Infectious Causes of Chronic Immune Thrombocytopenia

Roberto Stasi, MD*, Fenella Willis, MD, Muriel S. Shannon, MD, Edward C. Gordon-Smith, MD

Primary immune thrombocytopenia (ITP), the most common cause of severe thrombocytopenia in otherwise healthy young adults, is a diagnosis of exclusion.1–3 Thrombocytopenia may accompany or follow a variety of conditions from which ITP must be differentiated. Acute infections such as infectious mononucleosis, cytomegalovirus, rubella, mumps, and varicella may be associated with thrombocytopenia of varying severity that may be, at least in part, immune-mediated.3 In children, symptoms of the primary viral disease are usually well established (1–4 weeks) before the onset of the thrombocytopenia, which is often abrupt and severe. The thrombocytopenia generally resolves spontaneously within 2 to 8 weeks, but in occasional individuals it may persist for months before remitting.4 In adults, the most prevalent infections associated with thrombocytopenia are those from hepatitis C virus (HCV), human immunodeficiency virus (HIV), and Helicobacter pylori.5 In typical cases the thrombocytopenia presents with an insidious onset, has no tendency to remit spontaneously (although its severity may parallel the stage of the infectious disease), and may closely mimic chronic ITP.5

The aim of this article is to provide an updated review of thrombocytopenia associated with chronic infections, focusing on the current understanding of the mechanisms leading to the thrombocytopenia and on the evolving therapeutic strategies.

HEPATITIS C VIRUS–ASSOCIATED THROMBOCYTOPENIA

HCV infection evolves toward a chronic state in approximately 85% of patients, as demonstrated by the persistence of HCV-RNA in serum.6 However, severe and long-term complications of chronic HCV infection such as liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma develop only in a proportion of infected...
patients, after a period that can exceed 10 to 20 years.\textsuperscript{7} Chronic HCV infection has also been reported to be associated with the development of several extrahepatic alterations, including thrombocytopenia.\textsuperscript{8} Thrombocytopenia may be present even in the absence of clinically evident liver disease or splenomegaly, and may be diagnosed as chronic idiopathic thrombocytopenic purpura.\textsuperscript{9}

**Epidemiology**

HCV is now recognized as the most common viral infection causing chronic liver disease in humans worldwide.\textsuperscript{10} Of these individuals, approximately 55% to 85% have chronic infection that might need curative treatment.\textsuperscript{10} Thrombocytopenia either preexists and prevents the initiation of treatment with pegylated interferon (PEG-IFN) or develops as a consequence of PEG-IFN treatment, leading to dose modification in 19% of cases and discontinuation in 2% of cases.\textsuperscript{11} In patients with cirrhosis, thrombocytopenia complicates antiviral treatment much more frequently than in patients with HCV infection without cirrhosis.\textsuperscript{12}

**Table 1** summarizes the results on the prevalence of HCV infection from several cross-sectional studies in adult ITP patients. The major series published to date evaluated 250 patients fulfilling the diagnostic criteria for ITP of the American Society of Hematology (ASH).\textsuperscript{18} A positive serology was found in 76 (30%) of these patients. There were significant differences in demographic characteristics of HCV-positive patients when compared with HCV-negative ITP. HCV-positive patients were older (54.9 \(\pm\) 8 years vs 40.3 \(\pm\) 8 years, \(P<.001\)) and equally distributed between sexes in comparison with the female predominance in HCV-negative ITP. ITP was more frequent in Asian patients compared with the HCV-positive patients.

Whereas retrospective studies\textsuperscript{19,20} suggest that the prevalence of ITP among HCV patients is greater than would be expected by chance, the prevalence of HCV-positive ITP patients in some cohorts may be indirectly related to the background prevalence of HCV infection reported in the general populations.\textsuperscript{14,15,17,18} Chiao and colleagues\textsuperscript{21} calculated the incidence rate of ITP among 120,691 HCV-infected and 454,905 matched HCV-uninfected United States veterans who received diagnoses during the period 1997 to 2004. Their results indicate that HCV infection is actually associated with an elevated risk of developing ITP (hazard ratio, 1.8; 95% confidence interval, 1.4–2.3) among both untreated and treated patients.

