Biomedicine and Chemical Sciences 1(4) (2022) 278-288

37-BCS-1137-289

Content lists available at:
https://journals.irapa.org/index.php/BCS/issue/view/15

Biomedicine and Chemical Sciences

Journal homepage: https://journals.irapa.org/index.php/BCS

Helicobacter Pylori, Infection, Virulence Factors and Treatment: A Review

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ARTICLE INFO

Article history:
Received on: August 09, 2022
Revised on: August 20, 2022
Accepted on: August 23, 2022
Published on: October 01, 2022

Keywords:
Helicobacter Pylori
Infection
Virulence Factors and Treatment

ABSTRACT

Gastric and ulcer peptic disease is a common disease in the community. Considering the close relationship between peptic ulcer and gastritis caused by *Helicobacter pylori*. The prevalence of *H. pylori* increased markedly with age with the maximum colonization (81.5%) occurring in adults (40-60 years). *H. pylori* are bacteria that can cause an infection in the stomach or duodenum (first part of the small intestine). It is the most common cause of peptic ulcer disease. *H. pylori* can also inflame and irritate the stomach lining (gastritis). Untreated, long-term *H. pylori* infection can lead to stomach cancer (rarely). *H. pylori* multiply in the mucus layer of the stomach lining and duodenum. The bacteria secrete an enzyme called urease that converts urea to ammonia. This ammonia protects the bacteria from stomach acid. As *H. pylori* multiply, it eats into stomach tissue, which leads to gastritis and/or gastric ulcer. Symptoms include dull or burning stomach pain, unplanned weight loss and bloody vomit. *H-pylori*-caused ulcers are commonly treated with combinations of antibiotics. Usually two antibiotics are prescribed. Among the common choices are amoxicillin, clarithromycin (Biaxin®), metronidazole (Flagyl®) and tetracycline and Proton pump inhibitor: Commonly used proton pump inhibitors include lansoprazole (Prevacid®), omeprazole (Prilosec®), pantoprazole (Protonix®), rabeprazole (Aciphex®) or esomeprazole (Nexium®) and Bismuth subsalicylate: Sometimes this drug (eg, Pepto-Bismol®) is added to the antibiotics plus proton pump inhibitor combinations mentioned above. This drug protects the stomach lining. Combination treatment is usually taken for 14 days. One newer medication, Talicia®, combines two antibiotics (rifabutin and amoxicillin) with a proton pump inhibitor (omeprazole) into a single capsule.

1. Introduction

Helicobacter is a Gram-negative bacteria possessing a characteristic helical shape. They were initially considered to be members of the genus *Campylobacter*, but in 1989, Goodwin et al. published sufficient reasons to justify the new genus name *Helicobacter*. The genus *Helicobacter* contains about 35 species (Goodwin et al., 1989). Al-Baldawi (1997) was the first who isolate this bacterium. *H. pylori* in Iraq infects the stomachs of more than 50% of the world's population and has lived in such close association with modern humans since they migrated from East Africa more than 58,000 years ago (Linz et al., 2007).

Before the discovery of *H. pylori* in the early 1980s, stomach disorders such as gastritis and peptic ulcers were ascribed to bad diet, too much coffee, or a stressful lifestyle. The disorders were treated accordingly with drugs such as antacids and proton pump inhibitors to reduce the acidity of the stomach and thus eliminate the symptoms. Bacteria were seen in the stomach as early as 1874, but these findings were ignored because nothing was believed to survive the acidic environment in the stomach. In the early 1980s, *H. pylori* was isolated from the antrum of patients with gastritis and ulcer disease, and later experiments fulfilled Kosh's postulates and, importantly, antibiotic treatments got rid of the infection and the inflammation

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How to cite:

Haamadi, A. . A., Risan, M. H. ., & Almaali, H. M. A. (2022). Helicobacter Pylori, Infection, Virulence Factors and Treatment: A Review. *Biomedicine and Chemical Sciences, 1*(4), 278-288.

DOI: https://doi.org/10.48112/bcs.v1i4.289

dissapeared (Marshall & Warren, 1984). For this finding, Marshall and Warren were awarded with the Nobel Prize in Medicine and physiology in 2005. Hence, *H. pylori* was confirmed as the cause of gastritis and the more serious peptic ulcer diseases. In epidemiological studies, *H. pylori* infection was also found to correlate with gastric cancer, i.e. *H. pylori* is considered as an onco-pathogen. In 1994, the World Health Organization listed *H. pylori* infection as a carcinogen (IARC, 1994). The understanding that *H. pylori* infection is the causative agent of overt gastric disease opened a paradigm shift that has completely changed the treatment of stomach disorders, which are now considered as infectious diseases (Cellini et al., 2004).

2. Microbiological Characteristics of *H. pylori*

H. pylori is a slow-growing, microaerophilic, spiral shaped multi flagellated (Lophotrichus flagella) and gram-negative bacterium, about 3 micrometers long with a diameter of about 0.5 micrometers, whose surface is coated with 12–15 nm ring-shaped aggregates of urease and heat shock protein (Figure 1).

