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Helicobacter pylori-associated immune thrombocytopenia: Clinical features and pathogenic mechanisms

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Abstract

Immune thrombocytopenia (ITP) is an autoimmune disease mediated by anti-platelet autoantibodies. There is growing evidence that the eradication of *Helicobacter pylori* (*H. pylori*) effectively increases platelet count in a considerable proportion of ITP patients infected with this bacterium. In the majority of ITP patients responding to *H. pylori* eradication therapy, the anti-platelet autoantibody response is completely resolved with no relapse for more than 7 years, indicating that the disease is cured. Therefore, adult patients with suspected ITP should be examined for *H. pylori* infection, and eradication therapy is recommended if the infection is present. Notably, however, the efficacy of *H. pylori* eradication therapy in ITP patients varies widely among countries, with a higher response rate in Japan compared with the United States and European countries other than Italy. The pathogenesis of *H. pylori*-associated ITP is still uncertain, although the mechanisms are known to involve multiple factors. *H. pylori* may modulate the Fc γ -receptor balance of monocytes/macrophages in favor

of activating Fc γ receptors, and *H. pylori* components may mimic the molecular makeup of platelet antigens. Further studies of the pathogenic process of *H. pylori*-associated ITP may be useful for the development of new therapeutic strategies for ITP.

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Key words: Autoantibody; Childhood; *Helicobacter pylori*; Fc γ receptor; Immune thrombocytopenia; Idiopathic thrombocytopenic purpura; Systemic lupus erythematosus

Core tip: In this review, we summarize recent updates on basic and clinical aspects of *Helicobacter pylori* (*H. pylori*)-associated immune thrombocytopenia (ITP). We highlight the efficacy of *H. pylori* eradication in adult and childhood ITP as well as in secondary ITP, variability in the efficacy of eradication in various countries, factors predicting the eradication-related platelet response, and the mechanisms responsible for the development of ITP in association with *H. pylori* infection. It is apparent that in a distinct subgroup of *H. pylori*-associated ITP, this bacterial infection is central to the ITP pathogenesis.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), a gram-negative spiral bacterium, is the causative agent in chronic gastritis, gastric and duodenal ulcer disease, and gastric cancer. *H. pylori*

has also been implicated in the pathogenesis of extra-digestive disorders, including cardiovascular, hematologic, and autoimmune diseases^[1]. The strongest evidence has been reported for immune thrombocytopenia (ITP), with high-quality studies showing that the disease improved after *H. pylori* was successfully eradicated.

ITP is a typical organ-specific autoimmune disease; it is mediated by anti-platelet autoantibodies that bind to platelets and megakaryocytes, accelerating platelet destruction by the reticuloendothelial system and suppressing platelet production^[2]. The autoantibody response primarily targets platelet-surface glycoproteins such as GP II b/III a and GP I b. This condition is known as primary ITP when it occurs without an underlying disease, but it is also seen in patients with various diseases, including systemic lupus erythematosus (SLE). Although the etiology of ITP is obscure, microorganisms such as human immunodeficiency virus and hepatitis C virus are known to contribute to its development^[3], indicating that in a particular subset of ITP, infectious agents play a significant role in the pathogenesis of the autoimmune response.

First observed in 1988^[4], the increase in platelet counts in ITP patients after eradicating *H. pylori* has since been confirmed by several studies. Consequently, *H. pylori* eradication therapy is now a treatment option for ITP^[5]. However, a number of questions regarding the relationship between *H. pylori* infection and ITP remained unsolved, including the great variability in the efficacy of *H. pylori* eradication therapy among countries, factors predicting the platelet response after *H. pylori* eradication, and mechanisms responsible for the platelet response associated with *H. pylori* eradication^[6]. Some of these questions have been answered in the past few years. This review summarizes recent updates on clinical and therapeutic aspects of *H. pylori*-associated ITP, as well as the pathogenesis of this disease.