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<td>Sakuraya et al (2002)\textsuperscript{16}</td>
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<td>11 (14)</td>
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<td>Zhang et al (2003)\textsuperscript{17}</td>
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<td><strong>Total</strong></td>
<td><strong>799</strong></td>
<td><strong>159 (20)</strong></td>
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\(\textsuperscript{a}\) Seven patients of this series had an associated autoimmune disorder. Study only included patients with platelet counts of less than 25 \(\times\) 10\textsuperscript{9}/L.
**Pathophysiology**

A variety of pathogenic mechanisms are reported to be implicated in thrombocytopenia related to chronic HCV infection. These mechanisms include sequestration of platelets in the enlarged spleen secondary to portal hypertension (hypersplenism),

reduced hepatic production of the thrombopoietin,

bone marrow suppression by HCV or interferon antiviral treatment,

and increased platelet destruction mediated by immune mechanisms involving antiplatelet autoantibodies and platelet-associated immune complexes.

Although there is a higher prevalence of thrombocytopenia and antiplatelet antibodies in patients with liver disease caused by HCV than in patients with hepatitis B infection, the pathogenic significance of antiplatelet antibodies is uncertain. However, a recent study showed that HCV core envelope 1 can induce thrombocytopenia by molecular mimicry with an epitope on platelet surface integrin GPIIIa.

Other studies have shown that HCV-RNA can be detected in washed platelets of infected individuals, particularly if thrombocytopenic. Furthermore, there is a non-saturable binding of HCV to platelets. High-affinity binding of HCV to platelet membrane with subsequent binding of anti-HCV antibody could theoretically lead to “innocent bystander” phagocytosis of platelets. The improvement of thrombocytopenia after successful interferon therapy supports this kind of mechanism.

**Clinical Manifestations**

In one study from Japan the platelet counts in HCV-positive patients were lower than in the HCV-negative patients. In contrast, in an American series fewer HCV-positive patients had severe thrombocytopenia, defined as platelet count 10 × 10^9/L or less (4% vs 46% for ITP, P < .001).

However, 56 (74%) patients had a platelet count of 50 × 10^9/L or less. Symptoms and signs of thrombocytopenia were less frequent in HCV-positive ITP, but major bleeding was more frequent (25% vs 10%, P = .0059). Serum cryoglobulins and anticardiolipin antibodies were more frequent in HCV-positive ITP (90% and 62%, respectively), but rare in HCV-negative ITP (7% and 15%, P < .001 compared with HCV-positive ITP). In the French and Chinese studies the characteristics of ITP in HCV-positive patients did not differ from HCV-negative ones.

**Treatment**

Most case series of patients with HCV infection and chronic immune thrombocytopenia have reported a greater than 50% platelet response to steroids. Response to splenectomy was not found to differ significantly between HCV-positive and HCV-negative patients in 2 studies describing patients with chronic ITP.

Rajan and colleagues noted that only a minority of HCV-positive patients received some form of treatment for thrombocytopenia (29 [38%] vs 158 [91%] for HCV-negative ITP). Of the 7 patients treated with prednisone (4 responded, 57%), 6 developed elevations of hepatic transaminases of greater than twice pretreatment levels while receiving prednisone. All 6 patients had a documented increase in HCV viral load. Two patients developed elevated serum bilirubin levels, with one patient developing overt jaundice. Treatment with either intravenous immunoglobulin (IVIG) or anti-RhD Ig proved effective in increasing platelet counts in both the HCV-seropositive and -seronegative patients. Of 5 HCV-positive patients treated with interferon-α (IFN-α), 4 responded with increased platelet counts. Responders to IFN-α could be distinguished from the nonresponder by a decrease in HCV quantitative RNA, hepatic...
transaminases, and cryoglobulins. Considering the results of various studies, approximately half of HCV-positive adult ITP patients treated with IFN-α responded with an increase in platelet count.

Research has focused on developing compounds specifically to stimulate thrombopoietin (TPO) activity to prevent or treat thrombocytopenia in chronic liver diseases. Eltrombopag is a small-molecule nonpeptide oral platelet growth factor that acts as an agonist to the thrombopoietin receptor. A phase 2 multicenter, randomized trial of daily eltrombopag in patients with HCV-associated thrombocytopenia and compensated liver disease showed that after 4 weeks of therapy, platelet count increased to $100 \times 10^9/L$ or more in 75%, 79%, and 95% of patients treated with 30 mg, 50 mg, and 75 mg eltrombopag, respectively, compared with no response in placebo patients ($P<.001$). Significantly more patients in the eltrombopag treatment groups (36%, 53%, and 65% in the 30-mg, 50-mg, and 75-mg groups) completed 12 weeks of antiviral therapy compared with 6% of placebo patients, and 75% of these patients had platelet counts greater than baseline values at the end of the antiviral treatment phase. Because eltrombopag has shown remarkable activity in chronic ITP as well, this agent seems to be an adequate candidate for the management of HCV-related chronic thrombocytopenia.