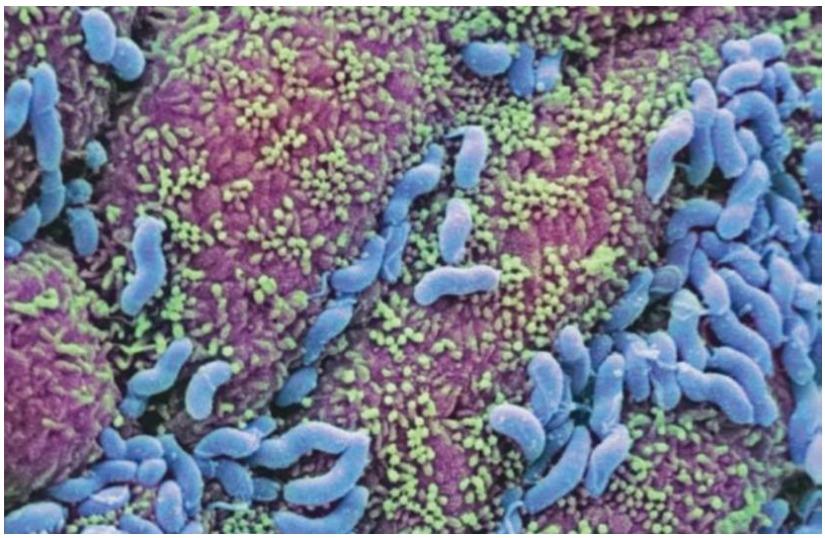

Fig. 1. Scanning electron micrograph images of *H. pylori* bacteria (in blue) (Abo Almaali, 2014).

The urease enzyme and the heat shock protein B are located almost exclusively within the cytoplasm in the fresh log-phase cultures of *H. pylori*. In subcultures, urease and heat shock protein B become associated with the bacterial surface, suggesting bacterial autolysis leading to release of protein and adsorption into the bacterial surface (Mégraud & Lehours, 2007).

Some of the lipopolysaccharide of the organism mimics the Lewis blood group antigens in structure. This molecular mimicry also helps in the continued existence of *H. pylori* in the unfavorable gastric environment. This bacterium colonizes gastric mucosa and elicits both inflammatory and immune lifelong responses, with release of various bacterial and host dependent cytotoxic substances (Figure 2). Under unfavorable circumstances it can become coccoidal, a non-culturable form with debatable viability. The bacterium is a microaerophilic and capnophilic organism, slowly growing with rigorous culture demands (Mégraud & Lehours, 2007).

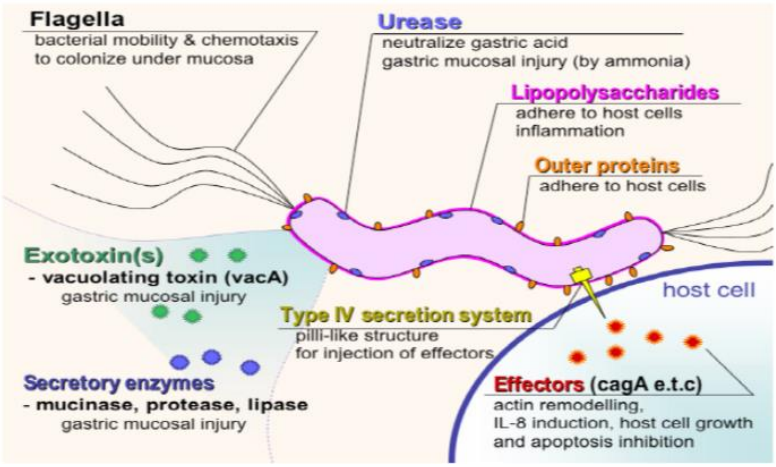

Fig. 2. Component of *H. pylori* with biological activities (Henriksson *et al.*, 2012)

3. Infection and Colonization of the Stomach

H. pylori colonizes the stomach and, in particular, the less acidic antrum (Figure 3). During disease progression, pH initially decreases due to hyper secretion and *H. pylori* might move into the first parts of the intestine, the duodenum. This region is less resistant to infection and peptic ulcer could develop. Long-term hyper secretion can cause atrophic gastritis to the mucosa and even loss of the acid producing parietal cells and higher stomach pH. Atrophy can also result in a gastric ulcer formation, which is sometimes a precursor to gastric cancer (Hidaka et al., 2001). Within the mucus layer, *H. pylori* is mainly confined to the 100 µm of mucus closest to the epithelial cells where pH is more neutral.

