Published in final edited form as:

Helicobacter. 2015 August ; 20(4): 239–251. doi:10.1111/hel.12200.

Helicobacter pylori Eradication in Patients with Immune Thrombocytopenic Purpura: A Review and the Role of Biogeography

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Abstract

Idiopathic thrombocytopenic purpura (ITP) is typically a diagnosis of exclusion, assigned by clinicians after ruling out other identifiable etiologies. Since a report by *Gasbarrini* et al. in 1998, an accumulating body of evidence has proposed a pathophysiological link between ITP and chronic *Helicobacter pylori* (*H. pylori*) infection. Clinical reports have described a spontaneous resolution of ITP symptoms in about 50% of chronic ITP patients following empirical treatment of *H. pylori* infection, but response appears to be geography dependent. Studies have also documented that ITP patients in East Asian countries are more likely to express positive antibody titers against *H. pylori*-specific cytotoxic-associated gene A (CagA), a virulence factor that is associated with an increased risk for gastric diseases including carcinoma. While a definitive mechanism by which *H. pylori* may induce thrombocytopenia remains elusive, proposed pathways include molecular mimicry of CagA by host autoantibodies against platelet surface glycoproteins, as well as perturbations in the phagocytic activity of monocytes. Traditional treatments of ITP have been largely empirical, involving the use of immunosuppressive agents and immunoglobulin therapy. However, based on the findings of clinical reports emerging over the past 20 years, health organizations around the world increasingly suggest the detection and eradication of *H. pylori* as a treatment for ITP. Elucidating the exact molecular mechanisms of platelet activation in *H. pylori*-positive ITP patients, while considering biogeographical differences in response rates, could offer insight into how best to use clinical *H. pylori* eradication to treat ITP, but will require well-designed studies to confirm the suggested causative relationship between bacterial infection and an autoimmune disease state.

Keywords

Helicobacter; thrombocytopenia; immunemediated; infectious; biogeography; CagA

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Competing interests: the authors of this paper have no conflict of interest to disclose.

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped, flagellated, microaerophilic bacillus that colonizes the gastric mucosa and is likely transmitted via the fecal–oral, or oral–oral route during childhood [1–6]. Prevalent in more than half of the world's population, *H. pylori* infection occurs more frequently in developing nations [1,3]. There are documented differences in virulence factors between Western and East Asian strains of *H. pylori*, with the Eastern Asian strains suspected to have higher pathogenicity in relation to gastritis and gastric carcinoma [7,8]. *Helicobacter pylori* is recognized as a causative agent for a variety of gastric diseases, including gastritis, peptic ulcer, and gastric atrophy, and is correlated with an increased risk for gastric cancer [9]. The bacterium has also been linked to a number of extragastric diseases including nutritional deficiencies, such as vitamin B12 deficiency, and hematological pathologies, such as idiopathic thrombocytopenic purpura (idiopathic immune-mediated thrombocytopenia, ITP) [10,11]. In this review, the "virulence" of a particular *H. pylori* strain will refer to the susceptibility of infected individuals to any of the above-mentioned diseases, as well as the severity of disease symptoms and associated pathophysiological changes.

ITP is an autoimmune disorder wherein platelets are opsonized by platelet-specific IgG autoantibodies (autoAbs), resulting in platelet destruction within the reticuloendothelial system [12,13]. Platelets are circulating anucelate cells derived from megakaryocytes within the bone marrow. In an adult human, there are approximately 100 billion new platelets produced each day with a life span of 8–10 days, which maintains a normal platelet count of 150–400 × 10^9 platelets per liter of blood [14,15]. Platelets are known to play a critical role in both hemostasis and inflammation [16]. The autodestruction of platelets can be a result of infectious, genetic, or environmental factors, with primary ITP having no identifiable underlying etiology and secondary ITP having a causative agent positively identified.

Previous reports have postulated various mechanisms for *H. pylori's* role in ITP including molecular mimicry, increased plasmacytoid dendritic cell numbers, and variable host immune response to virulence factors, including vacuolating-associated cytotoxin gene A (VacA), and cytotoxin-associated gene A (CagA) – a virulence factor that *H. pylori* injects into host gastric epithelial cells (ECs) via type a IV secretion system [17–20]. The presence of anti-CagA antibodies (Abs) has been shown to be predictive of platelet recovery in ITP patients treated for the eradication of *H. pylori* infection [19], which suggests that anti-CagA Ab titers can be used as a marker to determine whether eradication of *H. pylori* may be indicated in certain ITP patients. Additionally, molecular mimicry between CagA and platelet- associated IgG (PAIgG) has been previously documented [21]. These findings suggest that the host Ab response to CagA exhibits cross-reactivity with platelet surface antigens (Ags), promoting both platelet aggregation via immune complex formation and increased platelet clearance rates, resulting in thrombocytopenia.

Validating the ostensible etiological link between *H. pylori* infection and ITP could have a major impact on the clinical diagnosis and treatment of ITP. Current guidelines in multiple countries – including North America, Canada, and a number of countries in Asia – recommend *H. pylori* eradication in ITP patients that fail to respond to traditional treatments, if they test positive for the bacterium or reside in highly endemic areas.

