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Case Report

Helicobacter pylori: A Belittled Cause of Immune Thrombocytopenic Purpura (ITP) and Role of Helicobacter pylori Eradication Therapy for Treating ITP

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Abstract

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by production of auto antibodies against platelet surface antigens. ITP affects women more often than men and is more common in children than adults. ITP is a diagnosis of exclusion after other identifiable etiologies have been ruled out. After the first report by Gasbarrini et al. (1998) showing rising platelet counts in ITP patients following Helicobacter pylori (HP) eradication therapy, there is growing evidence that highlights the role of HP in triggering ITP. The H-pylori infection induced ITP is validated by many proposed mechanisms such as molecular mimicry due to production of auto antibodies against H-pylori surface virulent factors (CagA) and cross reactivity of these antibodies with platelet surface antigens (GP IIb/IIIa, GP Ib/IX, and GP Ia/IIa), phagocytic perturbation due to enhanced phagocytic activity of monocytes, enhanced dendritic cell numbers and response, platelets aggregation due to presence of anti- H-pylori IgG and von Willebrand factor (vWf) and finally host immune response against H-pylori virulent factors CagA and VacA leading to ITP.

Eradication of Helicobacter pylori infection has been variably associated with a platelet response in patients with immune thrombocytopenic purpura (ITP). Eradication therapy is simple and inexpensive, with limited toxicity and the advantage of avoiding long-term immunosuppressive treatment for those who respond. Although the evidence and follow-up are limited, it appears reasonable to routinely screen patients with ITP for H pylori, particularly in those populations with a high background prevalence of H pylori infection.

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by the production of autoantibodies against platelets membrane antigens leading to platelets destruction by the Reticuloendothelial system [1,2] and/or abnormal maturation of megakaryocytes in the bone marrow [3]. ITP is a diagnosis of exclusion, with fewer than 100000 platelets per liter of blood as the cut-off platelet count for making the ITP diagnosis [4]. The normal adult platelets range from 150–400 × 109/L of blood with a normal life span of 8–10 days. The formation of auto antibodies and immune complexes in the blood leads to a reduction in platelet count to 100 × 109 /L or less [5]. The pathophysiology associated with the development of immune thrombocytopenic purpura is the formation of IgG antibodies against platelets surface proteins like GPIIb-IIIa and GIb-IX; however, many unknown mechanisms need to be explored in the pathogenesis of ITP [6].

ITP is classified as acute, persistent and chronic. The acute ITP lasts for 3-months, most commonly presents in children but resolves spontaneously without any therapy. The persistent type of ITP lasts for 3–12 months and the chronic form lasts for more than 12-months. The chronic form of ITP is commonly seen in adults that may persist but can resolve in 20–40% of the patients later [7]. The etiological classification of ITP ranges from primary ITP with no identifiable cause to secondary ITP having secondary association with environmental factors, neoplastic disorders, bacterial and viral infections like hepatitis C virus (HCV), and human immunodeficiency virus (HIV), and chronic Hpylori infection [8].

Helicobacter pylori (H-pylori) is a gram-negative, spiral-shaped, flagellated, microaerophilic bacillus that resides inside the stomach and is transmitted through fecal-oral, oral-oral route [9-11]. It colonizes the gastric mucosal lining of the infected individuals for a lifetime. The spontaneous eradication of an HP

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infection rarely happens but is possible with antibiotics taken for an unrelated illness. It was first isolated from a gastric biopsy in 1983 [12]. HP is prevalent in more than half of the world's population either clinically or asymptomatically [11], with the majority of individuals, around 80%, infected in developing countries. The prevalence positively depends upon increasing age, poor socioeconomic conditions, population density, smoking, as well as untreated water supplies contaminated with fecal matter from infected individuals [13].