EFFICACY OF *H. PYLORI* ERADICATION IN ITP

Adult ITP

In 1988, Gasbarrini *et al*^[4] reported that platelet counts increased in all of 8 *H. pylori*-infected patients with ITP who were treated with a regimen to eradicate *H. pylori*, while the platelet counts were unchanged in 3 *H. pylori*-infected patients who did not receive the regimen. Reports followed of partial or complete platelet responses observed in a large proportion of ITP patients treated with an *H. pylori* eradication regimen consisting of a 1- to 2-wk standard triple therapy with a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole^[6-8]. A nation-wide survey in Japan involved 207 *H. pylori*-infected adult patients with ITP, making it the largest study on the efficacy of eradicating *H. pylori* in ITP patients^[9]. In that study, after the successful eradication of *H. pylori*, 63% of the patients achieved some degree of platelet recovery, and within this group, 23% showed

complete remission at 12 mo after the eradication. Although most early studies excluded patients with severe thrombocytopenia, who were at high risk of bleeding, several case series have reported the efficacy of eradicating *H. pylori* even in patients with refractory ITP, including patients with severe thrombocytopenia that resisted multiple therapeutic regimens including splenectomy^[9-11]. Although most studies began assessing the platelet counts one month after starting eradication therapy, we observed platelet recovery after just a week in almost half of those responding^[12]. Long-term follow-up studies showed that this platelet response lasted 7 or more years after *H. pylori* was eradicated, with very few cases of relapse^[13,14]. An assessment of circulating B cells producing anti-GP II b/III a antibodies before and after eradication treatment indicated that the anti-platelet autoantibodies disappeared after platelet recovery when *H. pylori* had been successfully eradicated^[12]. Thus, in certain patients, ITP appears to be clinically and immunologically cured by eradicating *H. pylori*.

In the first systematic review with meta-analysis, Franchini *et al*^[15] reviewed 788 patients with ITP, including 494 *H. pylori*-infected patients collected from 17 studies, in 2007. Platelet counts increased in ITP patients who received eradication treatment, compared with untreated patients, and the weighted mean difference (WMD) in platelet count was $34.0 \times 10^9/L$ regardless of the outcome of *H. pylori* eradication. The platelet counts increased significantly in *H. pylori*-infected patients after successful *H. pylori* eradication, compared with the following groups: untreated *H. pylori*-infected patients (WMD of $40.8 \times 10^9/L$), *H. pylori*-infected patients who failed eradication (WMD of $52.2 \times 10^9/L$), and *H. pylori*-uninfected patients (WMD of $46.4 \times 10^9/L$). Another systematic literature review involving 1555 patients revealed a weighted mean complete response (platelet count $\geq 100 \times 10^9/L$) after successful *H. pylori* eradication of 42.7%, and an overall response (platelet count $\geq 30 \times 10^9/L$, and at least doubling of the basal count) of 50.3%^[16]. Even in patients with a low baseline platelet count ($< 30 \times 10^9/L$), the overall response rate was 35.2%, including 20.1% with a complete response. These findings indicate that *H. pylori* eradication is closely related to platelet recovery in adult ITP patients. Finally, another systematic review evaluated the efficacy of the *H. pylori* eradication regimen in patients with ITP by comparing the platelet response in patients with or without an *H. pylori* infection^[17]. The odds of achieving platelet recovery following the eradication regimen were 14.5 times higher in 205 *H. pylori*-infected patients than in 77 *H. pylori*-uninfected patients. This clearly indicates that platelet recovery after the eradication regimen results from the eradication of *H. pylori* itself, rather than from *H. pylori*-independent mechanisms such as immune-modulatory effects of the drugs themselves, or the eradication of bacteria other than *H. pylori*.

The clear linkage between platelet recovery and the disappearance of *H. pylori* suggests a direct role for *H. py-*

lori infection in the ITP pathogenesis. In addition, in the majority of ITP patients who achieved a complete platelet response after *H. pylori* eradication, the anti-platelet autoantibody response was also eliminated. Thus, patients who are infected with *H. pylori* and who respond to the eradication therapy fall into a distinct, widely recognized ITP subgroup, termed *H. pylori*-associated ITP^[18,19], that is considered a type of secondary ITP^[5]. Given the relatively high efficacy, safety, and economy of *H. pylori* eradication therapy, *H. pylori* detection should be considered when examining adult patients who are suspected to have ITP, and eradication therapy is recommended if *H. pylori* infection is present^[5,8].