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED THROMBOCYTOPENIA

Thrombocytopenia was first linked to the acquired immune deficiency syndrome (AIDS) before the discovery of the HIV. Isolated thrombocytopenia may actually be encountered as the initial presentation of HIV infection several years before the development of overt AIDS, and the early disease is clinically indistinguishable from classic ITP.

Epidemiology

Before the use of highly active antiretroviral therapy (HAART), HIV-associated thrombocytopenia (platelet count <150 $\times 10^9/L$) was identified in approximately 5% to 30% of HIV-1 infected patients (Table 2). Although patients may present with thrombocytopenia at any time during the course of HIV infection, from asymptomatic infection to advanced AIDS, the incidence of thrombocytopenia seems to increase with progressive immunosuppression. The finding of an increased incidence and severity of

<table>
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<td>Kaslow et al (1987)</td>
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<td>Rossi et al (1990)</td>
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<td>Peltier et al (1991)</td>
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<td>Mientjes et al (1992)</td>
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<td>Sloand et al (1992)</td>
<td>1004</td>
<td>110 (11%)</td>
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<td>Sullivan et al (1997)</td>
<td>30214</td>
<td>2629 (8.7%)*</td>
</tr>
<tr>
<td>Total</td>
<td>34311</td>
<td>3020 (8.8%)</td>
</tr>
</tbody>
</table>

*Thrombocytopenia in this report was defined as platelets less than 50 $\times 10^9/L$.
thrombocytopenia in HIV-infected injection drug users, when compared with HIV-infected homosexuals, has been reported by several investigators. These differences may be explained, in part, by the finding of a higher incidence of coinfection with hepatitis C and underlying liver disease in HIV-infected intravenous drug users. With widespread use of HAART in patients with early HIV infection, the more recent prevalence of thrombocytopenia in patients under active antiviral treatment is unknown. However, recent prospective data from the Women’s Interagency HIV Study has documented a reduction in the incidence of anemia and neutropenia in HIV-infected women on HAART therapy. Therefore, one could assume a similar improvement in the incidence of thrombocytopenia.

Pathophysiology

The thrombocytopenia associated with HIV infection recognizes several mechanisms, which can be present simultaneously. A study in 6 patients has shown that thrombocytopenia in HIV infection is caused by a combination of: (1) shortening of platelet life span by two-thirds and doubling of splenic platelet sequestration; and (2) ineffective platelet production despite a threefold TPO-driven expansion in marrow megakaryocyte mass. The mechanism for the development of thrombocytopenia is dependent on the disease burden. HIV-associated thrombocytopenia of early HIV infection more often resembles classic ITP in which thrombocytopenia is mediated primarily by peripheral destruction, whereas patients with immunologic AIDS (CD4 lymphocytes <200/μL) have thrombocytopenia attributable predominantly to decreased platelet production and ineffective hematopoiesis.

Accelerated platelet destruction is primarily related to immune complexes and cross-reacting platelet antibodies. Antibodies specific against an epitope of integrin subunit β3 (GPIIIa) on the surface of platelets, GPIIIa, can be found in circulating immune complexes and can cross-react with a peptide sharing a known epitope region with HIV-1 protein nef. This antibody is unique in that it induces complement-independent platelet fragmentation in vitro by the generation of reactive oxygen species released through activation of 12-lipoxygenase and nicotinamide adenine dinucleotide phosphate–oxidase. The talin head domain (talin-H), a cleavage product of talin that can be generated by platelet activation or HIV-1 protease, has also been identified as an immunodominant epitope of the antiplatelet antibody response in 3 patients with HIV-associated thrombocytopenia. The role of antitalin antibodies in producing thrombocytopenia has not been investigated.

Ineffective platelet production has been linked to direct HIV cytopathic infection of the megakaryocyte. Megakaryocytes express the CD4 receptor and coreceptors necessary for HIV infection. In vitro studies have demonstrated megakaryocyte internalization of HIV and megakaryocytic expression of viral RNA. Electron microscopy of megakaryocytes from HIV-infected individuals with thrombocytopenia clearly demonstrates ultrastructural abnormalities not encountered in noninfected patients; blebbing of the surface membrane and vacuolization of peripheral cytoplasm are the most common. Other alterations in the bone marrow microenvironment may also contribute to poor platelet production.

