. pylori*, particularly *cagA*$^+$ *H. pylori*, were found to be at higher risk of microalbuminuria, which indicates endothelial leakage and is a risk factor for cardiovascular disease and diabetic nephropathy[217,218]. Studies also suggest at higher rate of diabetic complications, such as nephropathy, neuropathy, and retinopathy, in *H. pylori*-positive diabetics[219,220]. Coronary heart disease is also more prevalent in *H. pylori*-positive diabetics than *H.*

pylori-negative diabetics[221].

The mechanisms underlying the association between *H. pylori* and diabetes are unclear. Chronic inflammation due to *H. pylori* infection is believed to contribute to many *H. pylori*-associated diseases, and diabetics have higher levels of inflammatory markers than non-diabetics[222]. Nonetheless, Jeon *et al*[223] did not find that the inflammatory markers IL-6 and C-reactive protein were elevated in *H. pylori*-positive diabetics compared to *H. pylori*-negative diabetics. Therefore, it appears that other causes of inflammation, perhaps including adiposity, trump *H. pylori*-mediated inflammation in diabetics.

Does *H. pylori* eradication benefit patients who have already developed diabetes? Very few studies have sought to answer this important question. CagA$^+$ *H. pylori* strains are strongly associated with poor glycemic control[218,224], so one would naturally think that these patients would benefit from eradication therapy. In a study by Akanuma *et al*[225] found that *H. pylori* eradication did not improve glycemic control. Experiments in mice actually suggest that *H. pylori* infection improves glucose homeostasis[226]. *H. pylori* eradication regimens are not 100% effective in any population, but type 2 diabetics are at higher risk for eradication failure[227].

The impact of *H. pylori* infection on ghrelin production could complicate the interpretation of diabetes studies. *H. pylori* is known to suppress gastric ghrelin, and ghrelin levels in the stomach rise following *H. pylori* eradication[228]. Ghrelin stimulates appetite, which could explain why some studies have found that patients gain weight following *H. pylori* eradication[225,229]. It is also possible that resolution of gastric symptoms leads to weight gain, but regardless of the mechanism, weight gain is not beneficial to diabetic patients. Clearly, more studies are needed to clarify the impact of *H. pylori* eradication on diabetic patients, but at this point in time, treatment of *H. pylori* infection in diabetic patients cannot be recommended.

Cardiovascular disease

An association between *H. pylori* and coronary artery disease was first suggested in 1994, twelve years after Barry Marshall and Robin Warren discovered *H. pylori*[230]. The methodologies and endpoints used in studies are diverse, making it difficult to compare studies. The presence of CagA seropositivity tends to strengthen associations with cardiac diseases including atherosclerosis, unstable angina, and cardiac X syndrome[231-237]. A meta-analysis found that *cagA*-positive *H. pylori* increases the risk of both ischemic stroke and coronary heart disease[62]. There is ample evidence demonstrating that *H. pylori* infection alters biomarkers that are associated with CVD. For example, several studies have linked *H. pylori* infection to alterations in lipid profiles[238-240]. Moreover, the amount of LDL cholesterol elevation correlated with the degree of gastric inflammation[241] and *H. pylori* eradication normalized lipid profiles[242,243]. *H. pylori* infection has also been found to correlate with increased carotid intimal thickness, reduced serum paraoxonase-1 activity, and increased risk of peripheral artery disease[244,245].

The role of *H. pylori* in promoting atherosclerosis or other manifestations of cardiovascular disease remains controversial because a number of studies have failed to find any association between *H. pylori* infection and the disease parameters studied[246,247]. Studies of healthy adults and children failed to find associations between C-reactive protein levels and *H. pylori* infection[247]. *H. pylori* infection was also not found to correlate with fibrinogen or von Willebrand factor levels in coronary angiography patients[248]. McDonagh *et al*[246] failed to find an increased odds ratio for coronary heart disease in *H. pylori*-infected patients. With so many conflicting studies, it is impossible to recommend testing for or treatment of *H. pylori* in any CVD patient population. Moreover, few *in vivo* studies have been carried out in animal models. Nonetheless, the number of studies positively correlating *H. pylori* infection with various aspects of CVD warrants continued research on the potential for *H. pylori* to influence various types of cardiovascular disease.