Immune Thrombocytopenic Purpura

ITP is an autoimmune-mediated hematological disorder characterized by the destruction of host platelets and the impairment of megakaryocyte platelet production within the bone marrow [22]. The diagnosis of ITP relies upon a platelet count of $<100 \times 10^9$ platelets per liter of blood and can be categorized as acute (diagnosis to 3 months), persistent (3–12 months), or chronic (>12 months) [23]. ITP can be a primary disease or secondary to a variety of etiologies including infection, autoimmune, or neoplastic disease. A chronic inflammatory state following primary bacterial or viral infection can induce the host autoimmune response via multiple mechanisms, including the production of auto-Abs and immune complex formation. ITP has an incidence of about 2.7 per 100,000 persons in adults and 5 per 100,000 persons in children, with a female sex predilection of 1.7 (female: male ratio) [24]. While ITP is typically an incidental finding during routine hematological evaluation, the most common clinical presentation of ITP is mucocutaneous bleeding, with rare complications of life-threatening hemorrhages [24,25]. ITP has a more acute onset, is self-limited, and usually follows an infectious illness in children, while ITP is usually chronic with an insidious onset in adults [25–27].

ITP is a diagnosis of exclusion, where the underlying etiology of the thrombocytopenia is undetermined. Recent reviews of previously published clinical studies have shown that eradication of *H. pylori* infection in patients with chronic ITP (cITP) results in increased platelet counts in about half of the cases [24,28–31]. In the majority of these retrospective studies, this associative link is defined as a durable platelet response after *H. pylori* eradication. A 2009 systematic review and meta-analysis revealed a correlation between *H. pylori* infection and ITP with a positive effect of *H. pylori* eradication on platelet count [29]. A current review of the clinical literature confirms that eradication treatment in *H. pylori*-positive adult ITP patients resulted in about a 50% complete response rate (Table 1), although this is variable by geographic location and many of the studies did not differentiate between acute and chronic ITP. Despite mounting evidence suggesting that *H. pylori* infection may also play an etiological role in pediatric cITP, published studies are inconclusive and empirical treatment of *H. pylori* in children with ITP remains controversial [32,33]. Due to the scarcity of controlled clinical studies to date and some reports presenting conflicting evidence, further research must be performed to confirm *H. pylori* as a causative agent of cITP in both adults and children [24,30,34,35].

Proposed Mechanistic Pathways of ITP Induction

Different strains of *H. pylori* express a distinct range of virulence factors, resulting in increased pathogenesis (increased pathological changes in tissue histology and increased local inflammation). Notably, *H. pylori* strains that are positive ($cagA^+$) for the cytotoxin-associated gene pathogenicity island (*cag* PAI) are more virulent than *cag* PAI-negative strains ($cagA^-$) and have been strongly associated with gastric carcinoma [7]. The *cag* PAI encodes a type IV secretion mechanism, giving rise to inflammation via NF-kB activation [36,37] and interleukin 8 (IL-8) production [38] and mediates translocation of the 145-kDa *cagA* gene product, CagA, into gastric epithelial cells (ECs) (Fig. 1). Once injected, CagA undergoes intracellular tyrosine phosphorylation (pY) and perturbs host cell signaling,

promoting disturbance of ECs and gastric carcinogenesis [7,39,40]. While incompletely understood, tyrosine phosphorylation of CagA by the Src family protein tyrosine kinase mediates a growth-factor-like morphological change in infected gastric ECs known as the "humming-bird" phenotype, which is characterized by needlelike cellular protrusions [41–43]. This change in EC morphology can lead to increased cellular proliferation and has been used by researchers to explain the carcinogenic effect of *H. pylori* infection [44]. The severity of the "hummingbird" morphological change depends on the virulence of a given *H. pylori* strain and is a plausible indication of a strain's potential to induce ITP in infected subjects. CagA is noted for the diversity of its amino acid sequence among different *H. pylori* strains, and published reports have revealed differences in infection severity between Western and Eastern Asian strains of *H. pylori*, with the extent to which a given strain's CagA undergoes intracellular pY serving as a strong indicator of virulence [41].

Various mechanisms have been proposed for the induction of ITP as a result of *H. pylori* infection, incorporating both the innate (T-cell lymphocytes, neutrophils, monocytes, and cytokines) and acquired (B-cell lymphocytes) immune system. These include (1) the production of Ag-specific Abs that cross-react with platelet surface glycoproteins [21], (2) genetic differences in HLA class II allele patterns [45], (3) enhanced platelet activation from the interaction of *H. pylori*-bound von Willebrand factor (VWF) interacting with platelet surface Ag (GPIb) with subsequent aggregation supported by IgG [46], (4) the induction of the B-cell-mediated expansion of platelet-reactive Abs [47,48], (5) enhanced platelet activation from the binding of vacuolating cytotoxin (VacA) virulence factor to multimerin 1 on platelets [20], and (6) the downregulation of FcγRIIB receptors on monocytes, resulting in increased phagocytic activity, by *H. pylori* infection [49]. *Helicobacter pylori* Ags are currently known to induce a T- and B-cell-mediated response, which results in host production of *H. pylori*-specific Abs [50,51]. A recent study evaluated cytokine levels in patients with chronic ITP before and 6 months after *H. pylori* eradication. Antibiotic treatment, in patients with a positive platelet response to *H. pylori* eradication, resulted in a reduction in the cytokine profile consisted with Th1 and Th17 cells; also, there was an enhancement of a Th2 cytokine profile, as well as an increased number of T regulatory cells [52]. Some of the Abs generated during this immune response demonstrate cross-reactivity with host cells, including gastric and duodenal ECs, renal tubular cells, and salivary gland cells [53]. Recent clinical studies have elucidated an association between $cagA^+$ *H. pylori* and ITP [17–19,21]. Takahashi et al. [54] demonstrated that patients with ITP had PAIgGs that cross-reacted with *H. pylori*-specific CagA, and reported a decline in anti-CagA Abs, as well as an increase in total circulating platelet count, in patients who underwent successful *H. pylori* eradication treatment. These findings parallel those of Kodama et al. [19], who also reported that *H. pylori* eradication therapy improved platelet counts in *H. pylori*-positive ITP patients and led to a significant decrease in anti-CagA Abs. One explanation for this finding is the possibility of molecular mimicry between CagA Ags and platelet surface glycoproteins, resulting in the anti-CagA Ab targeting of host platelets (Fig. 2). Although no research published to date has definitively established CagA as a causative factor in ITP, retrospective clinical studies substantiate a correlation of *H. pylori*-specific CagA with clinical ITP [55].