Variability among countries

Although the efficacy of *H. pylori* eradication therapy in infected adults with ITP has been confirmed by high-quality systematic reviews, some studies have reported little to no platelet response after *H. pylori* eradication therapy. For example, Jarque *et al*^[20] and Ahn *et al*^[21] observed platelet recovery was in only 13% and 7%, respectively, of adult patients with ITP after successfully eradicating *H. pylori*. Michel *et al*^[22] found no platelet response in 14 *H. pylori*-infected ITP patients even after successfully eradicating the *H. pylori*. These widely varying reports of the efficacy of *H. pylori* eradication therapy in ITP patients are explained, in part, by different eligibility criteria and different definitions of platelet response among the various studies. However, response rates differed between the 57.9% reported by studies in Japan, and the 38.3% rate reported by studies from other countries^[16]. Studies from Japan and Italy tend toward better response rates, ranging from 28% to 100%, than studies from the United States and Spain (< 13).

Thus, variability in the efficacy of *H. pylori* eradication in different populations should be considered to establish recommendations for screening and eradicating *H. pylori*. For example, *H. pylori* screening is certainly worthwhile in Japan, a country with a high prevalence of infection and a high response rate to eradication treatment. In fact, in a recently developed reference guide for managing adult ITP in Japan, *H. pylori* eradication is a prominent strategy for managing ITP in adult patients^[23]. Namely, the guide states that all patients diagnosed with ITP should be screened for *H. pylori* infection, and eradication therapy is recommended as a first line of treatment, regardless of platelet count, if *H. pylori* infection is present. These recommendations may not be appropriate in the United States or in European countries (other than Italy), in which both the prevalence of infection and the response rates to eradication therapy are low. Indeed, *H. pylori* eradication is not mentioned in the international consensus report on the management of primary ITP^[24], while the eradication therapy is recommended in patients who are found to have *H. pylori* infection in the American Society of Hematology 2011 evidence-based practice guideline for ITP^[5].

A recent systematic review demonstrated a correla-

Table 1 Prevalence of *Helicobacter pylori* infection and platelet response after *Helicobacter pylori* eradication in children with immune thrombocytopenia *n* (%)

Ref.	Country	Prevalence of <i>Helicobacter pylori</i> infection	Platelet response
Rajantie <i>et al</i> ^[29]	Finland	0/17 (0)	ND
Jaing <i>et al</i> ^[30]	Taiwan	9/22 (41)	5/9 (50)
Hayashi <i>et al</i> ^[31]	Japan	2/10 (20)	1/1 (100)
Yetgin <i>et al</i> ^[32]	Turkey	11/35 (31)	0/9 (0)
Jaing <i>et al</i> ^[33]	Taiwan	10/63 (16)	ND
Loffredo <i>et al</i> ^[34]	Italy	8/39 (21)	0/8 (0)
Neeffes <i>et al</i> ^[35]	Netherlands	3/47 (6)	3/3 (100)
Wu <i>et al</i> ^[36]	Taiwan	6/32 (19)	ND
Bisogno <i>et al</i> ^[37]	Italy	8/24 (33)	1/8 (13)
Hamidieh <i>et al</i> ^[38]	Iran	4/31 (13)	0/4 (0)
Treepongkaruna <i>et al</i> ^[39]	Thailand	16/55 (29)	0/7 (0)
Ferrara <i>et al</i> ^[40]	Italy	8/24 (33)	8/8 (100)
Maghbool <i>et al</i> ^[41]	Iran	5/30 (17)	5/5 (100)
Russo <i>et al</i> ^[42]	Italy	50/244 (20)	13/33 (39)

ND: Not described.

tion in ITP patients between the prevalence of *H. pylori* infection and the platelet response rates to eradication therapy^[16]. The reason for such variability among countries is not clear, but differences in the epidemic *H. pylori* strains according to geographical area could account for differences in the clinical response. In this regard, *H. pylori* strains that possess cytotoxin-associated gene A (CagA) have been proposed to have a role in the pathogenesis of *H. pylori*-associated ITP based on the potential cross-reactivity between CagA and platelet glycoproteins^[25,26]. The frequency of CagA-positive strains varies by geographic location: the majority of the *H. pylori* strains found in Eastern Asia, including Japan, express CagA, whereas the proportion of CagA-positive strains in European countries and North America is much lower^[27]. However, genetic and other environmental factors are also likely to contribute to the variability in platelet recovery after *H. pylori* eradication among different populations.