Autoimmune disorders

A recent meta-analysis of studies revealed that CagA seropositivity increased the risk of autoimmune thyroid disease by 2.24 fold (95%CI: 1.06-4.75). Infection with any *H. pylori* strain significantly increased the risk for Grave's disease (OR = 4.35), but not for Hashimoto's thyroiditis[249]. While the overall *H. pylori* infection rate was not elevated in Hashimoto's thyroiditis, these patients did have a significantly higher rate of *cagA*$^+$ *H. pylori* infection than controls[250]. An exploration of both host genetics and *H. pylori* virulence factors revealed that CagA$^+$ strains were more strongly associated with Grave's disease than *cagA*$^-$ strains and certain HLA-DQA1 alleles altered the risk of developing Grave's disease[251]. *H. pylori* infection, especially *cagA*$^+$, was found to be more prevalent in patients with Grave's disease than controls; CagA has some homology with thyroid peroxidase, which could trigger an autoimmune response[252]. Autoantibodies against thyroid peroxidase dropped significantly in all 5 *H. pylori*-positive patients who accepted eradication therapy, but did not drop in 5 who refused to be treated. Anti-thyroglobin titers also dropped in 4/5 treated patients[253]. *H. pylori* infection may also decrease the efficacy of thyroxine therapy in patients with hypothyroidism[254]. In support of the potential for *H. pylori* to cause thyroid disease, euthyroid patients with thyroid nodules were significantly more likely to be infected with *H. pylori* than patients without thyroid nodules ($P = 0.002$)[255].

Systemic sclerosis is an autoimmune disorder caused by autoantibodies Information regarding the potential for *H. pylori* to cause or worsen systemic sclerosis is scant, but intriguing. A few studies have found positive correlations between systemic sclerosis and *H. pylori* infection[256-258]. The presence of *H. pylori* infection is strongly associated with worse gastrointestinal, skin, and joint symptoms, as well as increased erythrocyte sedimenta-

tion rate in systemic sclerosis patients[259]. Danese *et al*[256] found that 90% of *H. pylori* strains infecting systemic sclerosis patients were *cagA*$^+$, compared with only 37% in controls. Reinauer *et al*[260] demonstrated that *H. pylori* could be eradicated in systemic sclerosis patients, but did not follow up to determine whether symptom scores improved. Further studies are needed to confirm the association between *H. pylori* and systemic sclerosis and determine whether *H. pylori* eradication is beneficial.

Neuromyelitis optica and multiple sclerosis

In contrast to systemic sclerosis, several studies indicate a protective effect of *H. pylori* infection on multiple sclerosis[261,262], but the picture becomes more complicated when the presence of neuromyelitis optica (NMO) is included. NMO is an autoimmune disease in which antibodies against aquaporin lead to demyelination of the spinal cord and optic nerve, leading to paralysis and blindness. It has been considered to be a variant of multiple sclerosis, but is now proposed to be a separate disease[263]. Li *et al*[264] attempted to dissect the possible relationship between MS and *H. pylori* by correlating antibodies against HP-NAP with autoantibodies against aquaporin-4 (AQP4) and with circulating myeloperoxidase. Patients with MS and neuromyelitis optica were more likely than controls to be infected with *H. pylori* than those with conventional MS. There was a significant correlation between seropositivity for AQP4 and seropositivity for HP-NAP. HP-NAP seropositive patients also had higher myeloperoxidase levels and worse disability. *H. pylori* and *Chlamydia pneumoniae* seropositivity were found to be more prevalent in NMO patients who also have anti-AQP4 antibodies, but not in those lacking that autoimmune marker[265]. These data clearly indicate that MS and NMO patients must be studied separately with regard to the potential for *H. pylori* involvement. *H. pylori* antigens have been proposed as a treatment for multiple sclerosis[266], but the potential for causing or exacerbating other diseases makes this a risky proposition.

Campylobacter jejuni infection is known to be a risk factor for development of Guillain Barré syndrome, and *H. pylori* may contribute as well. Guillain Barré syndrome is an autoimmune attack on peripheral nerves that leads to paralysis, which is usually temporary. A few small studies have found higher *H. pylori* titers of *H. pylori* antibodies in serum or CSF in Guillain Barré patients than in controls[267-269]. Associations were particularly strong in patients with the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) type of Guillain Barré syndrome. Another study found anti-VacA in all AIDP patients[270]. Homology between VacA and [Na(+) + K(+)]-ATPase is suggested as a potential cause.