Injection of CagA into gastric epithelial cells results in a number of intracellular changes, morphological changes, and transcriptional activation (Fig. 1). A prospective clinical study performed by Asahi et al. [49], showed that *H. pylori* infection was correlated with an increase in monocyte phagocytic activity and a downregulation in FcγRIIB receptor expression on monocytes. Eradication treatment resulted in the resolution of these abnormalities as well as a decrease in circulating anti-CagA Abs. These findings suggest that the mechanism through which *H. pylori* induces an autoimmune disease state may very well be multifactorial: platelet clearance by macrophages in the reticular endothelial system, suppression of antigen presentation by macrophages, inhibition of lymphocyte responses to platelet surface antigens, direct increases in platelet activation, and cross-reactivity of autoplatelet Abs. A previous study exploring the pro-inflammatory activation of neutrophils and monocytes by *H. pylori* was not associated with the *cagA* or *vacA* genotype [56]. The lack of controlled scientific studies and the lack of establishment of Koch's postulate require additional research to be performed to confirm a definitive mechanistic pathway linking *H. pylori* infection and ITP.

The Role of Biogeography

Computational phylogeography of *H. pylori* indicates a trend of spreading, alongside populations of its human host, from east Africa as early as 63,000 years ago [57]. The findings of Linz et al. demonstrate that the biogeographical evolution of modern *H. pylori* strains has been marked by high mutation rates and frequent interstrain recombination [58,59]. *Helicobacter pylori* strains present today subdivide into biogeographic populations that appear to reflect human migration patterns [60–62]. A comparison of 38 representative isolates of complete *cag* PAI genomes from known biogeographic islands was performed, showing that *cagA* gene content is highly conserved and its genetic diversity is reflective of geographic location [63]. The *cag* PAI is present in 95% of strains assigned to hpAfrica1, hpEastAsia, and hpAsia2 populations, while no hpAfrica2 strains possess the island, and *cag* PAI is variably found in hpEurope, hpNEAfrica, hpSahul, and the hspAmerind subpopulation of hpEastAsia (Fig. 3A) [63].

There is evidence for differences in infection severity between Western and Eastern Asian *H. pylori* strains. Eastern Asian *H. pylori* strains have been documented as more pathogenic, correlating with an increased occurrence of gastric carcinoma (among other GI pathologies) in *H. pylori*-positive patients in East Asia (including the countries of Japan, Korea, China, and Russia) [41,64]. This observed increase in pathogenicity correlates with an increase in CagA phosphosite abundance [7]. Furthermore, increased CagA pY can induce greater pathologic morphology changes in host gastric ECs [7]. CagA proteins of most Western *H. pylori* isolates have a 34-amino acid sequence that variably repeats among different strains [7]. This repeating sequence contains a conserved Glu-Pro-Ile-Tyr-Ala (EPIYA) sequence, which encodes the site for tyrosine phosphorylation (pY) [7]. CagA proteins having multiple EPIYA motifs undergo more extensive pY, exhibit increased specific binding to SHP-2 phosphatase, and induce greater morphological changes ("hummingbird phenotype") in gastric ECs accompanied by sustained ERK activation, altered cellular migration (scattering), and induced apoptosis [65–67]. CagA proteins from Eastern Asian strains of *H. pylori* have distinct pY sequences at the region corresponding to the repeat sequence of

Western CagA [7] (Fig. 4). These findings suggest that the CagA pY state underlies *H. pylori's* pathologic effect in a range of diseases, including gastritis, gastric carcinoma, and ITP [41,68].

In East Asia, CagA seropositivity is reported to be higher in patients diagnosed with gastric cancer than in those with gastritis alone [69], suggesting that anti-cagA Abs may be used as a biomarker for gastric cancer in East Asian countries [70]. Most *H. pylori* infections in Japan are positive for East Asian-type cagA [71,72]. However, in southwestern regions of Japan such as Okinawa, where the incidence of gastric cancer is lower, there are markedly lower rates of East Asian-type CagA. It has been postulated that the horizontal transmission of Western *H. pylori* strains to Japanese natives may have occurred during post-WWII occupation of Okinawa by US citizens [64,73]. Although the isoform of CagA found in southwestern Japan ("J-Western" CagA) differs from Western-type CagA via a 12-bp insertion in the *cagA* gene, the similarity between CagA multimerization sequence in Okinawan and Amerindal strains suggests they share ancestral lines [64,70,74]. The presence of both Western and East Asian-type CagA within Japan, along with correspondingly decreased incidence of gastric cancer among Japanese natives who test positive for only Western- or J-Western-type CagA, supports previous findings that variation in the virulence of CagA is important in the pathogenicity of *H. pylori* infection. Although few studies have probed the link between CagA virulence and ITP as comprehensively as gastric cancer, it is conceivable that similar trends underlie the increased prevalence of cITP in patients with *cagA+ H. pylori* infections.