Secondary causes of thrombocytopenia during HIV infection are generally the result of underlying opportunistic infections, malignancy, medications, and comorbid conditions, resulting in hypersplenism (Box 1). Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) is a rare and potentially fatal cause of thrombocytopenia that must also be considered in the initial evaluation of HIV-infected patients with reduced platelet counts.
Box 1
Common causes of secondary thrombocytopenia in HIV-infected patients

*Infections*

**Bacterial**
- Bacteremia/sepsis
- Bartonellosis
- Ehrlichiosis

**Parasitic**
- Toxoplasma
- Babesia
- Leishmaniasis

**Mycobacterial**
- Disseminated tuberculosis
- Disseminated *Mycobacterium avium* complex

**Viral**
- Cytomegalovirus
- Epstein-Barr virus
- Rubella

**Fungal**
- Histoplasmosis
- Coccidioidomycosis
- Other disseminated fungal infections

*Malignancy*
- Kaposi sarcoma
- Metastatic adenocarcinomas
- Non-Hodgkin lymphoma
- Chemotherapy-associated thrombocytopenia
- Hodgkin lymphoma

*Medications*
- Trimethoprim-sulfamethoxazole
- Ketoconazole
- Trimetrexate
- Ganciclovir
- Pyrimethamine
- Foscarinet
- Flucytosine
- Cidofovir
- Pentamidine
- Acyclovir
- Pyrazinamide
Clinical Manifestations

HIV-associated thrombocytopenia is rarely a serious clinical problem. In most cases, platelet counts remain greater than $50 \times 10^9/L$ and the condition can be treated conservatively. Bleeding is rare, unless the platelet count falls to less than $10 \times 10^9/L$. If this occurs, bleeding gums, extremity petechiae, and easy bruising are common presentations. However, menorrhagia in fertile women may sometimes be so massive as to require transfusion therapy. Only a few cases of fatal hemorrhage have been reported. Two studies reviewed hemorrhagic complications of HIV-infected hemophiliacs. Finazzi and colleagues documented thrombocytopenia (platelets $<100 \times 10^9/L$) in 14 of 124 (11%) hemophiliacs, of which only one patient had a major hemorrhage. In contrast, Ragni and colleagues reported a platelet count of less than $100 \times 10^9/L$ in 30 of 87 (36%) hemophiliacs, with 11 (13%) having a platelet count of less than $50 \times 10^9/L$. Nine of the 11 patients (82%) had major bleeding complications and 3 patients suffered fatal hemorrhages.

Severe thrombocytopenia in patients with advanced HIV infection is frequently associated with additional cytopenias. In a study of 52 HIV-infected injection drug users with thrombocytopenia, 4 patients (8%) with advanced HIV infection had a hypocellular bone marrow examination responsible for their pancytopenia. HIV-infected injection drug users were also more likely to have antibodies to both hepatitis B and C, and have abnormal liver function studies.

Treatment

Antiretroviral therapy is the first-line and most effective therapy for the thrombocytopenia associated with HIV infection. In fact, HIV-associated cytopenias have been shown to correlate with the degree of HIV viral replication as measured by plasma viral load, and improve with effective antiretroviral therapies. Zidovudine monotherapy was efficacious in increasing the platelet count in 60% to 70% of HIV thrombocytopenia patients when given in doses greater than 1 g/d. Although other antiretroviral drugs as monotherapy have been shown to improve hematologic parameters in patients with advanced HIV infection, their efficacy as monotherapy for the management of HIV thrombocytopenia has been less often demonstrated. HAART likely is more effective than zidovudine monotherapy. One retrospective study compared patients with severe thrombocytopenia treated with zidovudine with those treated with HAART. After 6 months, HAART therapy more frequently resulted in

| Interferon |
| Rifampin |
| Chemotherapeutic agents |
| Rifabutin |
| Valganciclovir |

Secondary hypersplenism

Chronic viral hepatitis/cirrhosis

Other causes of hepatitis/cirrhosis

Thrombotic thrombocytopenic purpura

Disseminated intravascular coagulation
complete and sustained recovery of platelet counts. Responses were achieved even in those with zidovudine-resistant thrombocytopenia.

Responses to zidovudine and HAART may be more limited in HIV-infected injection drug users, possibly reflecting the impact of associated liver disease and HCV infection. A prospective, placebo-controlled, double-blind, randomized trial of IFN-α enrolled 14 zidovudine refractory HIV-infected injection drug users. Twelve patients had a statistically significant increase in their platelet counts by 4 weeks of therapy. Patients in this trial had elevated serum alanine aminotransferase, suggestive of underlying liver disease. Similar responses to IFN-α therapy alone have been reported in HIV-seronegative, HCV-infected patients, suggesting a possible role of IFN-α in suppressing associated HCV infection in these HIV-infected patients. However, an open label trial of IFN-α in predominately homosexual men reported responses in 9 of 16 patients enrolled, with responses occurring as early as 2 weeks. Such rapid responses preclude the possibility of improvement in the platelet counts due to suppression of concomitant HCV infection.

