

Association between *Helicobacter pylori* Infection and Idiopathic Thrombocytopenic Purpura in Adults

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Abstract

A Gram-negative spiral bacterium, *Helicobacter pylori*, has been known to be a causative agent of chronic gastritis and peptic ulcer disease and plays an important role in increasing the risk for the development of gastric cancer. In addition, the infection has also been implicated in the development of extragastric diseases, such as hematological, systemic, cardiovascular and neurological diseases. Accumulating evidence indicates that successful eradication of *H. pylori* results in an increase of the platelet count in approximately half of *H. pylori*-positive ITP patients. However, the efficacy of the eradication was quite different in ITP patients among different countries worldwide. In this review, we summarize the recent evidences with regard to the association between *H. pylori* infection and ITP. We also provide information about the possible pathogenetic mechanisms and the factors for predicting platelet recovery.

Keywords: *Helicobacter pylori*; Idiopathic thrombocytopenic purpura; Eradication therapy

Introduction

Helicobacter pylori (*H. pylori*) are a spiral-shaped microaerophilic Gram-negative bacterium that colonizes the human gastric mucosa, and is known as a causative agent of acute and chronic gastritis. Prolonged *H. pylori* infection leads to gastrointestinal diseases mediated by chronic inflammation, such as atrophic gastritis, peptic ulcer, gastric hyperplastic polyp, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma [1]. Although the immunological response to *H. pylori* infection has been suggested as a major factor involved in the gastric mucosal inflammation, it is still not clearly understood why *H. pylori*-infected individuals are at a high risk of development of such diverse diseases. Eradication of *H. pylori* has been shown to be effective for reducing the gastric mucosal damage and also reducing the incidence of peptic ulcer recurrence. Furthermore, it has been reported that more than half of the patients with MALT lymphoma are cured by successful eradication of *H. pylori*.

In addition, *H. pylori* has been implicated in the development of various systemic disorders, including autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, Sjogren's syndrome, and Schonlein-Henoch purpura, as well as iron-deficiency anemia, chronic urticaria, cardiovascular diseases, and neurological disorders [2]. However, because the number of reported cases is still few for many of these conditions, the relevance of *H. pylori* infection in the development of these disorders is yet to be firmly established.

Among the aforementioned diseases, however, accumulating evidence indicates that successful eradication of *H. pylori* results in an increase of the platelet count in approximately half of *H. pylori*-positive ITP patients. *H. pylori* eradication therapy has been

recommended as a useful measure in treatment of ITP by both the Maastricht IV Consensus [3] and The Second Asia-Pacific Consensus Guidelines [4]. In this review, we will summarize the currently available evidence concerning the relationship between ITP and *H. pylori* infection.

Basic Treatment of ITP

ITP is an acquired autoimmune disease in which the emergence of autologous antibodies directed against platelets triggers enhanced platelet destruction, resulting in thrombocytopenia. To establish a definite diagnosis of this disease, it is necessary to rule out other diseases that cause thrombocytopenia (e.g., collagen vascular diseases, malignant tumors, drug-induced or radiation-induced disorders, infectious diseases, coagulation abnormalities). ITP can be divided into acute and chronic types according to the clinical course of the illness. Acute ITP, which is more common in children, is characterized by a rapid onset and is associated with antecedent infection in about 80% of the pediatric patients. Spontaneous remission occurs at a frequency of more than 80% within 4 months after the onset. This disease entity has a good prognosis, with a final cure rate of 90%. On the other hand, chronic ITP, which is more common in adults, is associated with prolonged thrombocytopenia that typically persists for more than 6 months after the onset. In these patients, spontaneous remission is extremely rare, and it is not unusual for the patients to suffer from repeated relapses even after the initiation of therapy [5,6].

Because it is relatively rare for the sustained thrombocytopenia in these patients to result in fatal conditions such as intracranial hemorrhage, the conventional treatment for chronic ITP basically consists of observation of the course of illness. In the event of detection of a bleeding tendency or a decrease in the platelet count to 30,000/ μ L or lower, administration of corticosteroids or immunosuppressive drugs or splenectomy may be selected as the standard treatment. In the case of complications associated with childbirth or the need for surgical treatment of the patients for any

indication, platelet transfusion aimed at temporarily increasing the platelet count, with or without high-dose intravenous immunoglobulin therapy, is reported as a feasible treatment strategy [6].

More recently, new treatments including eradication of *H. pylori*, thrombopoietin receptor agonist therapy, and anti-CD20 antibody therapy have been introduced, and their efficacies have been documented in some studies [7-9].