H-pylori are recognized as a causative agent in the development of gastritis, peptic ulcer disease, gastric atrophy and poses an increased risk of gastric adenocarcinoma and mucosal-associated lymphoid tissue lymphoma (MALT) [10] and therefore has been designated as a class I carcinogen by International Agency for Research on Cancer (IARC)in 1994 [14]. H pylori Infection is also known to be associated with non-gastrointestinal diseases like coronary artery disease, pernicious anemia, ITP, and various other autoimmune disorders as well [15-17]. ITP is a diagnosis of exclusion, where the underlying cause of its development is unknown according to various literatures. The pathophysiological link between H-pylori and ITP was initially demonstrated by Gasbarrini et al., Who demonstrated the effectiveness of H-pylori eradication therapy in improving platelet count in patients with chronic ITP [17].

Case report

A 38-year-old lady with chronic ITP, not known to have any co morbidities presented to us after several episodes of hemoptysis and skin rash for last 3 days. She had flu like illness prior presentation. She denied cough, headache, body ache, melena/hematochezia, hematuria, menorrhagia, heartburn, use of non steroidal anti inflammatory drugs, or alcohol use. But she had episodic upper abdominal pain which was relieved with taking antacid. Retrospection of her past history revealed similar kind of attacks in the past 7 years and she had gingival bleeding, epistaxis and more noticeable bruising. She was treated with repeated course of steroid and azathioprine without any persistent benefit. On admission, she was hemodynamically stable. She was awake, alert, and answered all questions appropriately. There were multiple petechiae rash all over her body (Figure 1). Left subconjuctival hemorrhage was also noticed (Figure 2). Bony tenderness, lymphadenopathy was absent. The cardiac, pulmonary, and abdominal examinations were unremarkable.

Initial laboratory results showed a platelet count of 7000/µL, leukocyte count of 8,500/µL, and hemoglobin of 11.3 g/dL, with a mean corpuscular volume of 82.8 fL. Lactate dehydrogenase, haptoglobin, iron, and ferritin were normal. ANA, Anti HCV, HBsAg, Anti HIV were also normal. An upper gastrointestinal endoscopy showed erosive gastritis (Figure 3) and CLO test for the presence of H. pylori infection confirmed active infection.

Owing to the positivity to H. pylori infection, she was started treatment with triple therapy (amoxicillin- 1 gram twice daily, clarithromycin- 500 mg twice daily, and pantoprazole- 20 mg twice daily) for 14 days. Due to ongoing thrombocytopenia, she was prescribed a 4-day course of dexamethasone (40 mg daily). During discharge on 7th day of admission her platelet count was 75,000/µL. Same cycle of dexamethasone was repeated once at 2 weeks. Subsequent platelet counts at 1 month (171,000/µL), 3 months (192,000/µL), and 6 months (251,000/µL) improved and ultimately normalized.

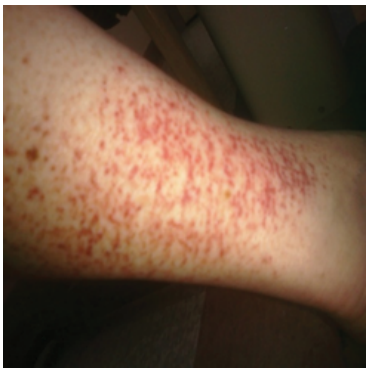

Figure 1 and 2 showing petechiae and sub conjunctival hemorrhage respectively.

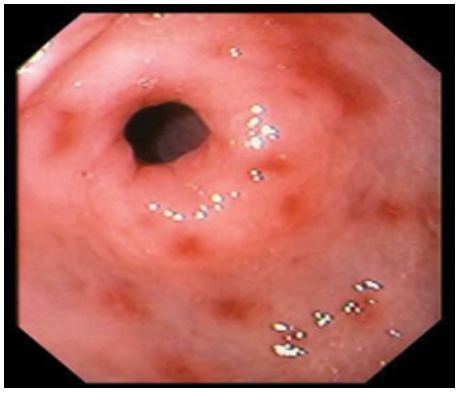

Figure 3 showing Erosive gastritis on upper GI endoscopy

Discussion

Helicobacter pylori is a Gram-negative microaerophilic bacterium that colonizes the human stomach of more than 50% of the world population. It is recognized as the causative agent of active chronic gastritis and is the predominant cause of peptic ulceration, i.e., gastric and duodenal ulcers [18].