Protection against allergies

The hygiene hypothesis proposes that inadequate exposure to certain bacteria during the first one or two years of life results in an immune system that is hypersensitive to environmental agents, leading to various allergic diseases. A Th2-skewed immune system favors allergies, while Th1 responses, which are induced by *H. pylori*, favor autoimmune and inflammatory diseases. The incidence of allergies has risen dramatically in recent decades, while the prevalence of *H. pylori* infection has fallen. This led investigators to search for a link between the two phenomena. Several studies suggested an inverse relationship between *H. pylori* infection and asthma. A meta-analysis confirmed this association[271]. Proof-of-principle has been established in a mouse model of asthma induced by ovalbumin or house dust mite allergen[272]. In accordance with the hygiene hypothesis, neonatal infection of mice proved most effective in preventing asthma. Protection correlated with infiltration of regulatory T cells into the lungs. Adoptive transfer of regulatory T cells from *H. pylori*-infected mice into allergic mice offered protection. Some evidence also suggests that *H. pylori* may be protective against food allergies, celiac disease, and allergic rhinitis as well[273-275]. CagA$^+$ strains do not appear to be relevant to asthma, but purified HP-NAP reduced lung eosinophilia and Th2-associated cytokines in ovalbumin-induced asthma in mice[53]. Certainly, *H. pylori* is not the only organism implicated in allergy prevention. Actinobacteria, *Bifidobacterium*, and certain *Clostridia* and *Bacteroides spp.*, are associated with a lower risk of allergic disease, as well as a higher overall diversity of organisms[276,277]. It is not known which organisms can most safely and effectively prevent or treat allergic disease.

Summary of extragastric diseases

Considering that *H. pylori* has numerous direct and indirect effects on host physiology, one should keep an open mind regarding the possibility that *H. pylori* contributes to a variety of extragastric diseases. *H. pylori* has now been detected by culture, PCR, or histology in several epithelial tissues, including the eyes, ears, nose, and skin. While it is not yet possible to draw firm conclusions regarding the role of *H. pylori* in most extragastric diseases, the evidence cannot be ignored. Studies with contradictory results could have several explanations. Regional variations in both human and *H. pylori* genotypes contribute to established *H. pylori*-associated diseases. Inconsistencies may also indicate that *H. pylori* is a minor contributor or serves to exacerbate, rather than cause, a particular disease. Just as *H. pylori* is not responsible for all cases of gastric cancer or ulcers, *H. pylori* is unlikely to be the sole cause of other disorders. Future studies should measure the presence of *H. pylori* virulence factors, in addition to overall seropositivity, since several diseases are associated with only some *H. pylori* genotypes. Studies designed to elucidate mechanisms through which *H. pylori* contributes to disease would also improve credibility.

TESTING INDICATIONS

Routine testing and treatment without endoscopy should be performed primarily in relatively young patients with evidence of dyspepsia, and without suspicion of severe

pathology[278,279]. The test and treat strategy is considered less useful in regions where the prevalence of *H. pylori* is low (20% or less). Patients who present with alarm symptoms of vomiting, gastrointestinal bleeding, or weight loss in patients or are over 45 years of age should proceed with an endoscopic evaluation[278].

Preemptive *H. pylori* eradication can reduce gastric cancer risk and is considered appropriate for (1) first degree relatives of gastric cancer patients, (2) patients previously treated for gastric neoplasia; (3) patients with severe pan-gastritis, corpus-predominant gastritis, or atrophy; and (4) patients with other risk factors such as heavy smoking or exposure to coal dust[279].

Testing should be considered for certain other populations. The combination of long-term NSAID use and *H. pylori* infection increases the risk of ulcer development. Therefore, testing for *H. pylori* is recommended prior to starting long-term NSAID therapy[280,281]. Individuals with unexplained iron deficiency anemia have been shown in several series to have an improvement in anemia with treatment of *H. pylori* in select patients[133,134,282]. *H. pylori* testing may be considered in patients with chronic idiopathic thrombocytopenia as eradication may result in improvement in platelet function[283]. There is not sufficient evidence to warrant *H. pylori* testing for most extragastric diseases at this time; however, many patients with potentially *H. pylori*-associated diseases also have gastric symptoms. Non-invasive tests may be considered for these patients.