Thirty percent are found within the first 5 µm and around 20% are found tightly attached to the cells (Hessey et al., 1990; Schreiber et al., 2004). The colonization of *H. pylori* is restricted to the superficial epithelial cells, colocalizing with the expression of the mucin MUC5AC (Hidaka et al., 2001). The strict colonization of the superficial zone might relate to the glandular mucin MUC6 that possesses terminal α1,4-GlcNAc. This structure inhibits cell wall synthesis in *H. pylori* thereby making these glandular regions toxic to *H. pylori* (Kawakubo et al., 2004). In addition to the extracellular habitat, *H. pylori* has also been found between cells, deeper in the tissue, and in intracellular vesicles of both cultured gastric epithelial cells and in gastric biopsies as in figure (3) (Aspholm et al., 2006; Necchi et al., 2007). These invasive bacterial cells can repopulate the extracellular environment suggesting that the intracellular lifestyle might be a way for *H. pylori* to escape the immune system as well as antibiotic treatment (Dubois & Borén, 2007).

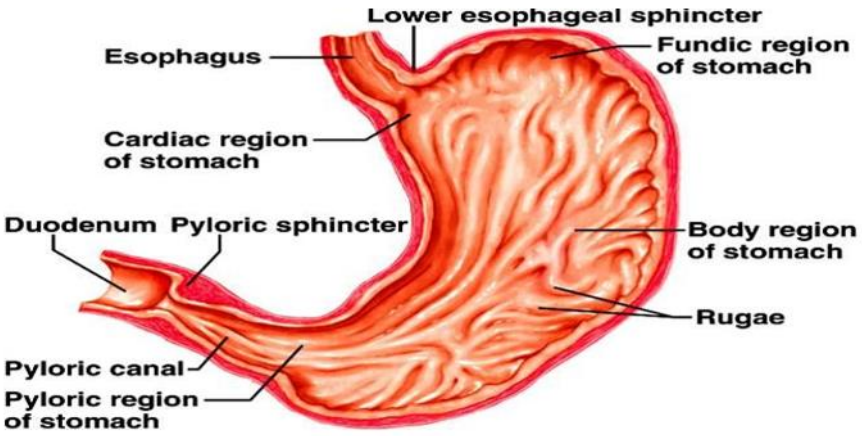

Fig. 3. Simplified anatomical illustration of the stomach (Henriksson et al., 2012).

4. Transmission of *Helicobacter pylori*

H. pylori has a narrow host range and is found almost exclusively in human and some nonhuman primates. Despite hostile, the human stomach is the only identified reservoir for *H. pylori*. Although extensively studied, efforts to confirm the exact route of transmission have been disappointing. It has been speculated that the person-to-person spread currently appeared to be the most likely mode of transmission, especially between family members (Kivi et al., 2005; Weyermann et al., 2006). Hence, the possible routes are fecal–oral, oral– oral and gastro–oral.

5. Clinical Features

Chronic *H. pylori* –associated gastritis such is asymptomatic but the initial acquisition of the infection cause acute gastritis with hypochlorhydria which may cause abdominal pain, nausea and vomiting that resolve within a few days. Uncomplicated peptic ulcers typically cause epigastric pain and less commonly, nausea, vomiting and weight loss, whereas some ulcers (particularly NSAID ulcers) are asymptomatic. The classically described pain of duodenal ulcer is felt as a growing or burning sensation, often with a relation to meals; occurring 1-3 hours after meals and /or at night and relieved by food.

Gastric ulcer pain is instead often precipitated by food. However, symptoms are actually very poorly discriminatory for ulceration site and even for whether or not an ulcer is present. Examination usually reveals epigastric tenderness but may be normal (Parsonnet et al., 1999).

6. Virulence Factors of *Helicobacter pylori*

The outcome of a bacterial infection is highly dependent on the prevalence and status of its virulence factors. The genetic diversity and variability of *H. pylori* is mirrored in the wide range of virulence factors that vary by disease, age, country and ethnicity. To be defined as an *H. pylori* virulence factors, the protein must be correlated with disease both *in vitro* and *in vivo* and with epidemiological disease patterns (Lu et al., 2005). Three main virulence factors of *H. pylori* are the cytotoxin-associated gene pathogenicity island (*cagPAI*), the vacuolating cytotoxin (*VacA*), and the outer membrane proteins (OMPs). Many of the OMPs are proposed to be involved in disease-associated mechanisms such as adherence and manipulation of the immune response. *VacA* and *CagA* are, together with *BabA* genes, associated with the more severe cases of gastric disease (Aljeboury et al., 2020; Haamadi et al., 2021b).