Vacuolating cytotoxin (VacA) virulence factor has also been proposed as a factor in the development of ITP, via the binding to multimerin 1 on platelets leading to platelet activation [20]. Although not as thoroughly explored as that of CagA, the VacA genome may also be a variant that is based on bacterial and host migratory patterns. Lu et al. [75], performed a full genome comparative analysis of an *H. pylori* isolate in Australia, Sahul 64. This study suggested that Sahul 64, which was found to lack the cagPAI, have highly divergent cell envelope proteins, encode no transportable VacA protein, and might be better adapted to cause endogenous infections in Australians, despite the fact that these infections were less virulent compared to other cagPAI-positive strains. Evaluation of polymorphisms in virulence factors, CagA and VacA, in patients from different countries showed that the presence of the cagA gene correlated with vacA signal sequence s1/ m1 or s1/m2, and cagA-negative samples correlated with type s2/m2, suggesting that *vacA* genetic variation may be correlated to cagA biogeographical variation. Additionally, in the French study, *cagA* was positively correlated with the presence of the s1/m1 *vacA* genotype as well as with the induction of interleukin-8 (IL-8) [76–78]. Due to limited studies published on the genetic phylogeny of *vacA*, further investigation into the biogeography of this virulence factor in relationship to ITP may offer greater clinical insight.

In addition to bacterial biogeography, a patient's biogeography may also play a role in the etiology of *H. pylori*-induced ITP. For example, monocyte FcγR receptor expression can be influenced by both environmental factors, such as infection, and genetic factors, such as polymorphisms [49]. An alteration in the expression of the FcγR gene can result in a change in a monocyte's affinity for binding IgG, which can cause a change in the clearance rate of

immune complexes [79]. Changes in receptor expression, such as the presence of single nuclear polymorphisms in the FcγRIIB gene or its promoter region, can change transcriptional activity and has been shown to be predictive of the development of chronic disease in children presenting acute ITP [80–83]. Studies evaluating these genetic changes in receptors have not evaluated cases of *H. pylori*-positive, eradication-responsive ITP. We hypothesize that the migratory patterns, genetic profiles, and biogeography of both patient and pathogen, *H. pylori*, are likely to play a role in the induction of an autoimmune disease state. The scarcity of published literature to date warrants further exploration on the genetic makeup of both the patient and the infecting *H. pylori* strains in relation to ITP.

Current Policies/Recommendations for *Helicobacter pylori* Eradication

Although the molecular basis for the association between ITP and *H. pylori* infection has not been conclusively established, various health organizations around the world currently advocate for the detection and eradication of *H. pylori* infection in the face of ITP. In 1987, the European Helicobacter Study Group (EHSG) was founded to promote multidisciplinary research centered on *H. pylori*-associated pathologies. The EHSG convenes consensus meetings on a regular basis to recommend when and how to treat patients infected with *H. pylori*. In 2010, 44 experts from 24 countries participated in the Maastricht IV/Florence Consensus Report and concluded that ITP is one of the extragastric diseases for which the detection and eradication of *H. pylori* infection is indicated [84]. While more conservative, current guidelines (2011) from the American Society of Hematology acknowledge *H. pylori* as a potential etiology for ITP and recommend that more extensive testing for infection be reserved for patients who either reside in highly endemic regions, or exhibit symptoms beyond thrombocytopenia (+/− anemia with concurrent bleeding) [26].

In 2009, the Asia-Pacific Conference convened to review the most current information on *H. pylori* management to synthesize new guidelines for the indication of its treatment and eradication and concluded that *H. pylori* eradication in infected patients with ITP was indicated [85]. The Japanese Society for Helicobacter Research considers *H. pylori* infection to be an indication for eradication therapy for four diseases: peptic ulcer, gastric MALT lymphoma, early gastric cancer, and ITP [85,86]. Because of the high prevalence of *H. pylori* infection in Japan, in addition to the increased pathogenicity of the endemic strains and subsequent risk of gastric cancer with long-term infection, eradication treatment has been approved by the Japanese health insurance system as a result of the recommendations from the Japanese Society for Helicobacter Research [70]. Other East Asian countries, including Korea, have also adopted *H. pylori* eradication guidelines for the treatment of both gastric and extragastric diseases (e.g., cITP) [87]. The findings of some reports suggest that ITP disease duration, along with the pathogenicity of infecting *H. pylori* strain (primarily the likelihood that a patient will be seropositive for CagA-specific autoAbs), is the chief predictor of patient platelet response following *H. pylori* eradication treatment, but more controlled clinical studies are required to confirm the biogeographical link between *H. pylori* strain and the likelihood of a positive platelet response (Fig. 3B, Table 1).

Clinical Relevance

A principle concern for individuals with ITP is life-threatening hemorrhage. A study of 117 adult cases of cITP revealed that 33% of treated adults achieved stable remission, with the incidence of hemorrhagic complications being more common in patients greater than 60 years of age (10.4%) than in patients younger than 40 years (0.4%) [88]. A case series review including 1817 patients with ITP revealed that the risk of fatal hemorrhage, before age adjustment, was 0.0162–0.0389 cases per patient-year [89]. Intracranial hemorrhage is the most life-threatening complication in patients with severe thrombocytopenia, with a mortality rate up to 5% in adults with cITP [90,91]. Thirty percent of pediatric patients will have a prolonged course and 5–10% will develop chronic severe refractory disease [92,93], with a 0.1–0.5% risk of intracranial hemorrhage, usually with platelet counts lower than 10×10^9/L [94]. Treatment for ITP is recommended for patients with a platelet count below 50×10^9/L, bleeding due to platelet dysfunction, the presence of other hemostatic defects, surgery, trauma, or other identified comorbidities [55].