Childhood ITP

The clinical course of ITP is quite different in children than in adult patients. ITP in children is usually an acute form with spontaneous recovery within 6 mo, although thrombocytopenia lasts more than 6 mo in about 20% of children with ITP^[28]. There are only a few pediatric studies evaluating the role of *H. pylori* infection in chronic ITP in children. Table 1 summarizes the studies assessing the prevalence of *H. pylori* infection and platelet response after eradicating *H. pylori* in children with ITP. Although a Finnish study failed to detect *H. pylori* infection in any of 17 children with chronic ITP^[29], other studies detected *H. pylori* infection in a small proportion of children with chronic ITP^[30-42]. The highest prevalence was reported in a study conducted in Taiwan, which showed an infection rate of 41%^[29]. A recent multicenter study in Italy revealed that 50 (20) of 244 children with ITP were in-

ected with *H. pylori*⁴⁴². In general, the prevalence of *H. pylori* infection is lower in children than in adults with ITP in a given population.

Reports of platelet recovery after *H. pylori* eradication therapy in children are highly variable and inconsistent. In the first study in Taiwan, platelet counts increased in 5 (56) of 9 *H. pylori*-infected children with ITP after eradication therapy²⁹¹. In studies from the Netherlands, Italy, and Iran, platelet counts increased measurably in all *H. pylori*-infected children after eradication treatment, although the number of subjects analyzed was very small (3, 8, and 5, respectively)^{35,40,41}. However, other studies from Turkey, Italy, Iran, and Thailand showed that none of the patients who underwent treatment to eradicate *H. pylori* infection responded to it^{32,34,38,39}. Even studies from the same country gave diametrically opposite accounts of the efficacy of *H. pylori* eradication. These contradictory results may be partly due to the small number of *H. pylori*-infected children with ITP. An Italian study, which had the largest number of patients, showed that 13 (39) of 33 children with *H. pylori* infection responded to the eradication treatment⁴². The prevalence of *H. pylori* infection in children with chronic ITP is generally low, suggesting that *H. pylori* infection plays only a minor role in the development of childhood ITP. However, we should recognize that some children infected with *H. pylori* can recover if the *H. pylori* is successfully eliminated. A large-scale study is necessary to confirm the relationship between *H. pylori* infection and childhood ITP.

Other forms of secondary ITP

ITP may develop in the context of other disorders or conditions, including lymphoproliferative, autoimmune, and infectious diseases⁴³. Although *H. pylori*-associated ITP is now categorized as a secondary ITP condition, the efficacy of *H. pylori* eradication therapy has not been deeply examined in patients with other types of secondary ITP. To evaluate the role of *H. pylori* infection in the pathogenesis of secondary ITP, we conducted an open-label prospective study involving 34 consecutive *H. pylori*-infected patients with ITP, including 16 with primary ITP, 8 with secondary ITP associated with SLE, and 10 with secondary ITP associated with liver cirrhosis. All the patients received a standard *H. pylori* eradication regimen consisting of amoxicillin, clarithromycin, and lansoprazole, and the *H. pylori* was successfully eradicated in all except one patient with primary ITP, and another with liver cirrhosis. As shown in Figure 1, the platelet count had increased 3 mo after eradication treatment in nearly all the patients with primary ITP, but was virtually unchanged in patients with SLE or liver cirrhosis. In addition, a decrease in circulating anti-GP IIb/IIIa antibody-producing B cells was observed in patients with primary ITP, but not in ITP patients with SLE or liver cirrhosis. These findings clearly indicate that the eradication of *H. pylori* fails to improve the pathogenic process in patients with some forms of secondary ITP. Thus, the efficacy of *H. pylori* eradication therapy is likely to be restricted to

patients in a subgroup of seemingly primary ITP (*H. pylori*-associated ITP), and *H. pylori* infection appears to be uninvolved in the pathogenic process of other secondary ITPs.

CHARACTERISTICS OF *H. PYLORI*-ASSOCIATED ITP

Features of ITP patients infected with *H. pylori*

Several authors have tried to identify characteristics of *H. pylori*-associated ITP by comparing the clinical features of adult ITP patients with or without *H. pylori* infection. ITP patients infected with *H. pylori* were significantly older than uninfected patients⁹, but this is predictable because the prevalence of *H. pylori* infection increases with age in the general population⁴⁴. Multiple studies have failed to detect significant differences in any other demographic or clinical characteristic, including sex, platelet count, or response to therapy.