6.1. *CagPAI* Gene

The *cagPAI* is a pathogenicity island in the *H. pylori* genome and encodes numerous genes that, upon cell contact, are expressed and assembled into the needle-like type 4 secretion system (T4SS) (Rohde et al., 2003). The T4SS is evolutionarily conserved among many Gram-negatives such as *Agrobacterium*, *Bordetella*, and *Legionella*, but differs in different organisms in terms of what substrates are transferred. *H. pylori* T4SS binds the integrin β1 receptor that is located on the basal membrane and transfers the cytotoxin associated gene A (*CagA*) which is also encoded by the *cag*PAI (Kwok et al., 2007; Jiménez-Soto et al., 2009). Once inside the cell, *CagA* is phosphorylated on specific EPIYA motifs by host kinases, and phosphorylated *CagA* goes on to manipulate the cell by interacting witnumerous host cell proteins. In addition, injected non-phosphorylated *CagA* manipulates proliferation and immune response of host cells. Cultured epithelial cells respond by forming the characteristic "hummingbird phenotype" that is the effect of both cell scattering and elongation (Tegtmeyer et al., 2011). *CagA* is not considered as a virulence factor only, but it is considered an oncoprotein and is associated with development of gastric adenocarcinoma. *H. pylori* infections of Mongolian gerbils resulted in more gastric adenocarcinomas in a *CagA*-dependent manner and so did mice that were transgenic for *CagA* expression (Ohnishi et al., 2008).

6.2. *VacA* Gene

Vacuolating cytotoxin A (*VacA*) is a multifunctional secreted cytotoxin. The *vacA* gene is found in all *H. pylori* isolates though there are differences among the alleles. The s1 allele, especially in combination with the m1 allele, is highly associated with the risk of developing peptic ulcers and gastric cancer (Palframan et al., 2012). The *VacA* toxin forms large vacuoles in gastric cells; however, such vacuoles are not seen in biopsies. *VacA* localizes to, and exerts effects on, the mitochondria where it triggers the apoptotic cascade and induces cell death by mitochondrial fission. The detailed molecular mechanisms for this, however, are not known (Palframan et al., 2012). In addition, *VacA* has been found to bind the integrin subunit CD18 on T-cells and suppressing their activities (Jain et al., 2011).

6.3. *BabA* Gene

The Blood group Antigen Binding Adhesin, *BabA*, mediates binding to the ABO/Leb blood group antigens. The first hint of the existence of an adhesion was provided by application of FITC-labeled *H. pylori* to paraffin-embedded tissue sections of human gastric mucosa and observed adherence to the foveola epithelial cells (Falk et al., 1993). Inhibition with various substrates such as human colostrum from secretors and non-secretors, antibodies, and glycoconjugates identified the receptor as the H1 and Lewis b (Leb) blood group antigens (Borén et al., 1993). H1/Leb is a terminal carbohydrate structure that defines blood group O. It is found on red blood cells and on gastro-intestinal (GI) epithelial linings such as in the stomach. Related to H1 and Leb structures are the A and B blood group antigens, but neither of these structures were identified receptors, nor did *H. pylori* bind the related Lea structure, demonstrating specificity for a fucose moiety (Borén et al., 1993). The cognate adhesin, Blood group Antigen Binding Adhesin (*BabA*), was identified by use of the re-tagging technique (Ilver et al., 1998). This technique utilizes a cross-linker attached to the receptor glycoconjugate.

Binding of this receptor exposes the adhesin for cross-linking and enables detection by streptavidin-biotin via SDS-PAGE and mass spectrometry to identify the cognate adhesin. The strain used in these studies, CCUG17875, was found to contain two *BabA* alleles of which one is silent due to defects in the translational sequence and signal peptide (Ilver et al., 1998; Bäckström et al., 2004). This allele was called *BabA1* and the allele encoding a functional *BabA* protein was called *BabA2*. Deletion of *BabA2* confirmed that the *BabA* protein is the functional adhesin for binding to H1/Leb. During these studies, another gene was identified and called *BabB*. It was homologous to *BabA* at the 3' and 5' ends but divergent in the middle (Ilver et al., 1998).

Both of these proteins were later classified as belonging to the Hop family of OMPs (Alm et al., 2000). H1 and Leb were identified as receptor structures for *BabA*, whereas ALeb and BLeb did not demonstrate any binding to the Peruvian isolate that was used in the original studies. When Aspholm-Hurtig *et al.* investigated the worldwide receptor specificity for *BabA*, they identified strains that, in addition to Leb/H1, could also bind the ALeb and Bleb structures. These strains were termed 'generalists' while those that were restricted to Leb/H1 were termed 'specialists' (Aspholm, et al., 2006).

Interestingly, the specialist strains originated from parts of the world, such as South America, where O group is the predominant blood group. The affinity of *BabA* for its receptors is high, with values in the μM to nM range, though they vary substantially between clinical isolates (Aspholm et al., 2006). In addition, the affinity for H1/Leb is stronger than for ALeb or BLeb, and this could explain the higher risk of peptic ulcer disease in blood group O individuals (Aspholm et al., 2006; Anstee, 2010). In addition to the *BabA*-mediated attachment to the epithelial cells, *BabA* also interacts with the mucins MUC5AC and MUC1 (Figure 4).