Because the beneficial effects of antiretroviral therapy may be seen after several weeks, during that time it may be necessary to support the platelet counts with other interventions. HIV-associated thrombocytopenia is generally responsive to the therapies used in classic ITP. Prednisone therapy can produce a major hematologic response in the platelet count (100 × 10^9/L) in over half the patients treated, although only a minority of patients will maintain platelet counts greater than 50 × 10^9/L after cessation of steroids. There was no evidence of increased risk of infections or progressive immunosuppression with short-term prednisone treatment in these patients. IVIG and anti-RhD are equally effective in acutely increasing platelet counts in severely affected patients. A cross-over study of comparing IVIG to anti-RhD in HIV-associated thrombocytopenia clearly demonstrated a longer duration of response to anti-RhD treatment.

Splenectomy, which is safe and results in stable complete or partial remissions in 60% to 80% of patients, should be reserved for patients with symptomatic thrombocytopenia after an adequate trial of antiretroviral therapy. A retrospective review of patients treated with splenic irradiation, as opposed to surgical splenectomy, failed to find evidence of efficacy for this procedure in the treatment of refractory HIV-associated thrombocytopenia.

Thrombopoiesis stimulation was explored in a pilot clinical trial that administered recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) to 6 adult HIV-positive patients with thrombocytopenia. All 6 responded; the elevated platelet counts were maintained through the 16 weeks of therapy and returned to pretreatment values 2 weeks after cessation of therapy. PEG-rHuMGDF and other first-generation thrombopoietic growth factors have not been developed further. The role of second-generation thrombopoietin receptor agonists, eltrombopag and romiplostim, has not yet been defined.

**HELICOBACTER PYLORI–ASSOCIATED THROMBOCYTOPENIA**

*H. pylori*, a Gram-negative bacterium, is recognized as the causative agent of active chronic gastritis and is the predominant cause of peptic ulceration (ie, gastric and duodenal ulcers). *H. pylori* is also a cofactor in the development of both adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas. Eradication of *H. pylori* infection can result in platelet responses in patients with chronic ITP, which
has led to speculation on a causal role of the bacterium in the development of thrombocytopenia.

**Epidemiology**

*H. pylori* is estimated to infect the gastric mucosa of at least half of the world’s population.\(^{101}\) The prevalence of *H. pylori* infection in adult ITP patients does not seem different from that reported in the general healthy population matched for age and geographic area (Table 3). The detection method in these studies was predominantly the \(^{13}\text{C}\)-urea breath test. Most studies were conducted in Japan, where the prevalence of the infection is greater than 70%,\(^{127}\) or in Italy, where the *H. pylori* rate in the middle-aged adult general population is nearly 50%.\(^{128}\)

**Pathophysiology**

Several hypotheses have been advanced. Molecular mimicry proposes that an *H. pylori* surface antigen evokes a host systemic immune response that produces antibodies cross-reactive with host platelets. The possible role of CagA-positive strains as a pathogenic candidate for ITP was recognized in 2 molecular studies.\(^{109,129}\) In this

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<td><strong>Total</strong></td>
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<td><strong>973 (62.3%)</strong></td>
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regard, it should be noted that most Japanese *H. pylori* strains are positive for CagA and have the intact Cag pathogenicity island. Further support to this hypothesis emerges from the results of an Italian study, showing that the prevalence of the *H. pylori* cagA gene was significantly higher in patients with ITP than in a control group. A recent study suggests that *H. pylori* urease B can be involved in molecular mimicry, as antibodies against this bacterial enzyme could cross-react with human platelet GPIIIa and partly inhibit platelet aggregation. Other putative targets of molecular mimicry are Lewis (Le) antigens, which are expressed by *H. pylori* in a strain-specific manner. Le antigens adsorb to platelets and might serve as targets for anti-Le antibodies in patients with an appropriate genetic background.

A role for the lipopolysaccharide (LPS) of gram-negative bacteria has been suggested by recent laboratory experiments showing that in the presence of antiplatelet antibodies LPS can significantly enhance Fc-dependent platelet phagocytosis. In addition, *H. pylori* eradication was associated with decreased phagocytic capacity and modulation of the inhibitory Fcγ receptor IIB (FcγRIIB) in peripheral blood monocytes. These results may provide the explanation why thrombocytopenia worsens in some patients with ITP during infections and, alternatively, resolves in other patients with ITP who are treated with bacterial eradication therapy.