H. PYLORI TESTS

A number of testing methods are available for detection of *H. pylori*. Invasive methods use endoscopy as the vehicle to obtain tissue for histology, rapid urease testing, polymerase chain reaction, or culture[278]. Culture is no longer considered necessary for confirmation of *H. pylori* infection, but cultured organisms can be tested for antibiotic resistance. Biopsies are also required for PCR analysis.

Noninvasive methods

The urea breath test or fecal antigen testing are the preferred methods for establishment of active infection[279]; however these recommendations come with caveats. The urea breath test consists of drinking carbon-13 labeled or carbon-14 labeled urea. The ingested radiolabeled carbon is converted to carbon dioxide and ammonia by the urease created by the *H. pylori*. The carbon dioxide is absorbed in the bloodstream and a sample of expired air is analyzed for the presence of the labeled carbon. The test also has the advantage of identifying active infection, which cannot be categorized by serology. The sensitivity and specificity for the urea breath test is 99% and 98%, respectively[284]. Since the urea breath test requires specialized equipment, it is not always feasible in small clinics.

Stool also may be submitted for analysis for *H. pylori* antigens using monoclonal or polyclonal antibodies. The test initially used an ELISA process, but has been modified into an immunocard, making it suitable for small clinics and field-testing in third world countries. The sensitivity and specificity for the test is 94.1% and 91.8%, respectively. Stool testing also is more economical than endoscopy for confirmation of eradication. Patient submission of stool samples may be a limitation of this test for some patients, but it is highly suitable for infants and children[285,286].

Proton pump inhibitors and H_2 receptor antagonists need to be withdrawn for several days prior to testing using the urea breath test or stool antigen test due to the potential for false negatives. In addition, antibiotics taken during the four weeks prior to testing can suppress the infection and lead to a false negative. Some studies suggest that waiting until 8 wk post-treatment improves test accuracy[285].

Serology testing for *H. pylori* is widely available and relatively inexpensive. Microtiter plates coated with *H. pylori* antigens, combined with a secondary antibody, and are used to detect *H. pylori*-specific IgG. Serology results are not affected by acid suppression therapy or recent antibiotic use; however, seropositivity is not a confirmation of current *H. pylori* infection. Likewise, serology cannot be used to confirm cure following an anti-microbial regimen. These antibodies persist for an extended period of time, often greater than half a year. Due to the often-patchy distribution of *H. pylori*, serum samples are more consistent than other tissue samples. The sensitivity and specificity of serology for detection of initial infection compares to the gold standard of histology with sensitivity of 85% and specificity of 79%[287].

Invasive methods

Endoscopy is required to obtain biopsy material and to assess the degree of pathology in the stomach. Giemsa, Warthin-Starry, and Diff-Quik stains in addition to standard hematoxylin and eosin staining can be used to identify *H. pylori*. Stains such as Giemsa provide identification of the bacteria, assessment of inflammation, and also provide evidence for intestinal metaplasia. No other tests allow for the identification of intestinal metaplasia. Multiple biopsies are needed for increased diagnostic yield targeting at least three areas including the angularis, the greater curvature of the corpus, and from the greater curvature of the antrum. The high cost of infrastructure, variability in pathologist review, and training of personnel are limitations that prevent this method from being considered as the gold standard for diagnosis[278,288]. Biopsies from the corpus, in addition to the antrum, increases the diagnostic yield by 10%[289].

Rapid Urease testing involves utilization of the *H. pylori* urease to identify active organisms. Samples of gastric tissue are placed on a reactive strip or agar gel. A pH sensitive color indicator, buffer, and urea are added to the sample. Urea is converted to ammonia causing a pH increase and subsequent color change in the sample area of the test device. Readings can be taken between 1 h and 24

Table 1 *Helicobacter pylori* treatment regimens-initial therapies

Therapy	Treatment
Triple therapy	Duration: 7-14 d
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Amoxicillin 1 g by mouth bid
	Clarithromycin 500 mg by mouth twice daily
Quadruple therapy	Duration: 10-14 d
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Tetracycline 500 mg by mouth four times daily
	Bismuth 120 mg four times daily
	Metronidazole 250 mg four times daily
Sequential therapy	Duration: 10 d
	Day 1-5
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Amoxicillin 1 g by mouth bid
	Day 6-10
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Clarithromycin 500 mg by mouth twice daily
	Tinidazole 500 mg by mouth twice daily

PPI: Proton pump inhibitor.

h based on the specific commercial test kit used. Sensitivity greater than 93% and specificity of 98% is reported for rapid urease testing[290].