Clinical isolates have exceedingly diverse *BabA* sequences, with the highest variability in the middle domain. In addition, not all strains express *BabA*, and not all expressed *BabA* proteins are functional (Kawai et al., 2011). Thus, presence of a *babA* gene is not necessarily evidence of a functional *BabA* protein. The mechanism by which this diversity is obtained is not known. The phylogenetic analyses of the *BabA* variable region in different populations reveal heterogeneous selective pressures, such as escape from host immune response, receptor specificity, and affinity, that act on the protein (Aspholm, et al., 2006).

During *H. pylori* infection studies in Rhesus macaques, mice, and gerbils, expression of *BabA* was frequently lost (Styer et al., 2010; Ohno et al., 2011). The loss of *BabA* in Rhesus macaques might be because of a higher inflammatory response to *BabA*-expressing adherent bacterial cells. However, it could also be because of the lower prevalence of the ABO/Leb blood group antigens in gastric mucosa during infection and hence selection against *BabA*-expression (Lindén et al., 2008).

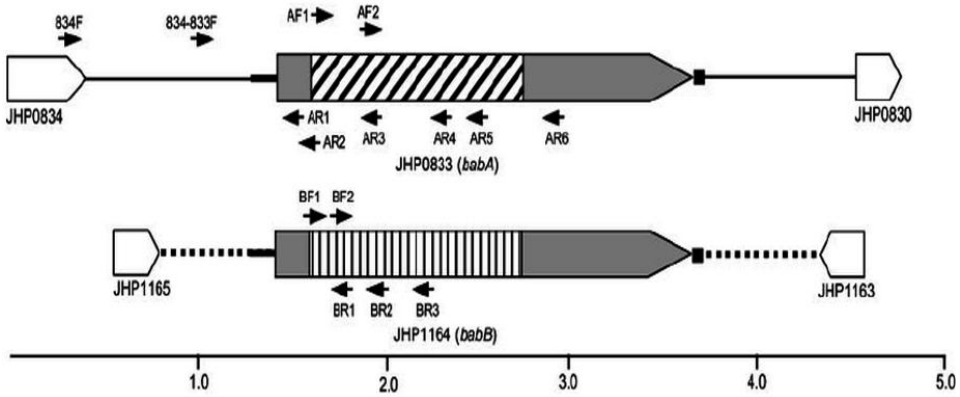

Fig. 4. Represented Bab gene of *H. pylori* (Henriksson et al., 2012)

6.4. *BabA, BabB,* and *BabC* Genes Recombination

Phylogenetic analysis of the OMP C-terminal regions reveals a close genetic relationship between *BabA*, *BabB*, and *BabC* where *BabA* and *BabC* are most similar. Despite this similarity, only *BabA* has been assigned a function (Alm et al., 2000). *BabA* and *BabB* are most prevalent, and *BabC* is less and was recently associated with strains of European origin (Kawai et al., 2011). The three alleles are commonly found at three different loci, A, B, or C, that are in each third of the genome. The existence of three similar OMPs suggested that *H. pylori* utilizes them to switch antigenic appearance to avoid the immune response (Lindén et al., 2008). Indeed, after the first genome comparison between strains 26695 and J99, it was clear that *BabA* and *BabB* were found at inverted loci. In addition, 26695 have the *BabC* gene at the C locus, which J99 is missing (Alm et al., 1999). Comparisons of clinical isolates demonstrated that these alleles frequently recombine and switch loci to form duplicates, deletions, and chimeric genes at a frequency of about 3 × 10-6 gene conversions per cell division (Hennig et al., 2006; Amundsen et al., 2008).

Interestingly, the C-terminal regions of *BabA* and *BabB* are more homologous within a genome/strain than between genomes/strains, and this suggests a concerted evolution between *BabA* and *BabB* (Pride & Blaser, 2002). No such analysis has been done for *BabC*, but the close relationship between these genes suggests similar results. The Leb-binding function of *BabA* is not affected by the loci from which it is expressed (Hennig et al., 2006). However, expression of *BabA* from the B or C loci could result in a gain of function because *BabA* could then make use of their CT-repeats for faster switching of expression (Bäckström et al., 2004; Colbeck et al., 2006).

The recombination frequency is very high, and a seemingly homogeneous population from a single clone can retain a subpopulation of single clones that demonstrate an altered arrangement of the *Bab* genes caused by recombination (Colbeck et al., 2006). Such rearrangements can also revive lost *BabA* expression demonstrating that loss of a functional *BabA* is reversible (Bäckström et al., 2004). Recombination is also seen during experimental infections, such as in the Rhesus macaque model, where the expression of *BabA* is sometimes switched off by *BabA-BabB* recombination.