Current treatment for ITP in the United States involves the use of immunosuppressive agents, such as corticosteroids, intravenous immunoglobulin therapy (IVIg), anti-D immunoglobulin (anti-D), Rituximab, or salvage splenectomy, all of which can be expensive and have associated risks and adverse effects [26]. About 20% of patients do not sustain a normal platelet count after medical therapy or splenectomy, and 10–20% of responders to splenectomy will relapse [55]. In a 2009 meta-analysis conducted by Stasi et al., positive platelet responses were found in roughly 50% of adult ITP patients after *H. pylori* eradication treatment, with more significant platelet count increases observed in less severe cases of ITP. As most of the studies included in the meta-analysis by Stasi et al. [29] considered *H. pylori* eradication in primarily severe cases of ITP, absolute patient response rates to bacterial eradication treatment may exceed 50% efficacy. In patients that respond to *H. pylori* eradication therapy, autoplatelet Ab responses are completely resolved, without relapse for over 7 years [95]. However, platelet response to *H. pylori* eradication for the treatment of ITP appears to correlate with geographic location: higher response rates are observed in Japan and Italy (ranging from 28 to 100%) than in the United States and other European countries (<13%) [95]. A study from Iran reported that *H. pylori* eradication led to increased platelet count in those with mild ITP (platelet count $>50 \times 10^3$ μL), but was less successful in patients with severe ITP (platelet count $<50 \times 10^3$ μL) [96]. Meanwhile, eradication of infection in *H. pylori*-positive children and adolescent ITP patients in Brazil had a response rate of 60% compared to untreated, infected patients, 18.2% [97]. Taken in aggregate, these clinical observations underscore the importance of patient biogeography as a predictor of response to *H. pylori* treatment and further implicate regional *H. pylori* strain variation.

Active *H. pylori* infections are diagnosed using the ^{13}C-urea breath test, detecting bacterial Ag in the stool, with bacterial culture or PCR via gastric biopsy, or silver staining of gastric tissue for visualization of *H. pylori*. Additionally, ELISA-based serum Ab testing may be performed, but may be insensitive, not necessarily indicative of active bacterial infection, and may be falsely positive after IVIg therapy. The currently recommended treatment regimen for *H. pylori* infection consists of a combination of antibiotic therapies, which

usually poses significantly less adverse effects and less overall costs than most ITP treatments. Historically, recommended eradication treatment has been a triple therapy cocktail, consisting of a proton-pump inhibitor, amoxicillin, and clarithromycin or metronidazole for up to 2 weeks. The addition of various probiotic compound supplements, containing *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and other bacteria, have also been implicated in both reducing the adverse effects of eradication treatment and improving eradication rates, although studies supporting this are contradictory [98]. The antibiotics chosen may vary by region due to the emergence of *H. pylori* antibiotic resistance in highly endemic areas [99,100]. This rise in antimicrobial resistance, particularly against clarithromycin and metronidazole, combined with poor patient compliance, has resulted in a <70% eradiation rate in most countries [101,102]. Resistant *H. pylori* strains necessitate sequential or quadruple therapy (either bismuth-based or nonbismuth-based), and the use of rifabutin and levofloxacin as salvage treatments when initial therapy fails [100,102]. Although new diagnostic tools are being developed for defining susceptibility profiles for *H. pylori* infections, there is no current “tailored” eradication therapy protocol in effect [102]. Taking into account the literature supporting the link between *H. pylori* infection and ITP, *H. pylori* should be considered as a potential etiology for ITP in both children and adults; however, eradication therapy should be reserved for those who test positive for active infection.

Conclusions

Literature over the past 20 years has elucidated the potential link between chronic *H. pylori* infection and the development of ITP in both adults and children. Most publications are retrospective clinical studies with variable treatment response rates, potentially due to biogeography and subsequent genetic variation of the bacteria and/or patient. Many studies have proposed that *H. pylori* virulence factor, CagA, stimulates the development of anti-CagA antibodies that are cross-reactive with platelet surface antigens, resulting in thrombocytopenia. Future studies exploring the potential molecular link between chronic *H. pylori* infection and ITP are justified by the fact that (1) upper gastrointestinal (GI) infection by *H. pylori* is prevalent in over 50% of the world’s human population [1], and because (2) clinical studies of ITP to date have remained largely observational in nature, with few having substantiated the proposed molecular mechanisms of disease pathogenesis by experimental means. Further studies exploring the potential pathophysiological mechanism between infectious agents (e.g., *H. pylori*) and ITP, via the role of genetic variation and biogeography, could open a new avenue with regard to the diagnosis and treatment of patients with idiopathic hematological disorders. Lack of robust animal models of ITP associated with *H. pylori* infections has hampered mechanistic studies underlying its potential relationship with cITP. However, with the recognition that controlled experiments are necessary in establishing a causative link, current published literature is substantial enough to suggest an associative link between *H. pylori* and ITP and to warrant empirical eradication treatment in patients that test positive for active *H. pylori* infection or those in highly endemic areas, whose populations are infected with CagA-virulent strains.