Culture provides a high specificity for the diagnosis of *H. pylori*; however, it often lacks the sensitivity seen with other invasive methods. From a practical standpoint, culture techniques are technically challenging and costly. *H. pylori* is a fastidious, microaerophilic organism requiring 5-7 d to form visible colonies on solid media. Laboratory personnel must culture specimens promptly and avoid prolonged exposure to ambient oxygen levels to maximize the organism's survival. Culture options for detection are primarily recommended for situations requiring specific antimicrobial sensitivity testing. The tissue may be placed directly on culture media, dragged across the agar surface, or gently homogenized and plated.

PCR techniques can be used to detect *H. pylori* DNA most reliably in biopsy samples, but saliva and feces have also been used. PCR sensitivity nearing 100% and specificity of 100% can be obtained[291]. Contamination from improperly cleaned endoscopes may create false positive results. False negative results may occur due to PCR inhibitors within gastric tissue or feces. Wide acceptance of PCR techniques in the clinical setting is limited and PCR is primarily used in research settings[292]. Fluorescence *in situ* hybridization (FISH) permits sensitive and specific detection of *H. pylori* in gastric biopsies without the need for DNA extraction. A fluorescently labeled DNA probe hybridizes with the complementary sequence within the bacterial chromosome. FISH can detect coccoid *H. pylori* and is more sensitive than standard staining procedures[293]. The use of different fluorescent dyes can permit simultaneous detection of *H. pylori* 16S rRNA and gene sequences associated with antibiotic resistance[294]. A commercially available kit has proven to be reliable and far more rapid than culture-based methods for simultaneous detection of *H. pylori* and clarithromycin resistance[295,296].

TREATMENT

Optimal treatment for *Helicobacter pylori* has yet to be defined for all patients. Furthermore, rates of antibiotic resistance vary by region, and local resistance data should be used to guide treatment where available. Suggested regimens have included quadruple therapy, triple therapy, and sequential therapy as summarized in guidelines published by the American College of Gastroenterology and Maastricht Conference (Table 1). Quadruple therapy utilizes a combination of a proton pump inhibitor (PPI), bismuth product, and antibiotics containing metronidazole and tetracycline for 10 to 14 d. Bismuth salts are not available in all areas of the world. Patients who receive triple therapy are usually administered a regimen containing a PPI, amoxicillin, and clarithromycin for 10-14 d[297,298]. Sequential therapy begins with amoxicillin plus a PPI for the first five days and finishes with triple therapy including a PPI, clarithromycin, and tinidazole[299]. The Maastricht Conference Guidelines suggest selection of *H. pylori* treatment regimen without clarithromycin if the resistance rate exceeds 20%[279].

Antibiotic resistance

Resistance of *H. pylori* to commonly used antibiotics is on the rise worldwide. Overall, *H. pylori* resistance to metronidazole is prevalent, while resistance to amoxicillin and tetracycline are low; however the picture is far more complex at the regional level. For example, amoxicillin resistance is below 3% in America and Europe, but over 60% in Africa[300]. Africa also has the highest rates of resistance to metronidazole (92.4%) and tetracycline (43.9%)[300]. Metronidazole resistance is above 50% in much of the world but there are indications that metronidazole resistance may be dropping in northern Europe[301]. Within Europe, resistance patterns vary by country and even within a country. For example, the reported clarithromycin resistance rate is 1.5% in Sweden, but 7.5% in Germany and clarithromycin resistance in Italy is lower in the north than in the south[301]. Increasing resistance to clarithromycin and levofloxacin has been attributed to widespread use of these antibiotics for respiratory tract and urinary tract infections, respectively[300]. In the (*Helicobacter pylori* Antimicrobial Resistance Monitoring Program), a resistance pattern showed 29.1% of United States isolates were resistant to one antimicrobial agent and 5% were resistant to two or more antimicrobial agents[302]. Multidrug resistance remains low worldwide[300], offering hope that rescue therapy will work in most patients. Previous treatment for *H. pylori* is the single largest risk factor for drug resistance[302]. Success rates of antimicrobial therapy do not always mirror *in vitro* susceptibility data. This could be partially due to variability in antibiotic resistance testing

protocols and on poor patient compliance[301]. In summary, local antimicrobial resistance data should be consulted to increase the chances of eradication success following the first treatment.