6.5. *BabA* Gene and Pathogenesis

The pathogenic importance of an ABO/Leb-mediated attachment by *BabA* was demonstrated in *H. pylori*-infected, Leb-transgenic mice that had higher inflammatory scores compared to their non-transgenic littermates (Falk et al., 1993). This study was later confirmed in Mongolian gerbils where the animals infected with a *BabA* mutant had lower infiltration of inflammatory cells and a reduced cytokine response (Sugimoto et al., 2011). In 1999, Gerhard et al., (1999) updated the old Type 1 (*CagA*+, *VacA*+) and Type 2 (*CagA*-, *VacA*-) classifications of *H. pylori* by adding a third denominator, *BabA2* (Gerhard et al., 1999). Genotypic studies demonstrated that *BabA2* was correlated with *cagA* and the more pathogenic *vacAs1* allele and was significantly associated with adenocarcinoma and better discriminated against gastritis compared to the conventional Type 1 vs. 2 definition. These results indicated that *BabA* expression has an important role in the disease process, and these strains were termed 'triple-positive strains' (Ishijima et al., 2011). Many groups tried to repeat the task of correlating *babA2* with gastric disease but obtained inconclusive results (Yamaoka, 2008). Because the prevalence of *BabA2* is not equivalent to expression of *BabA*, additional studies have investigated the correlation with *BabA* expression. Such studies demonstrated a correlation between *BabA,CagA*, and *VacA*, and also to more severe gastric disease such as intestinal metaplasia (Azevedo et al., 2008; Yamaoka, 2008; Odenbreit et al., 2009). Interestingly, Fujimoto et al. (2007) demonstrated a stronger correlation with duodenal ulcer and gastric cancer for strains with low levels of *BabA* expression than for those with high or no expression (Fujimoto et al., 2007).

Evidence for the functional correlation between *BabA, CagA*, and *VacA* is now being elucidated. Adherent *H. pylori* are frequently found associated with the intercellular junctions where they would have immediate access for penetration of the mucosa. Such tight adherence, mediated by *BabA* (or other adhesins), simplifies the secretion and delivery of *VacA* to host cells that could trigger separation of the cellular junctions and facilitate penetration of *H. pylori* through the intercellular space. On the basal side, these bacteria have access to the T4SS integrin β1 receptor that is located where the bacteria can deliver *CagA* (Wessler & Backert, 2008). Indeed, *CagA*-positive bacteria are found more tightly associated with epithelial cells during infection. This hypothesis has recently been supported by Ishijima *et al.* who demonstrated that the *BabA*-Leb interaction increases T4SS-mediated induction of mRNAs for pro-

inflammatory cytokines and precancerous factors in cell cultures, and stimulates intracellular levels of phosphorylated CagA (Ishijima et al., 2011). *BabA*, *SabA*, and *CagA* have also recently been demonstrated to share regulatory mechanism upon interaction with mucins (Skoog et al., 2012).

Although not all studies were able to demonstrate a correlation between *BabA, CagA*, and *VacA* in disease progression, there is a strong indication that *BabA* itself can cause damage to the epithelial cells. A recent finding has suggested that *BabA* is involved in induction of double-strand breaks and such grave DNA damage could tilt the disease state towards more aggressive pathogenesis (Toller et al., 2011). However, it is difficult to determine if these effects are mediated by a direct binding to the receptor, or are secondary and caused by the tighter association with host cells.

6.6. *SabA* Gene

SabA, the Sialic-acid binding adhesin, was discovered some years after *BabA*. Mahdavi et al., (2002) observed adherence of the CCUG17875 *babA2* mutant to human gastric mucosa from a gastritis patient. The receptor was characterized to be sialyl-dimeric-Lewis x antigen (sdiLex), but more detailed analysis of the binding specificity has identified the minimal binding epitope to be NeuAcα2-3Gal with a polymorphism for the core chain (Mahdavi et al., 2002; Aspholm et al., 2006).

Such sialylated antigens are expressed by inflamed tissues to recruit neutrophils and are, therefore, triggered by *H. pylori* infection. *SabA* expression is highly variable with both a PolyT tract in the promoter and CT-repeats in the coding region, and it has also recently been shown to be controlled by the acid-responsive *ArsRS* two component system that also regulates urease and carbonic anhydrase (Goodwin et al., 2008). Similarly to the recombination between *babA* and its related alleles, *sabA* can also recombine with its related allele *sabB,* and to some extent with *hopQ* (Talarico et al., 2012). This occurs at a frequency of 1.4 × 10 9 bp conversions per cell generation, which is lower than that seen for *babA* and *babB* recombination.

7. Treatment of *H. pylori* Infection

The goal of *H. pylori* treatment is the complete elimination of the organism. Once this has been achieved, reinfection rates are low; thus, the benefit of treatment is durable. Clinically relevant *H. pylori*–eradication regimens must have cure rates of at least 80 percent (according to intention-to-treat analysis) without major side effects and with minimal induction of bacterial resistance. Such goals have not been achieved with antibiotics alone. Because luminal acidity influences the effectiveness of some antimicrobial agents that are active against *H. pylori,* antibiotics are combined with proton-pump inhibitors or ranitidine bismuth citrate (Mégraud & Lehours, 2007). So-called triple therapies, combinations of one anti secretory agent with two antimicrobial agents for 7 to 14 days, have been extensively evaluated, and several regimens have been approved by the Food and Drug Administration (FDA) (Table 1).