H pylori can be readily detected at endoscopy by histology, culture or urease tests. Non-invasive methods for H pylori detection are generally used for the screening of patients who do not require direct examination of gastric mucosa and when obtaining biopsies is troublesome (e.g. bleeding ulcers, anticoagulant therapy, severe thrombocytopenia). Each detection method has strong and weak points and the methods differ in accuracy. Among the non-invasive methods, the 13C-urea breath test and antigen detection in stools are considered to be the most accurate, with both sensitivity and specificity in the range of 90% to 95% [19]. Serum antibody assays have the lowest cost per correct diagnosis, but their overall accuracy is lower (sensitivity and specificity: 80% to 95%) [19]. Furthermore, serology is not a specific indicator of active infection and, since antibody titers fall only slowly after successful eradication, cannot be used to determine H pylori eradication or to detect reinfection. Culture and sensitivity are not recommended unless there has been a treatment failure [43].

After ingestion, HP manages to colonize the mucosal lining of the stomach by eluding the host innate immunity through various adaptive mechanisms, including neutralizing the acidic stomach environment by

the production of ammonia using urease enzymes, altering the mucus viscosity in order to have easy mobility, motility due to flagella to avoid being washed out of the stomach by peristalsis, anergic lipopolysaccharide (LPS) cell wall/flagella, and having various adhesion proteins to help attach gastric epithelial cells (ECs) [20]. There are many proposed mechanisms of ITP development due to H-pylori infection, such as molecular mimicry, platelets aggregation, phagocytic perturbation, increased plasmacytoid dendritic cell (pDCs) response and host immune response to H-pylori virulent factors [8].

Molecular mimicry

The production of antibodies against H-pylori antigens such as cytotoxin-associated gene A (CagA) causes cross-reactivity against various glycoproteins antigens (GP IIb/IIIa, GP Ib/IX, and GP Ia/IIa) present on platelets membrane [21]. This mechanism of cross-reactivity was also observed in patients with Acquired Immune deficiency Syndrome (AIDS) caused by HIV that is also being recognized as a secondary cause of ITP. The production of antibodies against various glycoproteins like HIV gp24 and gp120 in HIV-infected patients are also known to react with platelets membrane antigens to the presence of similar epitopes [22]. .

Phagocytic perturbation

Another proposed mechanism of H-pylori infection-induced ITP is through inhibition of the Fcγ receptors on peripheral blood monocytes caused by H-pylori infection, leading to increased antiplatelets antibodies With increased platelets turn over due to reduced production of FcγRIIB [23]. The reduced expression of FcγRIIB and the emergence of autoreactive B-cells cause increased phagocytic activity of monocytes and reduction in platelet count [23,24].

Dendritic cells response to HP infection

Another proposed mechanism of H-pylori induced ITP is increased numbers of plasmacytoid dendritic cells having the exquisite role of antigen-presenting cells [25]. The extension of lamina podia of dendritic cells into the intact gastric epithelium through the paracellular pathway causes exposure to H-pylori antigen and ultimately enhanced host immune response against H-pylori antigens through Th1 and Th2 lymphocytes leading to the production of IL-12 and IL-10. The presence of outer membrane proteins (Omp's) such as recombinant HpaA (rHpaA) and recombinant outer membrane protein 18 (rOmp-18) on the H-pylori surface stimulates the production of IL-12 and IL-10 from dendritic cells because of their antigenic potential [25,26].

Platelets aggregation

Another proposed mechanism of H-pylori induced ITP is through platelet aggregation caused by some strains of H-pylori. The presence of anti- H-pylori IgG and von Wille brand factor (vWf) on cell membranes of various H-pylori strains causes platelet activation and aggregation [21]. The presence of von Wille brand factor on cell membranes of H-pylori causes platelets to aggregate through glycoprotein-Ib (gp-Ib) present on platelets surface; similarly, anti- H-pylori IgG interaction with IgG receptors (FcgRIIA) on platelets surface also causes platelets to aggregate. The binding of vWf with gp-Ib causes activation of signalling pathway intracellularly, leading to activation of gpIIb/IIIa and irreversible binding to platelets to vWf [27]. Similarly, H-pylori induced platelet aggregation in gastric microvasculature with the manifestation of systemic-onset disease is another proposed mechanism of H-pylori induced ITP [21].