Specific *H. pylori* mutations responsible for antibiotic resistance have been identified. Inactivation of the *rdxA* gene is well known to contribute to metronidazole resistance, though other mechanisms likely exist[303]. The point mutations A2143G, A2142G, and A2142C are responsible for clarithromycin resistance in *H. pylori*. Although the test is not yet available in the clinical setting, the A2143G mutation was associated with a lower eradication rate. In a clinical trial, sequential therapy was found to be more successful in eradication than triple therapy[300]. Certain *gyrA* mutations are associated with fluoroquinolone resistance[304]. For individuals who have failed eradication with the primary regimen, use of alternative antibiotics must be considered. In the future, it may be feasible to determine likely antimicrobial resistance patterns using *H. pylori* DNA isolated from stool without the need for endoscopy[305].

Recently, the concept of sequential therapy has been proposed with a 10-14 d regimen of a PPI twice daily and amoxicillin twice daily for five days, followed by a PPI plus clarithromycin and tinidazole twice daily[306]. Zullo *et al*[307] reported in a 2007 pooled-data analysis, an eradication rate greater than 90% with an intention to treat analysis thus revealing a higher eradication rate than standard therapy. A recent meta-analysis revealed an odds ratio (OR) for eradication of 2.99 (95%CI: 2.7-3.62), yielding a number needed to treat (NNT) of 6 in favor of sequential therapy compared to triple therapy. Additionally, the OR for eradication with sequential therapy compared with 10 d of triple therapy was 2.92 (95%CI: 1.95-4.38) with a NNT of 8 positive for sequential therapy. Factoring for clarithromycin resistance, the OR for eradication with sequential therapy was 10.21 (95%CI: 2.01-34.58) compared with triple therapy; however, the number of patients was small[299]. Another large meta-analysis found superiority compared to triple therapy with 93.5% eradication (95%CI: 91.3 to 95.5) compared to 76.9% (95%CI: 71.0-82.8) for standard triple therapy[308]. Sequential therapy appeared to be superior in subgroup analyses involving trial quality, smoking status, ulcer disease or non-ulcer dyspepsia, clarithromycin or imidazole resistance or both, duration of therapy and diagnostic method[308].

A novel regimen for treatment of *H. pylori* was proposed in an open label prospective trial of 653 patients using levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOAD) for 7 or 10 d compared to triple therapy with lansoprazole, amoxicillin, and clarithromycin (LAC). In this intention-to treat analysis, the rate of eradication for LOAD-7 d regimen was 90% and 88.9% for LOAD-10 d regimen and combination eradication rate of 89.4% *vs* 73.3% eradication rate with LAC. No adverse event differences were noted in the two groups[309]. The pill burden was limited to twice daily with both regimens, however, the current cost of the LOAD regimen, in particular nitazoxanide, may limit its widespread usage. Additionally, more comprehensive multi-center trials will be needed to confirm these results.

Salvage therapy

In a pooled analysis of several refereed studies and abstracts, retreatment with triple and quadruple therapies were found to achieve eradication rates in the range of 70%-76%. Additionally, the substitution of two antibiotics compared to one antibiotic in the re-treatment regimen was found to be superior for eradication[310]. Attempts should be made to avoid antibiotics previously utilized for *H. pylori* eradication. As clarithromycin is utilized for most triple therapy regimens, quadruple therapy is often utilized as the salvage therapy. A levofloxacin 500 mg daily, PPI, and amoxicillin 1 g twice daily regimen is suggested in the American College of Gastroenterology guidelines with an eradication rate possibly higher than quadruple therapy[278]. In a multicenter, prospective trial, rifabutin-based rescue therapy with amoxicillin and PPI for ten days after three previous treatment failures was found to have an approximate 50% eradication rate providing an additional strategy for refractory infections[311]. After the second attempt at treatment and confirmation of failure of eradication, antibiotic sensitivity testing should be implemented with tissue acquisition and culture for guidance in selecting the appropriate antimicrobial regimen.