The combination of two or more antimicrobial agents increases rates of cure and reduces the risk of selecting for resistant *H. pylori.* The chief antimicrobial agents used in these regimens are amoxicillin, clarithromycin, metronidazole, tetracycline, and bismuth. Primary resistance to amoxicillin and tetracycline remains uncommon, but the frequency of clarithromycin resistance is now around 10 percent in most European countries and the United States and even higher in Japan (Meyer et al., 2002). Metronidazole resistance ranges between 20 percent and 30 percent and is more frequent among women and among both men and women in the developing countries, because of the frequent use of nitroimidazoles to treat other diseases (Meyer et al., 2002). Resistance of *H. pylori* to macrolides is caused by point mutations in the 23S ribosomal RNA genes. Resistance to metronidazole is caused primarily by mutations in nitroreductase genes (*rdxA* and *frxA*) that interfere with the intracellular activation of nitroimidazoles (Mégraud & Lehours, 2007).

8. First-line Therapies

8.1. Proton-Pump-Inhibitor–Based Triple Therapies

Following the success of initial trials of proton pump-inhibitor–based triple therapy in Italy and France, large, randomized trials confirmed the effectiveness of treatment twice daily for seven days with 20 mg of omeprazole, given either with 1 g of amoxicillin and 500 mg of clarithromycin, or with 400 mg of metronidazole and 250 mg of clarithromycin (Lind, et al., 2006; Zanten, 2009). Several comparative trials have demonstrated the equivalence of 30 mg of lansoprazole twice daily, 40 mg of pantoprazole twice daily, 20 mg of rabeprazole daily, and 20 mg of esomeprazole twice daily with omeprazole in these triple therapies, in a meta-analysis of 666 studies that included 53,228 patients, combinations of a proton-pump inhibitor, clarithromycin, and a nitroimidazole; a proton- pump inhibitor, clarithromycin, and amoxicillin; and a proton-pump inhibitor, amoxicillin. It is indicated for patients who are either allergic to or intolerant of clarithromycin or for infections with known or suspected resistance to clarithromycin. Although it is not approved by the FDA for this indication, amoxicillin has been substituted for tetracycline in patients for whom tetracycline is not recommended (Laine, et al., 2000; Misiewicz, et al., 2007).

Table 1
Food and Drug Admostration - Approved treatment option for *H. pylori* eradication (Sebastian, and Pierre, 2002)

Therapy	Dose	Duration
Omeprazole	40 mg	daily
clarithromycin	500 mg daily	three times
and amoxicillin	1g	twice daily for 10 days
Omeprazole	20 mg	daily
clarithromycin	500 mg daily	three times
and amoxicillin	1g	twice daily for 10 days
Lansoprazole	30 mg	twice daily
Clarithromycin	500 mg daily	three times
Amoxicillin	1g	twice daily for 10 days
Lansoprazole	30 mg	twice daily
Clarithromycin	500 mg daily	three times
Amoxicillin	1g	twice daily for 2 week
Lansoprazole	30 mg	twice daily
Amoxicillin	1g	twice daily for 2 week
Esomeprazole	40 mg	daily
Clarithromycin	500 mg	twice daily
Amoxicillin	1 g	twice daily for 10 days
Ranitidine bismuth citrate clarithromycin	400 mg	twice daily
	500 mg	three times daily for 2 weeks
Ranitidine bismuth citrate clarithromycin	400 mg	twice daily
	500 mg	twice daily for 2 weeks
Bismuth	525 mg	four times daily
subsalicylate metronidazole tetracycline	250 mg	four times daily
	500 mg	four times daily for 2 weeks

In another pooled analysis, no effect of larger doses of proton-pump inhibitors was observed among the triple therapies. The duration of therapy remains controversial. In Europe, 7-day treatment is recommended, (Dore, 2000; Haamadi et al., 2021a).) Whereas in the United States, 14-day courses have been found to be better than shorter courses and are approved by the FDA. In a recent meta-analysis, 14-day treatment achieved rates of cure 7 to 9 percentage points better than 7-day treatment. Primary resistance to clarithromycin and metronidazole decreases the rates of cure by 50 percent and 37 percent, respectively. The indication for therapy, bacterial factors, patient compliance, and geographic differences can further affect rates of cure (Lee, et al., 2008).

8.2. Ranitidine Bismuth Citrate–Based Therapies

Ranitidine bismuth citrate in dual therapy with clarithromycin for two weeks has been approved by the FDA (Peterson, et al., 2006). Meta-analyses suggest that ranitidine bismuth citrate, with clarithromycin and amoxicillin, or with clarithromycin and a nitroimidazole, performs as well as corresponding proton-pump-inhibitor–based therapies (Rossum, 1999). Ranitidine bismuth citrate–based regimens may be less influenced by antibiotic resistance than their proton-pump-inhibitor–based counterparts (Beek & Craen, 1999). No ranitidine bismuth citrate–based triple therapy has been approved by the FDA.