Host immune response and Helicobacter-pylori infection

Various studies have reported the association of H-pylori with various outer membranes proteins (Opm's) like outer inflammatory protein A (OipA), blood group antigen-binding adhesion A (BabA), and sialic acid-binding adhesion (SabA) with the exquisite role of H-pylori binding with gastric epithelium [28,29]. In the same vein, studies have also reported the association of H-pylori with various virulent factors such as cytotoxin-associated gene A (CagA) and vacuolating associated gene A (VacA), which help in colonization and infection [30]. The CagA is known to be located in a 40Kb cluster of terminal genes on cytotoxin antigen pathogenicity island (Cag PAI) that codes for the production of Cag A proteins and type IV secretion system (T4SS) [31]. Those infected with the Cag PAI+ strain of H-pylori are more likely to develop gastric ulceration and gastric carcinoma than those with Cag PAI-negative strain. The type IV secretory system (T4SS) acts as a transport vehicle for transporting CagA proteins from gastric mucosal surface to endothelial cells where CagA protein is tyrosine-phosphorylated at the site containing Glu-Pro-Ile-Tyr-Ala (EPIYA) sequence and initiate strong host immune response by induction of IL-8 (a pro-inflammatory cytokine) and NF-KB mediated immune inflammatory response [32,33]. Soon after immune system activation, the host immune system starts producing anti-CagA antibodies (IgG) with a strong affinity for platelets surface glycoproteins (GP IIb/IIIa, GPIb/IX, and GP Ia/IIa) through the mechanism of cross-reactivity and platelets destruction and clearance by reticuloendothelial system (RES) [21].

Similarly, the role of VacA (the second most important virulent factor of H-pylori) is also of paramount importance in the pathogenesis of H-pylori induced ITP. The studies have shown the exquisite role of VacA in blocking T-Helper cells by an interruption in the T-cell receptor IL-2 pathway [34]. In the same vein, the binding of VacA with multimerin-1, a massive, soluble, disulfide-linked homo polymeric protein also called elastin microfibril interfacer 4 (EMILIN-4) expressed on megakaryocytes and platelets encoded by the MMRN1 gene, enhances the platelets activation and clearance [35,36]. The role of genetic factors such as HLA-class II allele patterns has also been demonstrated in the pathogenesis of H-pylori induced ITP but still, very rare work has been done so far to accept this fact as a generalized mechanism [37].

Clinical Characteristics of H Pylori–Associated ITP

H pylori–infected ITP patients were found to be significantly older than H pylori–uninfected patients [38,39]. This is not unexpected, as the prevalence of H pylori infection in the general population increases with increasing with age [18]. In contrast, all prospective series that we reviewed failed to detect significant differences in other characteristics, such as sex and platelet count. A significant association between H pylori infection and the presence of symptoms of dyspepsia has been reported by Michel et al 6 but not by Stasi et al. [40]. A cross- sectional study by Fukui et al did not find any correlation between H pylori infection and thrombocytopenia during pregnancy [41]. In a retrospective Japanese study, the H pylori– positive group was significantly older ($P < .005$) and had more cases of hyperplastic megakaryocytes in the bone marrow ($P= .01$) than patients without H pylori infection [42].

Helicobacter-Pylori Eradication therapy and Immune thrombocytopenic Purpura

ITP is characterized by a low platelet count and can lead to life-threatening bleeding. Therefore, the diagnosis and evaluation of the underlying etiology are very important for appropriate treatment. Since ITP is a diagnosis of exclusion, appropriate testing must be done to identify all the possible causes of low platelet count. Also, testing needs to be done to exclude infections like HIV and HCV.