Acknowledgments

We would like to acknowledge Dr. Jacquin C. Niles, MD, PhD, and Dr. Ram Sasisekharan, PhD, in the Department of Biological Engineering at Massachusetts Institute of Technology for their guidance and support in the development of this review. We would like to thank Alyssa Terestre for her assistance in manuscript preparation. This review was supported by the following grants: NIH T320D010978-26(JGF), P01CA028842-23 (JGF), P30ES002109(JGF).

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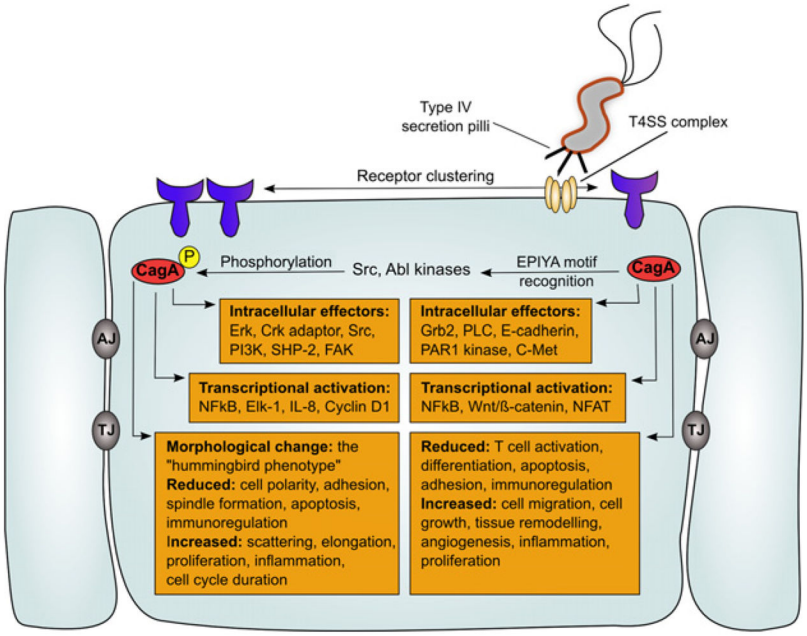

Figure 1.

Effects of *Helicobacter pylori* CagA virulence factor on host cell. *Helicobacter pylori* injects CagA (red) into a host gastric epithelial cell via a type IV secretion system (T4SS, tan). Dimerizatiom of primary receptors activated by T4SS core complex: $\alpha_5\beta_1$ integrin and receptor tyrosine kinases (purple). Within ECs, CagA EPIYA motif is recognized by major host kinases, Src, and Abl, resulting in tyrosine phosphorylation (yellow). Phosphorylated CagA (red and yellow) induces host cell pathology. Both, intracellular CagA and phosphorylated CagA, induce major effects on host cell signaling, resulting in changes in cell morphology, cell cycle regulation, and pro-inflammatory cytokine transcription. Intercellular junctions (gray): AJ, adherens junctions; TJ, tight junctions. This figure is an adaptation of Figures 2, 3, and 4 from [103].

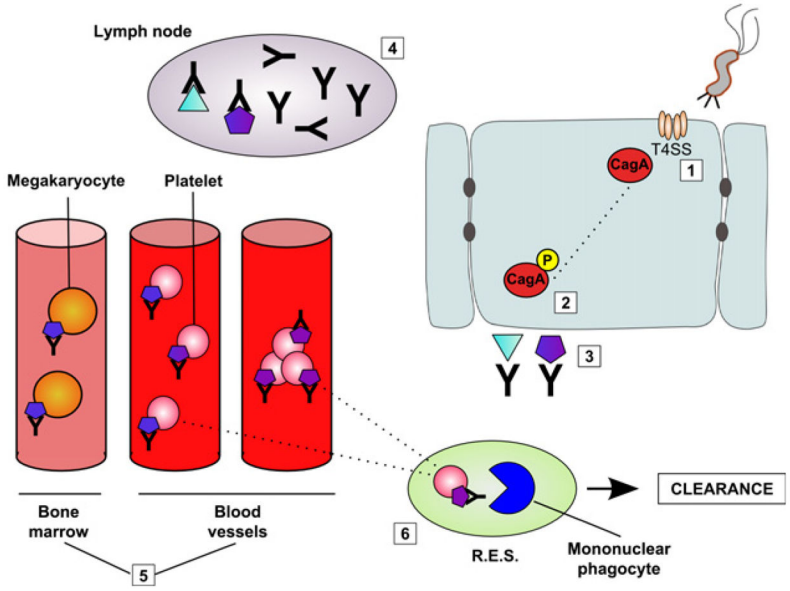

Figure 2.

Host production of anti-CagA Abs, resulting in ITP. (1) *Helicobacter pylori* injects CagA (red) into host gastric ECs via T4SS (tan). (2) CagA undergoes intracellular phosphorylation (red and yellow). (3) Two Ags are produced and presented on the cell surface of the infected host cell: one specific for CagA (light blue) and one that shows molecular mimicry to platelet surface glycoproteins (purple). (4) Host Abs recognizing either Ag undergo replication within the host lymph nodes. (5) These Abs are then released into the circulatory system, resulting in a secondary immune-mediated thrombocytopenia. (6) Increased platelet clearance is a result of Ab-Ag recognition in the reticuloendothelial system (R.E.S.), increased immune complex formation, and decreased platelet production in the bone marrow. (pink: platelet; orange: megakaryocyte; blue: mononuclear phagocyte; green: R.E.S.)