Therapeutic Efficacy of *H. pylori* Eradication in ITP

In 1998, Gasbarrini et al. [10] administered *H. pylori* eradication therapy to 11 *H. pylori*-positive patients with chronic ITP, and reported recovery of the platelet counts in all 8 patients in whom the bacterium had been successfully eradicated. On the other hand, no increase of the platelet count was observed in the remaining 3 ITP patients in whom the eradication therapy was unsuccessful or who *H. pylori*-negative. Thereafter, in 2001, Emilia et al. [11], who followed the study of Gasbarrini and colleagues, administered *H. pylori* eradication therapy to 13 patients with ITP who were *H. pylori*-positive, and observed recovery of the platelet count in 6 of these patients. Both of these studies were performed in Italy. Like Italy, Japan is among the countries with a high prevalence of *H. pylori* carriers. Various studies in Japan have revealed that the efficacy rate of *H. pylori* eradication in inducing recovery of the platelet count in *H. pylori*-positive ITP patients is approximately 50%, which is comparable to the reports from Italy [12-17].

The following observations have been cited as evidence corroborating the causal relationship between *H. pylori* and chronic ITP:

1) Platelet count recovery did not occur or was not sustained in patients with ITP in whom *H. pylori* eradication was unsuccessful;

2) in patients in whom primary *H. pylori* eradication failed to increase the platelet count, successful secondary eradication resulted in recovery of the platelet counts;

3) Among patients who underwent no *H. pylori* eradication in prospective randomized trials, none showed any recovery of the platelet counts;

4) No recovery of the platelet counts occurred- in *H. pylori*-negative ITP patients who underwent eradication therapy [12-14].

While a number of reports have been published on the efficacy of *H. pylori* eradication in inducing the recovery of platelet counts in chronic ITP patients, Jarque et al. reported in 2001 that the platelet counts increased in only 3 of 23 *H. pylori*-positive ITP patients who received *H. pylori* eradication therapy, and that the efficacy rate of *H. pylori* eradication therapy in inducing platelet count recovery in Spain was only 5% [18]. Michel et al. reported a similar frequency of *H. pylori* infection between ITP patients (29%) and controls (29%) in France, and that there were no significant differences in the clinical features between *H. pylori*-positive and *H. pylori*-negative patients with ITP (e.g., sex, age, frequency of hemorrhagic symptoms, platelet count at the time of diagnosis, anti-platelet antibody positivity rate, steroid response). Thus, they expressed doubts as to the direct involvement of *H. pylori* in the development of ITP [19]. In addition, the efficacy rates of *H. pylori* eradication in inducing platelet count recovery in ITP patients in the US, Serbia, and Mexico are also extremely low, similar to the case in Spain. On the other hand, a recent study conducted in Colombia revealed an extremely high prevalence of *H. pylori* infection (91%), and a high percentage of patients (83%) showing a favorable platelet response to *H. pylori* eradication therapy [20]. It remains unclear why there are variations in the platelet response to *H. pylori* eradication therapy in ITP patients among different countries worldwide (Table 1). One possibility is host factors, such as racial differences in the immune responses to the infection. Other explanations for the geographic discrepancy include bacterial factors and environmental factors. However, the precise factors have yet to be clarified.

Study year, Reference	Country	Mean Follow-up time (Month)	Plate response (%)	Prevalence (%) of <i>H.pylori</i> infection
Gasbarrini et al. [10]	Italy	4	8/8 (100)	11/18 (61)
Emilia et al. [11]	Italy	8.3	6/12 (50)	13/30 (43)
Jarque et al. [18]	Spain	24	3/23 (13)	40/56 (71)
Kohda et al. [17]	Japan	148	12/19 (63)	22/35 (62)
veneri et al. [32]	Italy	11.7	11/15 (73)	25/35 (71)
Michel et al. [19]	USA	11.5	4/14 (29)	16/74 (22)
Suzuki et al. [12]	Japan	6	6/13 (46)	25/36 (69)
Fujimura et al. [14]	Japan	12<	88/161 (55)	300/435 (69)
Suvaidzic et al. [37]	Serbia	18	6/23 (26)	39/54 (72)
Sayan et al. [38]	Turkey	13	8/20 (40)	34/20 (59)
Campuzano-Maya et al. [20]	Colombia	12.2	24/29 (83)	29/32 (91)
Estrada-Gomez et al. [39]	Mexico	4.6	3/14(21)	14/23 (60)

Sivapathasingam et al. [40]	Australia	12.2	5/9 (56)	9/16 (56)
Joakson et al. [41]	Canada	48	3/4 (75)	4/22 (18)
Tag et al. [42]	Korea	57.6	25/17 (68)	23/25 (92)
Payandeh et al. [43]	Iran	6	26/15 (58)	35/52 (67)
Gan et al. [44]	Malaysia	6	3/10 (30)	11/50 (22)