Although the exact mechanism of H-pylori induced ITP is not conclusively elaborated, it is now considered standard practice to test for H-pylori infection in the face of ITP. In the year 2010, many experts from different countries concluded in a consensus report that ITP is one of the extragastric manifestations of Helicobacter pylori infection and a strong indication for H-pylori eradication therapy44. According to guidelines of the American society of Hematology (2011), H-pylori infection is acknowledged as a secondary cause of ITP and recommended the testing for H-pylori infection in patients with ITP and living in endemic areas [45]. Similarly, in 2009, the Asia-Pacific conference about the management of H-pylori infection also concluded the use of H-pylori eradication therapy for the treatment of ITP [46].

The major complication associated with ITP individuals is life-threatening hemorrhage, particularly intracranial hemorrhage [47]. The treatment of ITP is recommended when the platelet count becomes less than 50×109 /L and in patients undergoing surgery or suffered trauma [48]. According to the American society of Hematology, the currently known treatment for patients of ITP is through Intravenous immunoglobulin (IVIG), corticosteroids, immunosuppressive therapy, anti-D immunoglobulin, and splenectomy. Similarly, according to the revised guidelines of ITP management by ASH (2019), the role of rituximab, eltrombopag (Revolade) and romiplostim have also been implicated in treatment of ITP [45]. In the same vein, the H-pylori eradication therapy consisting of triple therapy like Proton pump inhibitors (omeprazole, lansoprazole, pantoprazole) and antibiotics like amoxicillin, clarithromycin, and metronidazole for two weeks is also now recommended for patients of ITP as a long-term treatment [36].

HP stool antigen testing and blood platelet count is done eight weeks post therapy to check the efficacy of treatment [40]. It has shown promising results with improved platelet counts and the normalization of auto-platelet antibodies without relapse [49]. Also, these treatment modalities have fewer side effects and are cost-effective.

Response criteria for rise in platelet count following eradication therapy

Various studies have reported variable response criteria in terms of complete, partial and no response. In a study by Payandeh et al. [50], the response criteria defined was as followed:

- Complete response (CR): when platelet count become $>150 \times 10^3$ /μL of baseline count at 6 months of treatment.
- Partial response (PR): when platelet count rises to $>30 \times 10^3$/μL of baseline count at 6 months of treatment.
- No response (NR): when rise in platelet count follows none of the above given values.

Similarly, according to international working group guidelines on ITP51, the response criteria were defined as follows:

- Complete response (CR): Platelet count of at least 100×10^3 /μL at 2 months of follow-up with or without maintenance therapy.
- Partial response (PR): Platelet count of at least 30×10^3 /μL at 2 months of follow-up or doubling of platelet count over a period of more than 2 months.
- No response (NR): Platelet counts of less than 30×10^3 /μL at 2 months of follow-up or didn't increase above 50% of pre-treatment level at 2 months of treatment.

Most of the studies conducted for assessment of platelet responses after Helicobacter pylori eradication therapies follow these international working group guidelines criteria to categorize platelet response in terms of complete, partial and no response. However, no matter which criteria are being followed, the ultimate goal is the assessment response of platelet count after H-pylori eradication therapy to validate the effectiveness of H-pylori eradication therapy in treatment of ITP.

Predictors of Platelet Response to H pylori Eradication

The pretreatment factor that was more consistently associated with a platelet response to H pylori eradication was a shorter ITP duration [40,42]. Patients with very low platelet counts ($< 30 \times 109$/L) also appear to have fewer chances of response, although this issue has not been systematically addressed in most published reports. In the Italian/UK study

platelet responses were observed in 17 (33%) of 52 patients, but only 1 response was observed among patients with severe thrombocytopenia [40]. Other clinical features, such as age, sex, and previous therapies, including corticosteroids and splenectomy, were not useful to predict the platelet response. In one study, HLA-DQB1*03 haplotypes were shown to be associated with a higher probability of the platelet response, although the number of patients analyzed in that study was too small to draw conclusions. As reported in the previous section, there is a significant discrepancy in the platelet response to eradication therapy among various countries. Cohorts from Japan