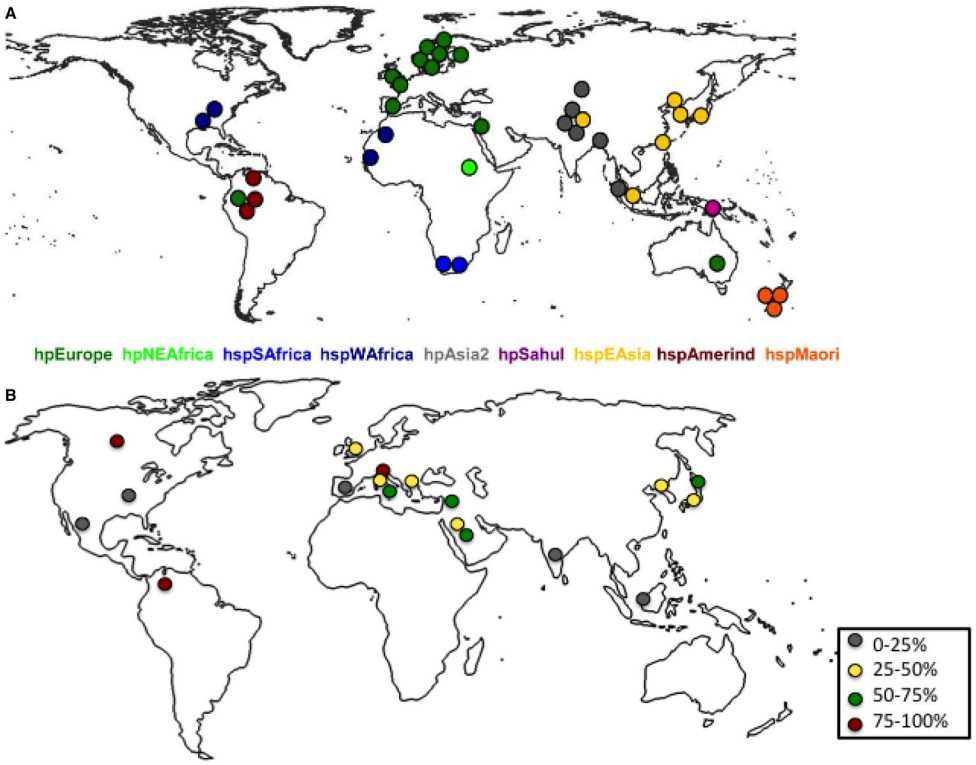

Figure 3.

Distribution of *cag* PAI in a collection of *Helicobacter pylori* strains from different world populations. Geographic sources of strains whose *cag* PAI sequences are now available. Each dot indicates the source of isolation of one of the 38 *cag* PAI sequences that were analyzed. The dots are color-coded by population or subpopulation as in (*A*). Representation of geographical distribution of platelet response after eradication treatment in *H. pylori*-positive adult patients (*B*). Data extrapolated from Table 1. Gray (0–25% response), yellow (25–50% response), green (50–75% response), and red (75–100% response) (modified with permission from [63]).

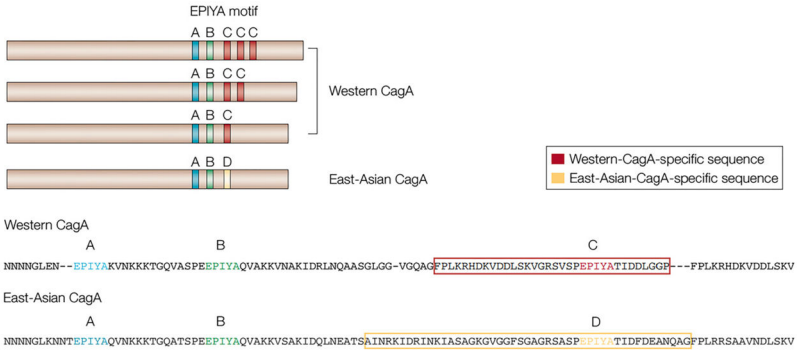

Figure 4.

Diversity in CagA tyrosine phosphorylation (pY) sites. Tyrosine phosphorylation of cytotoxin-associated antigen A (CagA) by SRC kinase occurs at the EPIYA motif. There are four different EPIYA sites, called EPIYA-A, -B, -C, and -D, based on the sequence surrounding the EPIYA motif. Western strains of *Helicobacter pylori* express a form of CagA that contains the EPIYA-A and EPIYA-B sites, followed by 1–3 repeats of the 34-amino acid sequence that contains the EPIYA-C site (red boxes). East Asian strains of *H. pylori* express a form of CagA in which the EPIYA-C site is replaced with the EPIYA-D site (yellow box) (reprinted with permission from [41]).

Table 1

Platelet response to eradication treatment in *Helicobacter pylori*-positive adult ITP patients