Table 1: Platelet response to *H. pylori* eradication therapy in ITP patients

While several studies have been conducted in various countries, as discussed above, we demonstrated the usefulness of *H. pylori* eradication in patients with ITP for the first time in a randomized controlled study carried out in 2005 [12]. More specifically, in our series, there were no cases in the non-*H. pylori* eradication group (n=12) that showed recovery of the platelet counts at the measurement carried out 6 months after enrollment, whereas 46.2% (including 6 cases showing a complete response and 4 showing a partial response) of patients in the *H. pylori* eradication group (n=13) showed obvious platelet count recovery (P=0.02). Moreover, Asahi et al. administered *H. pylori* eradication therapy to 37 patients with ITP (including 26 *H. pylori*-positive and 11 *H. pylori*-negative ITP patients), regardless of whether or not *H. pylori* infection had been detected. *H. pylori* eradication was successful in all the 26 *H. pylori*-positive patients, and increased of the platelet counts was observed in 16 (62%) of these 26 patients; in contrast, none of the *H. pylori*-negative patients showed any platelet count increases [13]. Furthermore, Fujimura et al. reported the results of a large-scale multicenter retrospective study carried out in Japan [14]. According to their report, eradication therapy administered to 228 of 300 *H. pylori*-positive ITP patients, and eradication was successful in 78% of these cases. Platelet responses were observed in 88 (57%) of the 155 patients who were followed up for at least 12 months. Furthermore, in 2007, Franchini et al. carried out a meta-analysis of 17 studies involving a total of 788 patients with ITP, and established the usefulness of *H. pylori* eradication therapy in inducing platelet count recovery in these patients [21]. In 2009, Stasi et al. analyzed 1555 *H. pylori*-positive patients with chronic ITP included in 25 studies, and reported that the percentage of patients showing platelet count recovery in response to eradication therapy was 50.3%, with a tendency for the response rate to be higher in countries where the prevalence of *H. pylori* infection was higher [22]. As for the long-term prognosis of ITP patients after *H. pylori* eradication, the platelet responses were sustained at adequate levels for many years [23-25]. Adverse reactions to eradication therapy included mild abdominal pain, diarrhea and rash, which occurred in no more than 5% of the patients. None of these adverse reactions were serious, confirming the safety of this therapy.

Distinctive Clinical Features and Predictors of the Platelet Responses to *H. pylori* Eradication

In ITP patients in whom eradication therapy was effective in inducing platelet count recovery, the PAIgG level and anti-platelet antibody titer were decreased after the treatment. Therefore, it was inferred that *H. pylori* infection may be involved in the production of the anti-platelet antibody, although the underlying mechanisms still remain rather unclear. Several hypotheses have been proposed to explain the mechanisms by which *H. pylori* may cause chronic ITP. On the basis of recent evidences, some plausible pathogenetic

mechanisms have been proposed, including cross-reactivity between platelet glycoproteins and *H. pylori* CagA protein, genetic host factors and bacterial factors. In addition, clinical evidence is available regarding the predictors of a platelet count response to *H. pylori* eradication.

Patient background factors

The Patients' age, sex, history of transfusion, history of peptic ulcer, platelet count prior to eradication, and history of treatment prior to the eradication had no effect on the recovery of the platelet count in response to *H. pylori* eradication [12,14]. Accordingly, it is presumed that eradication therapy may be beneficial in patients with intractable ITP who show poor response to either steroid therapy or splenectomy. Sato et al. studied the effect of eradication therapy in 31 patients, and reported that the pepsinogen I/II ratio was significantly lower, and the endoscopic atrophy of the gastric mucosa was more severe, in patients who responded to the eradication therapy than in those who did not [26]. In addition, Fujimura et al. recommended early eradication therapy because they found significantly greater increases of the platelet counts after eradication in patients with shorter disease duration than in those with longer disease duration [14].

Bacterial factors

Immunological response to *H. pylori* can cause gastric mucosal inflammation, and initially consists of recruitment of polymorphonuclear leukocytes, followed by that of T and B lymphocytes, plasma cells, and macrophages, along with gastric epithelial cell damage. According to previous reports, the virulence factors of *H. pylori* are closely related to the development of diseases in the host via modulating the host immune response: *H. pylori* strains possessing both *cagA* and *vacA* genes have been linked to higher cytotoxicities; the CagA protein was translocated into the gastric epithelial cells by a type IV secretion system, eventually promoting epithelial cell proliferation [27]; VacA causes vacuolation of the target cells; *vacA* s1/m1 strains produce higher levels of the vacuolating cytotoxin than other strains, inducing a greater degree of inflammatory cell infiltration; *iceA1* has also been recognized as another pathogenic factor and been suggested as a marker for peptic ulcer. Therefore, detailed examination of the virulence factors of *H. pylori* may be of importance for understanding the pathogenesis of chronic ITP [28,29].