Several studies have looked for differences in genetic factors in ITP patients with or without *H. pylori*. Veneri *et al*⁴⁵ examined the human leukocyte antigen (HLA)-DRB1 and *DQB1* alleles in Italian patients with ITP, and found that *H. pylori*-positive patients had a lower frequency of *DRB1*03*, and higher frequencies of *DRB1*11*, *DRB1*14*, and *DQB1*03*, compared with *H. pylori*-negative patients. However, we failed to detect any association between *H. pylori* infection and HLA-DRB1 or *DQB1* alleles in Japanese patients with ITP⁴⁶. Instead, we found that gene polymorphism within the loci for interleukin (IL)-1 β was associated with *H. pylori* infection in patients diagnosed before age 50. While these observations suggest an involvement of genetic background in *H. pylori*-related ITP, the associations should be confirmed by replication studies enrolling patients from other populations.

On the other hand, there was no difference in the IL-2, IL-4, or IL-6 serum levels between patients with and without *H. pylori* infection⁴⁷. The serum levels of chemokines, including monocyte chemoattractant protein-1, regulated upon activation normally T-cell expressed and secreted, and epithelial cell-derived neutrophil attractant-78, were significantly higher in patients with *H. pylori* infection than in those without⁴⁸, although increased levels of these chemokines were also observed in individuals that had *H. pylori*-related gastrointestinal disorders but did not have ITP. Thus, studies have failed to identify demographic, clinical, genetic, or immunologic characteristics unique to ITP patients infected with *H. pylori*. This is probably because there are at least two distinct subgroups of *H. pylori*-infected ITP patients: those with *H. pylori*-associated secondary ITP, who respond to eradication therapy, and those with primary ITP and a coincidental *H. pylori* infection.

Factors predicting a positive response to *H. pylori* eradication therapy

Parameters that predict the platelet response to *H. pylori* eradication therapy have been extensively analyzed in