8.3. Bismuth-Based Triple Therapies

Bismuth in association with metronidazole and tetracycline compares well in meta-analyses with therapies based on proton-pump inhibitors or ranitidine bismuth citrate, even if the duration of treatment is reduced to seven days. This inexpensive regimen remains an important option. Metronidazole resistance negatively affects efficacy. Furazolidone, a nitrofuran derivative, has also been proposed for use in bismuth-based triple therapies. Triple therapy for two weeks, consisting of 100 mg of furazolidone four times daily, amoxicillin, and bismuth, was successful in 86 percent of cases. However, furazolidone, particularly when combined with bismuth for two weeks, is associated with substantial side effects. Standard bismuth-based therapy and its furazolidone-containing alternatives were recommended at the 1999 Latin American Consensus Conference (Coelho, León-Barúa, & Quigley, 2000).

Three regimens were recommended in 1998 by U.S. Consensus Conference76: a proton-pump inhibitor, clarithromycin, and either amoxicillin or metronidazole for two weeks; ranitidine bismuth citrate,clarithromycin, and amoxicillin, metronidazole, or tetracycline for two weeks; and a proton-pump inhibitor, bismuth, metronidazole, and tetracycline for one to two weeks. The regimens recommended by the European Maastricht 2 conference are a proton pump inhibitor (or ranitidine bismuth citrate), clarithromycin, and amoxicillin or metronidazole for seven days. Because there are insufficient data for the pediatric age group, no treatment regimen for children infected with *H. pylori* was recommended by the European Paediatric Task Force.

9. Second-line Therapies

Eradication is more difficult when a first treatment attempt has failed, usually because of either poor patient compliance or the development of antibiotic resistance. Therefore, a 10 to 14-day treatment course is advocated for second-line therapies. However, the optimal strategy for retreatment after the failure of eradication has not yet been established. Because the failure of therapy is often associated with secondary antibiotic resistance, retreatment should ideally be guided by data on susceptibility (Hojo, et al., 2001).

However, such information is often unavailable, so quadruple therapies, in which a proton-pump inhibitor or an H2-receptor antagonist is added to a bismuth-based triple regimen with a high-dose metronidazole, have been suggested an optimal second-line therapy. According to a recent meta-analysis, the pooled eradication rate in 30 trials in which this strategy was tested, was 76 percent. This second-line therapy was recommended at major consensus conferences, (Lam & Talley, 1998; Bazzoli, 2001). Although it may prove disappointing, given the failure of regimens containing metronidazole (Hojo, et al., 2001). Another approach for retreatment without susceptibility testing is to prescribe a second course of proton- pump- inhibitor–based triple therapy, avoiding antimicrobial agents against which prior therapy may have induced resistance and avoiding less effective combinations, such as amoxicillin and tetracycline.

If a clarithromycin-based regimen is used first, a metronidazole- based regimen should be used afterward, or vice versa. This concept is supported by pooled analysis (Hojo, et al., 2001). Nevertheless, prospective studies of

consecutive combinations of triple therapies are needed. Alternative approaches to second-line proton-pump-inhibitor– based therapies have been reported recently, but mostly in abstract form. Rifabutin, given in association with amoxicillin and pantoprazole for 10 days, achieved an 86 percent rate of cure, even in patients with resistant strains (Perri et al., 2001a). In a pooled analysis of nine studies, retreatment with ranitidine bismuth citrate–based triple therapy yielded an 80 percent rate of cure (Coelho et al., 2000). Similar to the rates with quadruple therapies, and in a recent randomized trial, ranitidine bismuth citrate, clarithromycin, and tinidazole achieved an 81 percent rate of cure after the failure of triple therapies based on proton pump inhibitors (Perri et al., 2001b). In locations where ranitidine bismuth citrate is available, triple therapies based on this compound can be used for second-line treatment.

10. Conclusions

Helicobacter pylori are bacteria that can cause an infection in the stomach or duodenum. It is the most common cause of peptic ulcer disease. *H. pylori* can also inflame and irritate the stomach lining (gastritis). Untreated, long-term *H. pylori* infection can lead to stomach cancer (rarely). *H. pylori* multiply in the mucus layer of the stomach lining and duodenum. The bacteria secrete an enzyme called urease that converts urea to ammonia. This ammonia protects the bacteria from stomach acid. As *H. pylori* multiply, it eats into stomach tissue, which leads to gastritis and/or gastric ulcer. Symptoms include dull or burning stomach pain, unplanned weight loss and bloody vomit. *H-pylori*-caused ulcers are commonly treated with combinations of antibiotics.

Competing Interests

The authors have declared that no competing interests exist.

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