References	Age[a]	Disease duration[b]	Bacterial eradication (%)	Platelet count before eradication[c]	Platelet count post eradication[c]	Complete response rate[d] (%)	Study location (primary patient ethnicity)
Gasbarrini et al. (1998) [104]	43 ± 14	NR	8/11 (73)	95 ± 39	140 ± 34	8/8 (100)	Italy (Caucasian)
Jarque et al. (2001) [105]	54 (17–80)	NR	23/32 (72)	58 ± 24	65 ± 32	3/23 (13)	Spain (Caucasian)
Kohda et al. (2002) [106]	54 ± 14	41.2 ± 38.2	19/19 (100)	67 ± 54	120 ± 50	12/19 (63)	Japan (Japanese)
Hino et al. (2003) [107]	55 ± 15	78 ± 42.4	18/21 (86)	37 ± 21	67 ± 54	10/18 (56)	Japan (Japanese)
Hashino et al. (2003) [108]	53.2 ± 12.9	125.5 ± 77.1	13/14 (93)	58 ± 30	99 ± 56	5/13 (38)	Japan (Japanese)
Ando et al. (2003) [109]	58 ± 11	78.1 ± 65.1	27/29 (93)	56 ± 24	93 ± 49	16/27 (59)	Japan (Japanese)
Michel et al. (2004) [110]	52.5 ± 15.9	10 (1–21)	14/15 (93)	32 ± 15	66 ± 98	0/14 (0)	USA (Caucasian)
Takahashi et al. (2004) [54]	54 ± 13	52.5 ± 6.4	13/15 (87)	40 ± 27	101 ± 86	7/13 (54)	Japan (Japanese)
Sato et al. (2004) [111]	62 (37–87)	59.4 (6–264)	27/32 (84)	54 ± 17	110 ± 21	10/27 (37)	Japan (Japanese)
Ando et al. (2004) [112]	62 (38–83)	NR	15/17 (88)	49 ± 26	168 ± 43	10/15 (67)	Japan (Japanese)
Nomura et al. (2004) [113]	NR	NR	12/28 (43)	29 ± 6	78 ± 11	15/28 (54)	Japan (Japanese)
Veneri et al. (2005) [114]	57 (24–72)	NR	41/43 (95)	57 ± 23	122 ± 33	20/41 (49)	Italy (Caucasian)
Inaba et al. (2005) [115]	57 (25–82)	48 (6–180)	25/25 (100)	52 ± 26	NR	11/25 (44)	Japan (Japanese)
Stasi et al. (2005) [116]	58 ± 13	25 ± 19	52/64 (81)	42 ± 25	129 ± 61	17/52 (33)	Italy/UK (Caucasian)
Fujimura et al. (2005) [117]	59 ± 14	98.2 ± 81.6	161/207 (78)	NR	NR	101/161 (63)	Japan (Japanese)
Suzuki et al. (2005) [118]	NR	NR	11/13 (85)	55 ± 27	114 ± 90	6/13 (46)	Japan (Japanese)
Suvajdzic et al. (2006) [119]	54 ± 13	NA	23/30 (77)	68 ± 33	84 ± 45	6/23 (26)	Serbia (Caucasian)
Ahn et al. (2006) [120]	56.8 ± 18.5	NA	15/15 (100)	72 ± 45	69 ± 65	2/15 (13)	USA (Caucasian)
Sayan et al. (2006) [121]	50.8 ± 16.2	NA	18/20 (90)	39 ± 16	100 ± 63	NA	Turkey (Middle Eastern)
Asahi et al. (2006/08) [49,122]	NR	NR	26/26 (100)	35 ± 13	114 ± 61	16/26 (62)	Japan (Japanese)
Kodama et al. (2007) [19]	57.9 ± 14.3	57.9 ± 14.3	44/52 (85)	40 ± 29	NR	27/44 (62)	Japan (Japanese)
Campuzano-Maya (2007) [123]	NR	NR	26/29 (90)	57 ± 38	198 ± 98	20/26 (78)	Colombia (South American)
Estrada-Gomez et al. (2007) [124] 3	NR	NR	14/14 (100)	NR	NR	NR	Mexico (Mexican)
Satake et al. (2007) [125]	NR	65 (1–272)	23/25 (92)	NR	NR	12/23 (52)	Japan (Japanese)
Emilia et al. (2007) [126]	58 ± 19	11.5 ± 6.4	34/38 (89)	41 ± 24	134 ± 96	23/34 (68)	Italy (Caucasian)
Rostami et al. (2008) [127]	29.2 ± 7	64.5 ± 49.5	62/71 (87)	60.2 ± 18.14	140.5 ± 34	28/62 (45)	Iran (Middle Eastern)
Jackson et al. (2008) [128]	47.5	NR	2/4 (50)	NR	NR	3/4 (75)	Canada (Caucasian)

References	Age[a]	Disease duration[b]	Bacterial eradication (%)	Platelet count before eradication[c]	Platelet count post eradication[c]	Complete response rate[d] (%)	Study location (primary patient ethnicity)
Tag et al. (2010) [129]	55 (35–76)	2.5 (0–27.1)	23/23 (100)	78 (6–96)	100 (46–172)	11/23 (48)	Korea (Korean)
Sato et al. (2011) [130]	62 ± 13	42 ± 41	31/31 (100)	<100	>130	18/31 (58)	Japan (Japanese)
Veneri et al. (2011) [131]	52.2 (15–87)	52.7 ± 116.1	11/12 (92)	9.6 ± 4	>100	6/12 (50)	Italy (Caucasian)
Payandeh et al. (2012) [132]	38.2	NR	26/29 (90)	49.5 ± 15	69 ± 21.9	15/26 (58)	Iran (Middle Eastern)
Gan et al. (2013) [133]	50 (19–71)	109 (36–216)	NR	47.5 ± 12	64.5 ± 33.2	2/11 (18)	Malaysia (Malay/Chinese/Indian)
Takezako et al. (2013) [134]	55 ± 21	19 ± 13	17/19 (89)	65 ± 48	200 ± 140	5/17 (29)	Japan (Japanese)

[a] Mean or median (range).

[b] Months, (mean ± SD) (median, range).

[c] $\times 10^9$/L.

[d] ≥6 months.