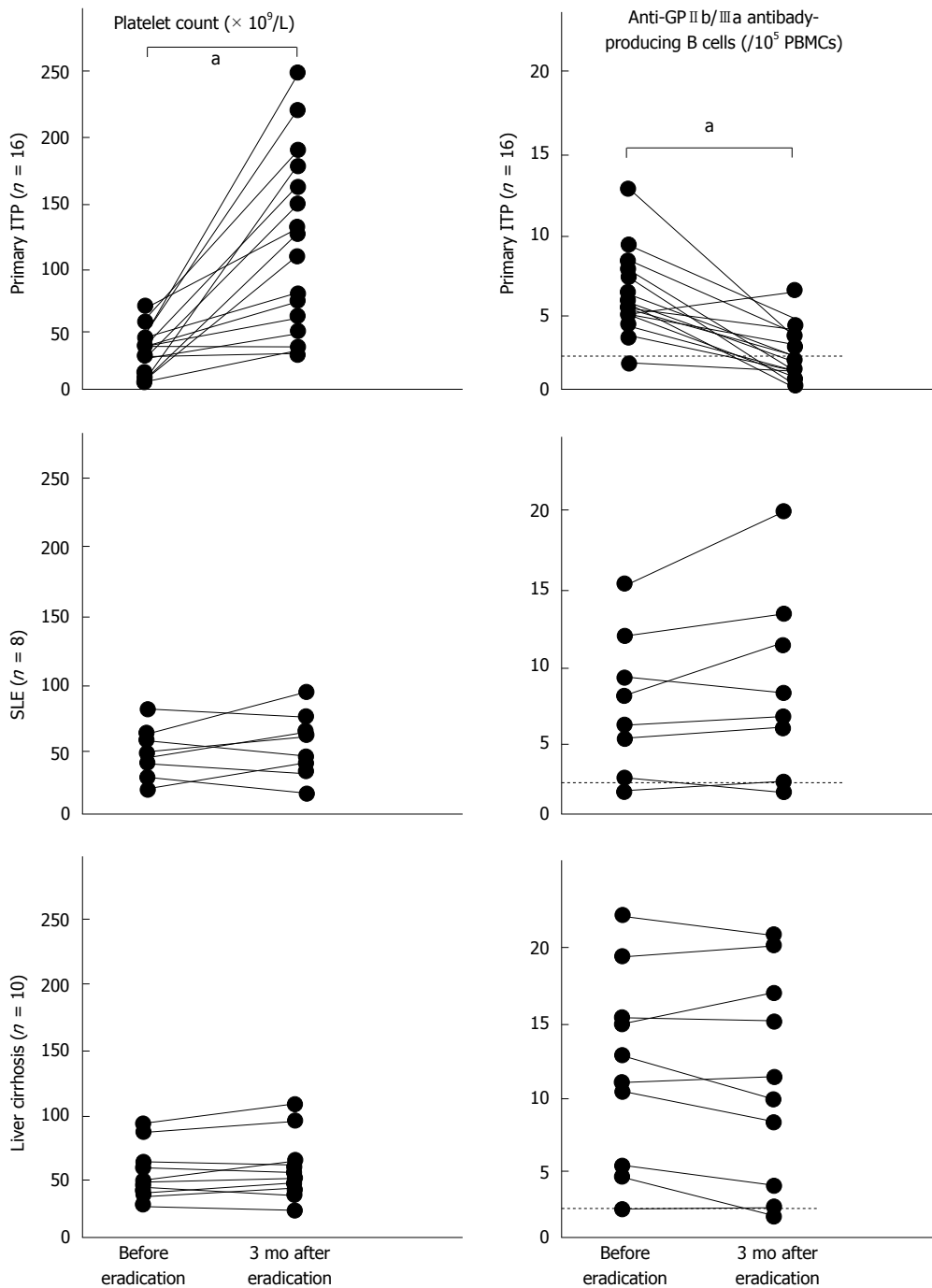


Figure 1 Changes in platelet count and in anti-GP II b/III a antibody-producing circulating B cells before and 3 mo after an *Helicobacter pylori* eradication regimen in *Helicobacter pylori*-positive immune thrombocytopenia patients with no additional disease, or with systemic lupus erythematosus or liver cirrhosis. Changes in absolute values were compared by paired *t* test. ^a*P* < 0.05. A dotted line indicates the cut-off for circulating anti-GP II b/III a antibody-producing B cells, which was 2/10⁵ peripheral blood mononuclear cells (PBMCs). ITP: Immune thrombocytopenia; SLE: Systemic lupus erythematosus.

H. pylori-infected ITP patients. The most consistently reported feature that predicts a favorable response is a shorter duration of ITP^[9,49,50], but other studies have not found this association^[51-53]. Other clinical characteristics, including an age less than 65 when diagnosed with ITP^[49], a higher baseline platelet count^[49], no prior corticosteroid therapy^[51], no concomitant corticosteroid therapy^[54,55], and no prior therapy for ITP^[49], have been reported as factors predicting the platelet response, but other studies have reported conflicting results.

Several studies have examined whether there is a genetic predisposition to the platelet response. An association was shown between the *HLA-DQB1*03* haplotypes and a higher probability of the platelet response^[45]. Moreover, single nucleotide polymorphisms within the genes for tumor necrosis factor-β and an inhibitory Fcγ receptor II B (FcγR II B) were found to be useful for predicting the response to the eradication treatment^[55,56]. In terms of the anti-platelet autoantibody specificity, we found that the presence of an anti-GPIb autoantibody

response predicts resistance to *H. pylori* eradication therapy. Interestingly, a study from Italy reported that ITP patients with antibodies to CagA were more likely to respond to eradication therapy than patients without these antibodies^[57]; although a study conducted in Japan failed to confirm this observation^[56], we should recognize that CagA-positive strains are more common in Japan than in Italy.

Finally, Sato *et al*^[58] assessed potential associations of the platelet response to *H. pylori* eradication with upper gastrointestinal endoscopic findings and histologic features of stomach tissue obtained by biopsy. A severe degree of gastric atrophy on endoscopy and intense inflammation and atrophy in the gastric corpus detected by biopsy were predictors for a favorable response. These findings together indicate that both genetic background and bacterial factors, which collaboratively regulate the host inflammatory response to the bacterium, can account, at least in part, for the variable response to *H. pylori* eradication therapy.