And Italy had response rates of 39% to 100% in H pylori–infected ITP patients [38,39]. However, studies from Spain [52] and the United States [53,54] have documented little or no platelet response to triple therapy. Moreover, recent studies conducted in Serbia [55] and Turkey [56] showed a relatively low response rate (26% and 40%, respectively), whereas the single study from Colombia shows a very high and sustained response rate (80.8%) [57]. Further analysis shows that in almost every series where there was a platelet response as a result of a successful eradication treatment, the H pylori infection rate in patients with ITP was relatively higher than in those where no association was found. So in the US, where the background prevalence of H pylori is low, there are also low chances of obtaining a platelet response to eradication therapy; in Japan, where the prevalence of H pylori in the general population is around 70%, eradication therapy produces platelet responses in a high proportion of cases. In this regard, it is noteworthy that the CagA positivity of H pylori varies depending upon geographic location. In Japan, most H pylori strains express CagA, whereas the proportion of CagA-positive strains in Western countries is lower [58].

Conclusion

HP infection is an important, yet underrated, cause of secondary thrombocytopenia. Literature over the past few years has elucidated a paramount association between HP infection and development of ITP. Various mechanisms of HP induced ITP have been proposed by various researches in literature; however, the most commonly discussed mechanism is the role of molecular mimicry (production of auto antibodies against HP virulent factor Cag A and cross reactivity of these antibodies with various surface antigens such as GP IIb/IIIa, GP Ib/IX, and GP Ia/IIa, on platelet membranes. Every patient with unexplained thrombocytopenia should undergo HP testing, including non-invasive tests, such as urea breath test, anti-HP antibodies, and stool antigen test, followed by invasive tests such as endoscopy and biopsy. HP eradication therapy with triple therapy (amoxicillin, clarithromycin, and PPI) should be tried in every ITP case where HP testing is positive or patients aren't responding to conventional therapies.

Conflict of interests

None declared

References

1. Terrell DR, Beebe LA, Neas BR, Vesely SK, Segal JB, George JN. Prevalence of primary immune thrombocytopenia in Oklahoma. Am J Hematol. 2012;87(9):848-852.
2. Psaila B, Bussel JB. Immune thrombocytopenic purpura. Hematol Oncol Clin North Am. 2007;21(4):743-vii.
3. Khodaii Z, Vakili H, Ghaderian SM, Najar RA, Panah AS. Association of Helicobacter pylori infection with acute myocardial infarction. Coron Artery Dis. 2011;22(1):6-11.
4. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood. 2004; 15:1364-1369.
5. Jang JH, Kim JY, Mun YC, et al. Management of immune thrombocytopenia: Korean experts recommendation in 2017. Blood Res. 2017;52: 254–263.
6. Fan H, Zhu HL, Li SX, et al. Efficacy of amifostine in treating patients with idiopathic thrombocytopenia purpura. Cell Biochem Biophys. 2011;59:7–12.
7. Zain MA, Zafar F, Ashfaq A, et al. Helicobacter pylori: An underrated cause of Immune Thrombocytopenic Purpura. a comprehensive review. Cureus. 2019;11: e5551.
8. Pezeshki S, Saki N, Ghandali MV, et al. Effect of Helicobacter Pylori eradication on patients with ITP: a meta-analysis of studies conducted in the Middle East. Blood Res. 2021;56:38–43.
9. Rothenbacher D, Brenner H. Burden of Helicobacter pylori and H. pylori-related diseasesin developed countries: recent developments and future implications. Microbes Infect. 2003;5:693–703.
10. Rothenbacher D, Winkler M, Gonser T, et al. Role of infected parents in transmission ohelicobacter pylori to their children. The Pediatric Infect Dis J. 2002;21:674–679.
11. Burucoa C, Axon A. Epidemiology of Helicobacter pylori infection. Helicobacter. 2017;22 Suppl 1:10.1111/hel.12403.
12. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis . Lancet. 1983;321:1273-1275.
13. Brown LM. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev. 2000; 22:283-297.
14. Graham DY. Helicobacter pylori infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. Gastroenterology. 1997;113:1983-1991.
15. Pasceri V, Cammarota G, Patti G, et al. Association of virulent Helicobacter pylori strains with ischemic heart disease. Circulation. 1998;97:1675–1679.
16. Annibale B, Lahner E, Bordi C, et al. Role of Helicobacter pylori infection in pernicious anaemia. Dig Liver Dis. 2000;32:756–762.
17. Gasbarrini A, Franceschi F, Tartaglione R, et al. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet. 1998;352:878.
18. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med. 2002;347:1175-1186.
19. Logan RP, Walker MM. ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of Helicobacter pylori infection. BMJ. 2001;323:920-922.
20. Hasni S, Ippolito A, Illei GG. Helicobacter pylori and autoimmune diseases. Oral Dis. 2011; 17:621-627.
21. Jackson S, Beck PL, Pineo GF, et al. Helicobacter pylori eradication: novel therapy for immune thrombocytopenic purpura? A review of the literature. Am J Hematol. 2005;78:142–150.
22. Bettaieb A, Fromont P, Louache F, et al. Presence of cross-reactive antibody between human immunodeficiency virus (HIV) and platelet glycoproteins in HIV-related immune thrombocytopenic purpura. Blood. 1992;80:162–169.
23. Asahi A, Nishimoto T, Okazaki Y, et al. Helicobacter pylori eradication shifts monocyte Fc gamma receptor balance toward inhibitory Fc gamma RIIB in immune thrombocytopenic purpura patients. J Clini Invest. 2008;118: 2939–2949.
24. Yamanishi S, Iizumi T, Watanabe E, et al. Implications for