Other studies have shown that some strains of *H. pylori* bind von Willebrand factor (vWF) and induce glycoprotein Ib (GPIb) - and FcRIIa-dependent platelet aggregation in the presence of *H. pylori* antibodies. Activation may promote platelet clearance and antigen presentation, which augments production of antibacterial antibodies. Somatic mutation may lead to the development of antibodies that either recognize bacterially derived factors that bind to platelets or cross-react with platelet antigens.

Both *H. pylori* infection and ITP are associated with a polarized Th1-type phenotype. It may accordingly be speculated that *H. pylori* infection creates an immunologic environment that facilitates the onset or persistence of ITP.

The last 3 hypotheses are not mutually exclusive, and can account for the observation that clinical responses may occur as early as 1 week from initiation of eradication therapy, before antibody synthesis by plasma cells is affected.

The importance of genetic factors emerged from the results of an Italian study, indicating that *H. pylori*–positive patients had a lower frequency of DRB1*03 and higher frequencies of DRB1*11, DRB1*14, and DQB1*03 relative to *H. pylori*–negative cases.

**Clinical Manifestations**

*H. pylori*–infected ITP patients were found to be significantly older than *H. pylori*–uninfected patients. This is not unexpected, as the prevalence of *H. pylori* infection in the general population increases with increasing with age. In contrast, all prospective series 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 and colleagues but not by Stasi and colleagues. A cross-sectional study by Fukui and colleagues did not find any correlation between *H. pylori* infection and thrombocytopenia during pregnancy. 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.

**Treatment**

In almost all studies eradication therapy consisted of the so-called triple therapy, a combination of amoxicillin, clarithromycin, and a proton pump inhibitor usually given for 1 or 2 weeks. Adverse events from eradication therapy have been described as...
mild, usually consisting of abdominal pain and diarrhea, and lead to discontinuation of treatment in less than 5% of cases.

An overall response rate (platelet count ≥30 x 10⁹/L and at least a doubling of the basal count) of 52.7% in eradicated patients was noted using individual patient data from 25 series worldwide. Responses were consistently high in Japan, of heterogeneous magnitude across European countries, and very low in the United States (Table 4). Further analysis shows that in almost every series in which 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 in which no association was found. So in the United States, 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. Of note, in most studies the mean platelet count was greater than 30 x 10⁹/L, and relatively few patients with severe disease were investigated. The long-term results of H. pylori eradication have been reported recently by Italian and Japanese groups. In 29 of the 31 cases whose course could be followed up for 5 to 7 years, only 2 relapses occurred. The pretreatment factor that was more consistently associated with a platelet response to H. pylori eradication was a shorter ITP duration. Patients with very low platelet counts (<30 x 10⁹/L) also seem to have fewer chances of response, although this issue has not been systematically addressed in most published reports.

In the only phase 3 trial, Suzuki and colleagues evaluated the platelet count in a group of 25 H. pylori–positive chronic ITP patients who were randomized to receive treatment or no treatment for H. pylori infection. Response to the treatment was defined as complete (CR) if the platelet count was greater than 150 x 10⁹/L, and partial (PR) if the platelet count increased by more than 50 x 10⁹/L 6 months after the eradication therapy. The investigators found that the eradication of H. pylori infection in patients with ITP was associated with a platelet response: 46.2% in the eradication group (4 CR and 2 PR) and 0% in the noneradication group (P<.01). The platelet response was also significantly more common in patients with infection sustained by CagA-positive strains of H. pylori (P = .04). However, given the small number of patients recruited in the trial, these results should be interpreted with some caution.

The uncertainties regarding the actual role of standard eradication therapy warranted a prospective study in which 37 ITP patients were treated with triple therapy irrespective of the presence or absence of H. pylori infection. With a therapeutic response defined as a platelet count greater than 100 x 10⁹/L at 24 weeks, 16 of 26 H. pylori–positive patients (62%) were responders, whereas none of the H. pylori–negative patients was a responder. Besides, anti-GPIIb/IIIa antibody-producing B cells were significantly decreased at 12 and 24 weeks in H. pylori–positive responders (P<.0001) and, to a lesser extent, in nonresponders (P = .02), but not in H. pylori–negative patients. This study clearly supports the notion that platelet recovery after H. pylori eradication results from the disappearance of H. pylori itself, rather than from other H. pylori–independent mechanisms. It has been advanced that the increased platelet count in some patients who failed the H. pylori eradication or in those who received proton pump inhibitor monotherapy could have been mediated through a reduction in the quantity of H. pylori or a bacteriostatic effect of the regimen.