MECHANISMS OF

H. PYLORI-ASSOCIATED ITP

It has become clear that *H. pylori*-associated ITP is a subset of ITP in which *H. pylori* infection is actively involved in the pathogenic process. In patients with *H. pylori*-associated ITP, *H. pylori* eradication increases the platelet count in parallel with a suppression of anti-platelet autoantibody production, and results in the remission or even cure of the disease in many patients. Since eradicating *H. pylori* does not increase the platelet count in non-ITP subjects^[59], the platelet recovery after successful *H. pylori* eradication is specific to ITP patients, and is likely to be mediated through the inhibition of an ongoing autoimmune response to platelets.

Molecular mimicry

Several hypotheses have been proposed regarding the mechanism by which *H. pylori* induces the development of ITP. One intriguing theory is that cross-reactive antibodies are produced that react with both *H. pylori* components and platelet surface antigens through molecular mimicry. Michel *et al*^[22] investigated this molecular-mimicry hypothesis by testing platelet eluates derived from *H. pylori*-infected ITP patients, and found that platelet eluates with the capacity to react with GP II b/IIIa or GPIIb failed to recognize any *H. pylori* antigens. On the other hand, Takahashi *et al*^[25] reported that platelet eluates from *H. pylori*-infected ITP patients recognized CagA in immunoblots, but those from *H. pylori*-infected non-thrombocytopenic individuals did not. Unfortunately, since the IgG concentrations in the eluates were not adjusted in these studies, the intensity of individual bands was not quantitative. In addition, since platelets are known to take up and concentrate circulating IgG in intracellular granules, it is not clear whether the anti-CagA antibodies detected truly cross-react with platelet-

surface antigens. Although it was recently reported that monoclonal antibodies generated against recombinant *H. pylori* urease B react with GP II b/IIIa expressed on the platelet surface, this study failed to show the presence of this cross-reactive antibody repertoire in patients with *H. pylori*-associated ITP^[60]. While these findings suggest that cross-reacting antibodies against *H. pylori* may be present in patients with ITP, their pathogenic role remains obscure.

Non-specific activation of the immune system

In another potential mechanism, chronic *H. pylori* infection may act on the host's immune system to stimulate acquired immune responses, causing autoreactive T and B cells to emerge. Yamanishi *et al*^[61] showed that *H. pylori* components are able to initiate autoimmune responses *via* autoantibodies that are produced through the activation of B-1 cells. However, this non-specific mechanism alone does not explain how an autoimmune response specific to platelet glycoproteins, such as that observed in ITP patients, would develop. In fact, there is no difference in the production of non-specific autoantibodies, including anti-nuclear, anti-microsome, and anti-smooth muscle antibodies, in individuals with and without *H. pylori*^[62].

Modulation of monocyte/macrophage function

We have been evaluating mechanisms that elicit and maintain autoantibody responses to platelet glycoproteins in patients with ITP^[63-65]. After detailed analyses of the GP II b/IIIa-reactive CD4⁺ T cells and B cells in ITP patients, we proposed a "pathogenic loop" model for the ongoing IgG anti-platelet autoantibody response in ITP patients^[64]. Specifically, macrophages in the reticuloendothelial system capture opsonized platelets *via* Fcγ receptors, and present antigenic platelet glycoprotein-derived peptides to T cells. Autoreactive CD4⁺ T cells are then activated by their recognition of the antigenic peptides and exert helper activity to stimulate B cells to produce IgG anti-platelet autoantibodies, which in turn bind to circulating platelets. Theoretically, once this pathogenic loop is established, the production of IgG anti-platelet autoantibodies continues endlessly. Since anti-platelet autoantibodies are eliminated after eradicating *H. pylori* in patients with *H. pylori*-associated ITP^[12], this pathogenic loop would consequently be disrupted and blocked. To elucidate the mechanism by which *H. pylori* eradication changes the ongoing pathogenic loop in ITP patients, we conducted a prospective study in which the phenotype and function of the autoreactive T and B cells and of the monocytes/macrophages involved in the pathogenic loop were serially measured in *H. pylori*-infected and -uninfected ITP patients treated with a standard eradication regimen^[67]. At baseline, we found enhanced phagocytic capacity and low expression levels of inhibitory FcγR II B in the circulating monocytes from *H. pylori*-infected patients, but not in those from uninfected patients. Suppression of this activated-monocyte phenotype was observed one week after starting the *H. pylori* eradication regimen,

when eradication was successful. The anti-platelet auto-antibody responses and platelet kinetic parameters subsequently improved, indicating that suppression of the activated-monocyte function precedes the improvement in the autoantibody response.