Adjuvant therapy

A number of studies have investigated the roles of probiotics in improving eradication rates and decreasing antibiotic side effects, but there is not yet a consensus regarding their utility. A recent meta-analysis evaluating probiotics including both *Lactobacillus* and *Bifidobacterium* species reports increased eradication in adults, but no effect in children. Total side effects were decreased with the supplementation of probiotics. Individual side effects were not assessed in this meta-analysis; however, the effects of confounders could not be assessed due to the small trial sizes[312]. Another recent meta-analysis differentiated between studies using *Lactobacillus* alone *vs* combinations containing other genera[313]. They found that the eradication rates were raised significantly by 17% when *Lactobacillus* was used alone, compared with only 2.8% in patients treated with a combination of species. Contrary to the findings of the aforementioned study, they did not detect a reduction of overall side effects. Diarrhea may be reduced with the usage of *Saccharomyces boulardii,* but other adverse effects (epigastric pain, taste disturbances, nausea, and gas/bloating) were not affected. Trial numbers are limited with this organism[314]. A few trials have evaluated lactoferrin as adjuvant therapy. A meta-analysis in 2009 found benefit, but small sizes of the trials and lack of robust data necessitate additional clinical trials[315]. A recent study compared the effects of probiotics or a combination of probiotics and lactoferrin on eradication and severity of antibiotic-related side effects[316]. Neither

treatment improved eradication, but both reduced side effects and increased patient compliance. The addition of lactoferrin to probiotics did not confer any additional benefit compared to probiotics alone. In summary, there is some evidence that probiotics improve eradication rates, but evidence that probiotics can reduce the side effects of eradication therapy is not conclusive. Given the excellent safety profile of probiotics, it may be reasonable to suggest that patients eat yogurt or take an over-the-counter supplement containing *Lactobacillus* and/or other probiotic species.

Simvastatin as a supplement to clarithromycin, amoxicillin, and omeprazole has been shown to increase the eradication rate of *H. pylori* when used as an adjuvant in a randomized controlled trial. No differences were noted in compliance or side effects. The proposed mechanism for augmented eradication is the anti-inflammatory effects of Simvastatin, which are unrelated to its cholesterol-lowering activity (Nseir, 22646167). Further studies are needed for confirmation before advocating this strategy.

Special considerations

Generally, bismuth compounds, tetracycline, and flouroquinolones regimens should be avoided in pregnancy due to potential teratogenic effects. Metallic taste is a common side effect with metronidazole and clarithromycin. Photosensitivity with doxycycline and tetracycline is possible. Additionally, metronidazole may cause an adverse reaction with alcohol and with prolonged usage may create a peripheral neuropathy. Other less common side effects are noted with each of these medications.

Confirmation of eradication

Based on Maastricht Ⅳ/Florence Consensus Report, eradication of *H. pylori* should be confirmed with a urea breath test or a laboratory-based, validated monoclonal stool test 4 wk after the conclusion of treatment. In cases of a gastric ulcer or gastric MALT lymphoma, follow-up is suggested with an esophagogastroduodenoscopy and biopsy of gastric tissue[279]. The ACG Guidelines also suggests testing with individuals with persistent dyspepsia symptoms following resection with an early gastric cancer[278].

CONCLUSION

H. pylori has proven to be a more complex pathogen than early research indicated. Multiple surface carbohydrate structures, outer membrane proteins, and toxins interact to modify host cell signaling and the immune response. While CagA remains the dominant virulence factor, HP-NAP and others significantly alter host physiology. The reach of *H. pylori* extends beyond the stomach. *H. pylori* can occasionally colonize the mouth, nose, ears, and skin. Whether *H. pylori* is a primary cause of disease in these locations or colonizes only after other agents initiate disease remains to be determined. *H. pylori* causes or is suspected to cause several autoimmune diseases. It is not known whether *H. pylori* must be present outside the stomach to initiate autoimmune disease. As of yet, routine testing for *H. pylori* is recommended only for patients with gastric symptoms, iron deficiency anemia, and idiopathic thrombocytopenic purpura. Recommendations will likely change as more is learned about *H. pylori*'s potential to cause other diseases. In addition to the urea breath test, the fecal antigen test has proven reliable and useful for detecting current *H. pylori* infection. The fecal antigen test does not require specialized equipment. Increasing antibiotic resistance is reducing the utility of metronidazole and clarithromycin, necessitating the use of alternative treatment regimens. Sequential therapy has proven to be a more effective than standard triple therapy for eradication of *H. pylori*. Thirty years after its discovery, *H. pylori* remains an enigmatic pathogen with many secrets yet to be revealed.

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