MISCELLANEOUS INFECTIONS ASSOCIATED WITH THROMBOCYTOPENIA

A myriad of chronic infections can cause thrombocytopenia, but most of the time the associated clinical and laboratory features readily allow to discriminate them from ITP.
<table>
<thead>
<tr>
<th>Study</th>
<th>Bacterial Eradication (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Platelet Response&lt;sup&gt;a&lt;/sup&gt; (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up Duration (months)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>No. of Relapsed Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kohda et al (2002)&lt;sup&gt;104&lt;/sup&gt;</td>
<td>19/19 (100)</td>
<td>12 (63)</td>
<td>14.8 (9–39)</td>
<td>0</td>
</tr>
<tr>
<td>Hino et al (2003)&lt;sup&gt;105&lt;/sup&gt;</td>
<td>18/21 (86)</td>
<td>8 (44)</td>
<td>37.8</td>
<td>NR</td>
</tr>
<tr>
<td>Hashino et al (2003)&lt;sup&gt;106&lt;/sup&gt;</td>
<td>13/14 (93)</td>
<td>9 (69)</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Ando et al (2003)&lt;sup&gt;107&lt;/sup&gt;</td>
<td>27/29 (93)</td>
<td>16 (59)</td>
<td>11 (4–15)</td>
<td>1</td>
</tr>
<tr>
<td>Takahashi et al (2004)&lt;sup&gt;109&lt;/sup&gt;</td>
<td>13/15 (87)</td>
<td>7 (54)</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Sato et al (2004)&lt;sup&gt;110&lt;/sup&gt;</td>
<td>27/32 (84)</td>
<td>15 (56)</td>
<td>12</td>
<td>0</td>
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<tr>
<td>Ando et al (2004)&lt;sup&gt;111&lt;/sup&gt;</td>
<td>15/17 (88)</td>
<td>10 (67)</td>
<td>24</td>
<td>0</td>
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<tr>
<td>Nomura et al (2004)&lt;sup&gt;112&lt;/sup&gt;</td>
<td>12/28 (43)</td>
<td>12 (100)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Inaba et al (2005)&lt;sup&gt;114&lt;/sup&gt;</td>
<td>25/25 (100)</td>
<td>11 (44)</td>
<td>NR</td>
<td>0</td>
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<tr>
<td>Fujimura et al (2005)&lt;sup&gt;116&lt;/sup&gt;</td>
<td>161/207 (78)</td>
<td>88 (55)</td>
<td>12 (3–12)</td>
<td>NR</td>
</tr>
<tr>
<td>Suzuki et al (2005)&lt;sup&gt;117&lt;/sup&gt;</td>
<td>22/25 (88)</td>
<td>6 (28)</td>
<td>6</td>
<td>NR</td>
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<tr>
<td>Asahi et al (2006)&lt;sup&gt;120&lt;/sup&gt;</td>
<td>26/26 (100)</td>
<td>16 (61)</td>
<td>&gt;12</td>
<td>0</td>
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<tr>
<td>Kodama et al (2007)&lt;sup&gt;121&lt;/sup&gt;</td>
<td>44/52 (85)</td>
<td>27 (61)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Satake (2007)&lt;sup&gt;124&lt;/sup&gt;</td>
<td>23/25 (92)</td>
<td>13 (57)</td>
<td>25.4* (6–48)</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td>445/535 (83.2)</td>
<td>250 (56.2)</td>
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### Europe

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Success</th>
<th>Failure</th>
<th>Median (Range)</th>
<th>*</th>
<th>NR</th>
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</thead>
<tbody>
<tr>
<td>Jarque et al (2001)</td>
<td>23/32 (72)</td>
<td>3 (13)</td>
<td>21 (18–24)</td>
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<tr>
<td>Veneri et al (2005)</td>
<td>32/34 (94)</td>
<td>18 (56)</td>
<td>24.2 (3–62)</td>
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<tr>
<td>Stasi et al (2005)</td>
<td>52/52 (100)</td>
<td>16 (31)</td>
<td>25 (7–42)</td>
<td>6</td>
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<td></td>
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<tr>
<td>Suvajdzic et al (2006)</td>
<td>23/30 (77)</td>
<td>6 (26)</td>
<td>18 (14–32)</td>
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<tr>
<td>Emilia et al (2007)</td>
<td>34/38 (89)</td>
<td>25 (74)</td>
<td>43.5 (18–90)</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td>172/197 (87.3)</td>
<td>68 (41.5)</td>
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</table>