Interestingly, modulation of the Fcγ-receptor balance toward an activating phenotype has also been observed in *H. pylori*-infected mice, through a downregulation of inhibitory FcγR II B in splenic and circulating monocytes/macrophages. A study in China recently confirmed that the FcγR II B expression on circulating monocytes is down-regulated in *H. pylori*-infected ITP patients^[68]. Therefore, *H. pylori* infection plays an important role in ITP pathogenesis by altering the Fcγ receptor balance of monocytes/macrophages in favor of activating Fcγ receptors, through downregulation of the inhibitory receptor FcγR II B. These findings indicate that the platelet recovery after *H. pylori* eradication in ITP patients is mediated, at least in part, through a change in Fcγ receptor balance toward the inhibitory FcγR II B. The molecular events that induce this change in monocytes/macrophage properties are unclear. Although *H. pylori* does not invade the gastric epithelium, it can induce both the secretion of soluble inflammatory mediators and cellular apoptosis in the host, leading to local inflammation in the epithelium and the subepithelial layers. Released *H. pylori* components have been reported to be responsible for activating dendritic cells and macrophages through toll-like receptor signaling^[69,70].

Interestingly, a change in Fcγ receptor balance toward the inhibitory FcγR II B in monocytes/macrophages has also reported in the therapeutic action of other established treatment regimens for ITP, such as intravenous immunoglobulin and high-dose dexamethasone. Samuelsson et al. demonstrated that intravenous immunoglobulin requires the presence of FcγR II B to prevent antibody-induced thrombocytopenia in a murine model of passive ITP^[71], in which the FcγR II B expression on splenic macrophages was upregulated upon intravenous immunoglobulin treatment. The upregulation of inhibitory FcγR II B expression on circulating monocytes was also reported in ITP patients successfully treated with high-dose dexamethasone^[72]. These findings point to the Fcγ receptor balance of monocytes/macrophages as an attractive therapeutic target for ITP.

A multifactorial mechanism

The pathogenesis of *H. pylori*-associated ITP most likely involves several factors. The mechanism of Fcγ-receptor-balance modulation in monocytes/macrophages does not exclude other proposed mechanisms for platelet recovery in ITP after *H. pylori* eradication, such as molecular mimicry between CagA and platelet-surface antigens. Moreover, some *H. pylori* strains induce platelet aggregation that is dependent on the interaction of von Willebrand factor and IgG antibodies against *H. pylori* with their corresponding receptors, GPIb and FcγR II A, on platelets^[73]. In this model, anti-*H. pylori* antibodies are capable of op-

sonizing platelets by binding to *H. pylori*, von Willebrand factor, and GP I b, like anti-platelet autoantibodies. However, we should recognize that *H. pylori* infection is usually established in infants with an immature immune system, and that the prevalence of ITP among *H. pylori*-infected individuals is extremely low. Therefore, it is apparent that *H. pylori* infection alone is insufficient to induce the onset of ITP. Additional triggers would be necessary to elicit the anti-platelet autoimmune response observed in *H. pylori*-associated ITP.

CONCLUSION

The past few years have witnessed important advances in our understanding of the relationship between *H. pylori* infection and ITP. The sustained efficacy of the *H. pylori* eradication regimen in adults with ITP has affected decision-making in clinical practice. The importance of detecting and eradicating *H. pylori* in patients with seemingly typical ITP is now recognized, especially where *H. pylori* infection is prevalent, such as in Japan. A growing body of evidence indicates that *H. pylori*-associated ITP is a unique ITP subset in which the bacterium is central to the pathogenic process. The development of *H. pylori*-associated ITP appears to depend on multiple factors. Among these, modulation of the Fcγ receptor balance of monocytes/macrophages through inhibition of the immunosuppressive FcγR II B signal, which is a host immune response associated with *H. pylori* infection, is a key mechanism for initiating and maintaining the anti-platelet autoantibody response. These insights provide valuable clues that may assist in the development of new therapeutic strategies for ITP.

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