induction of autoimmunity via activation of B-1 cells by Helicobacter pylori urease. Infect Immun. 2006;74:248–256.

25. Appelmelk BJ, van Die I, van Vliet SJ, et al. Cutting edge: carbohydrate profiling identifies new pathogens that interact with dendritic cell-specific ICAM-3-grabbing non integrin on dendritic cells. J Immunol. 2003;170:1635–1639.
26. Voland P, Hafsi N, Zeitner M, et al. Antigenic properties of HpaA and Omp18, two outer membrane proteins of Helicobacter pylori. Infect Immun. 2003;71:3837–3843.
27. Byrne MF, Kerrigan SW, Corcoran PA, et al. Helicobacter pylori binds von Willebrand factor and interacts with GP Ib to induce platelet aggregation. Gastroenterology. 2003;124:1846–1854.
28. Hessey SJ, Spencer J, Wyatt JI, et al. Bacterial adhesion and disease activity in Helicobacter associated chronic gastritis. Gut. 1990;31:134–138.
29. Guruge JL, Falk PG, Lorenz RG, et al. Epithelial attachment alters the outcome of Helicobacter pylori infection. Proceedings of the National Academy of Sciences of the United States of America. 1998;95:3925–3930.
30. Andersen LP. Colonization and infection by Helicobacter pylori in humans. Helicobacter. 2007;12:12–15.
31. Odenbreit S, Püls J, Sedlmaier B, et al. Translocation of Helicobacter pylori CagA intogastric epithelial cells by type IV secretion. Science. 2000;287:1497–1500.
32. Asahi M, Azuma T, Ito S, et al. Helicobacter pylori CagA protein can be tyrosine phosphorylated in gastric epithelial cells. J Exp Med. 2000;191:593–602.
33. Tummuru MK, Sharma SA, Blaser MJ. Helicobacter pylori picB, a homologue of the Bordetella pertussis toxin secretion protein, is required for induction of IL-8 in gastric epithelial cells. Mol Microbiol. 1995;18:867–876.
34. Holland RL, Bosi KD, Harpring GH, et al. Chronic in vivo exposure to Helicobacter pylori VacA: Assessing the efficacy of automated and long-term intragastric toxin infusion. Sci Rep. 2020;10: 9307.
35. Satoh K, Hirayama T, Takano K, et al. VacA, the vacuolating cytotoxin of Helicobacter pylori, binds to multimerin 1 on human platelets. Thromb J. 2013;11:23.
36. Frydman GH, Davis N, Beck PL, et al. Helicobacter pylori eradication in patients with immune thrombocytopenic ourpura: a review and the role of biogeography. Helicobacter. 2015;20:239–251.
37. Veneri D, De Matteis G, Solero P, et al. Analysis of B- and T-cell clonality and HLA class II alleles in patients with idiopathic thrombocytopenic purpura: correlation with Helicobacter pylori infection and response to eradication treatment. Platelets. 2005;16:307–311.
38. Liebman HA, Stasi R. Secondary immune thrombocytopenic purpura. Curr Opin Hematol. 2007;14:557-573.
39. Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of Helicobacter pylori eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. J Antimicrob Chemother. 2007;60:237246.
40. Stasi R, Rossi Z, Stipa E, Amadori S, Newland AC, Provan D. Helicobacter pylori eradication in the management of patients with idiopathic thrombocytopenic purpura. Am J Med. 2005;118:414-419.