### North America

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Success</th>
<th>Failure</th>
<th>Median (Range)</th>
<th>*</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahn et al (2006)</td>
<td>15/15 (100)</td>
<td>1 (7)</td>
<td>(6–24)</td>
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<tr>
<td>Jackson et al (2008)</td>
<td>2/4 (50)</td>
<td>2 (100)</td>
<td>48.5</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td>31/34 (91)</td>
<td>7 (22.6)</td>
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### Other countries

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Success</th>
<th>Failure</th>
<th>Median (Range)</th>
<th>*</th>
<th>NR</th>
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</thead>
<tbody>
<tr>
<td>Sayan et al (2006)</td>
<td>18/20 (90)</td>
<td>11 (61)</td>
<td>11 (4–24)</td>
<td>0</td>
<td></td>
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<tr>
<td>Campuzano-Maya (2007)</td>
<td>26/29 (90)</td>
<td>21 (81)</td>
<td>12.2</td>
<td>NR</td>
<td></td>
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<tr>
<td>Estrada-Gomez (2007)</td>
<td>14/14 (100)</td>
<td>2 (14)</td>
<td>5 (2–7)</td>
<td>1</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td>58/63 (92.1)</td>
<td>34 (58.6)</td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td>706/829 (85.2)</td>
<td>369/698 (52.9)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** NR, not reported; NA, not assessable.

\(\text{a}\) Among patients who were successfully eradicated.

\(\text{b}\) Complete or partial response among patients with successful eradication.

\(\text{c}\) Median, with range in parentheses.

\(\text{*}\) Mean value.
Notable exceptions are cytomegalovirus (CMV) infection and malaria. The presence of CMV infection among asymptomatic or paucisymptomatic immunocompetent individuals with ITP is a rare finding but is well described in the literature. The mechanisms by which cytomegalovirus can cause thrombocytopenia include direct cytotoxicity, infection of the megakaryocytes, immune-mediated destruction, impairment of bone marrow stromal cells, and induction of specific or nonspecific autoantibodies resulting in antibody-mediated destruction of the platelets. A review of 17 anecdotal cases suggests that the treatment schedule should include a short trial of corticosteroids as first-line therapy. Splenectomy should be avoided in those who fail to respond. Although observation is a reasonable option after failure of corticosteroids, intravenous immunoglobulin should be the treatment of choice in cases of severe bleeding, given its rapidity of action. As the overall outcome is favorable in CMV thrombocytopenia, usually within a few weeks, probably 1 or 2 infusions of intravenous immunoglobulin are sufficient.

Thrombocytopenia during plasmodium infection may appear even before fever, anemia, and splenomegaly become manifest. The mechanism of thrombocytopenia in malaria is uncertain. Immune-mediated lysis, sequestration in the spleen, and a dyspoietic process in the marrow with diminished platelet production have all been postulated. Platelet agglutination as a result of endothelial cell activation and release of activated vWF has also been suggested as a mechanism of thrombocytopenia during the early stages of infection. Abnormalities in platelet structure and function have been described as a consequence of malaria, and in rare instances platelets can be invaded by malarial parasites themselves. Thrombocytopenia in malaria is rarely severe, and no particular precautions have to be observed. Treatment is focused on the eradication of the plasmodium.

**SUMMARY**

Chronic infections with HCV, HIV, and *H. pylori* may be associated with isolated thrombocytopenia and should be considered in the differential diagnosis of ITP. The thrombocytopenia in infection-associated ITP occurs via various potential mechanisms, including accelerated platelet clearance due to immune complex disease, cross-reactivity of antiplatelet glycoprotein antibodies and viral or bacterial antibodies, defective platelet production in HCV and HIV infections, and splenic sequestration of platelets secondary to portal hypertension and decreased production of thrombopoietin in HCV infection.

Serologic evaluation for HIV and HCV infection is indicated in patients with ITP because of the potentially adverse effect of prolonged corticosteroid usage on the underlying infection and the utility of antiviral therapy in treating both the underlying infection and the thrombocytopenia. *H. pylori* screening seems certainly worthwhile in Japan, a country with a high background prevalence of the infection, where significant response rates have been consistently reported. For countries such as the United States, in which both the prevalence of infection and the response rates to eradication therapy are low, testing for *H. pylori* infection remains controversial.

**REFERENCES**