Takahashi et al. reported that anti-platelet antibodies show high cross-reactivity with the CagA protein [15]; Franceschi et al. also reported that anti-CagA antibody cross-reacted with platelet protein in patients with chronic ITP [30]. In our previous study, the serum anti-CagA antibody titers were significantly higher in the platelet responders than those in the non-responders [12]. These studies

suggest the existence of a positive association between the platelet response to *H. pylori* eradication therapy and the presence of CagA. Our studies revealed that cagA, vacAs1, vacAm1, and iceA1 were found similarly in both patients showing and not showing a platelet response to *H. pylori* eradication therapy, suggesting that these *H. pylori* virulence factors may not be related to the platelet recovery [12]. However, Emilia et al. compared the infecting strains obtained from ITP patients and those from control participants, and reported that the frequency of the *H. pylori* cagA gene and concomitant *H. pylori* cagA, vacAs1, and iceA genes was statistically significantly higher in the ITP patients than in the controls [23]. Further studies are needed to establish the clinical relevance of the *H. pylori* virulence factors in chronic ITP patients.

Host factors

Chronic persistent infection with *H. pylori* triggers increased production of various cytokines in the gastric mucosa [31]. Hashino et al. measured the serum levels of IL-2, INF γ , IL-6, IL-15, TPO, and TGF β 1 in patients with ITP to examine the differences between the patients showing and not showing a platelet response to *H. pylori* eradication therapy. They found that the blood TGF β 1 levels were significantly higher in platelet responders after successful *H. pylori* eradication [16]. Veneri et al. reported that *H. pylori*-positive ITP patients showed a lower frequency of HLA-DRB1*03 and higher frequency of HLA-DRB1*11, HLA-DRB1*14, and HLA-DQB1*03 than *H. pylori*-negative patients [32]. Moreover, a HLA-DQB1*03 pattern was associated with a higher probability of a platelet response to *H. pylori* eradication therapy.

Ishiyama et al., who carried out single-strand conformation polymorphism analysis of complementarity-determining region 3 (CDR3) of the T cell receptor β chain gene of peripheral blood T cells, noted that V β 5.2, V β 15, and V β 19 gene usage by clonally expanded T cells in the peripheral blood obtained before the *H. pylori* eradication therapy was significantly higher in the platelet responders than in the non-responders or healthy controls. An abrogation of clonally expanded T cells was observed after eradication therapy in some responders. Based on these findings, they concluded that specific T cell clones were highly likely to play an important role in thrombocytopenia in *H. pylori*-related ITP patients [33]. We reported the importance of gene polymorphism of TNFB (+252) as a predictor of the platelet recovery in ITP patients after *H. pylori* eradication. The prevalence of platelet responders in ITP patients with the G/G or G/A genotype of TNFB (+252) was significantly higher than that in the ITP patients with the A/A genotype [34]. Asahi et al. have suggested that *H. pylori* infection may facilitate platelet destruction via the reduced levels of the inhibitory Fc γ receptor IIB in peripheral blood monocytes, leading to the onset of ITP [35]. In addition, Yeh et al. reported that *H. pylori* IgG is required for bacteria to induce P-selectin expression and that a significant release of P-selectin is essential for *H. pylori* to induce platelet aggregation, resulting in a decreased platelet count [36].

Since relatively small numbers of patients were recruited in the aforementioned trials, further studies involving larger numbers of patients will be needed to establish the findings as clinical evidence.

Position and Future Perspectives of *H. pylori* Eradication Therapy in the Treatment of ITP

Before publication of the studies indicating an association between *H. pylori* infection and thrombocytopenia, chronic ITP was considered to be an autoimmune disease of unknown etiology. It was commonly treated with steroids, splenectomy or high dose intravenous immunoglobulin, which do not give rise to cure of the ITP, but maintain the platelet count within a safe range. However, previous studies have shown that *H. pylori* eradication therapy is effective in inducing platelet recovery in about half of all *H. pylori*-positive chronic ITP patients, and its long-term efficacy and safety have also been confirmed. Thus, *H. pylori* eradication has become a standard first-line therapy for *H. pylori*-positive chronic ITP patients.

However, much remains unclear as to the etiologic mechanisms of *H. pylori*-related ITP, including the geographical discrepancies of the platelet responses after *H. pylori* eradication and inconsistencies among the predictors of the platelet responses to *H. pylori* eradication. Thus, further in vitro and clinical studies are required to address these issues.

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