41. Fukui O, Shimoya K, Shimizu T, Fukuda H, Wasada K, Murata Y. Helicobacter pylori infection and platelet counts during pregnancy. Int J Gynaecol Obstet. 2005;89:26-30.
42. Fujimura K, Kuwana M, Kurata Y, et al. Is eradication therapy useful as the first line of treatment in Helicobacter pylori-positive idiopathic thrombocytopenic purpura? Analysis of 207 eradicated chronic ITP cases in Japan. Int J Hematol. 2005;81:162-168.
43. Bazzoli F. Key points from the revised Maastricht Consensus Report: the impact on general practice . Eur J Gastroenterol Hepatol. 2001;13:3-7.
44. Malfertheiner P, Megraud F, O'Morain, CA, et al. Management of Helicobacter pylori infection--the Maastricht IV/Florence consensus report. Gut. 2012;61:646–664.
45. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3:3829–3866.
46. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. J Gastroenterol Hepatol. 2009;24:1587–1600.
47. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, et al. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med. 2000;160:1630–1638.
48. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115:168–186.
49. Kuwana M. Helicobacter pylori-associated immune thrombocytopenia: clinical features and pathogenic mechanisms. World J Gastroenterol. 2014;21:714-723.
50. Payandeh M, Raeisi D, Sohrabi N, et al. Poor platelet count response to Helicobacter Pylori eradication in patients with severe idiopathic thrombocytopenic purpura. Int J Hematol Oncol Stem Cell Res. 2013;7:9–14.
51. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113: 2386–2393.
52. Jarque I, Andreu R, Llopis I, et al. Absence of platelet response after eradication of Helicobacter pylori infection in patients with chronic idiopathic thrombocytopenic purpura. Br J Haematol. 2001;115:1002-1003.
53. Michel M, Cooper N, Jean C, Frissora C, Bussel JB. Does Helicobacter pylori initiate or perpetuate immune thrombocytopenic purpura? Blood. 2004;103:890-896.
54. Ahn ER, Tiede MP, Jy W, Bidot CJ, Fontana V, Ahn YS. Platelet activation in Helicobacter pylori-associated idiopathic thrombocytopenic purpura: eradication reduces platelet activation but seldom improves platelet counts. Acta Haematol. 2006;116:19-24.
55. Suvajdzic N, Stankovic B, Artiko V, et al. Helicobacter pylori eradication can induce platelet recovery in chronic idiopathic thrombocytopenic purpura. Platelets. 2006;17:227-230.
56. Sayan O, Akyol Erikci A, Ozturk A. The Efficacy of Helicobacter pylori eradication in the treatment of idiopathic thrombocytopenic purpura—the first study in Turkey. Acta Haematol. 2006;116:146-149.
57. Campuzano-Maya G. Proof of an association between Helicobacter pylori and idiopathic thrombocytopenic purpura in Latin America. Helicobacter. 2007;12:265-273.
58. Van Doorn LJ, Figueiredo C, Megraud F, et al. Geographic distribution of vac A allelic types of Helicobacter pylori. Gastroenterology. 1999;116:823-830.