Immune thrombocytopenic purpura (ITP) is an acquired disease in which autoantibodies to platelets cause their sequestration and destruction by mononuclear macrophages, principally in the spleen. If increased production of platelets by megakaryocytes does not compensate for platelet destruction, the number of circulating platelets decreases (thrombocytopenia), resulting in a characteristic bleeding tendency (purpura). While most children with the disease experience a relatively short and benign clinical course, ITP in adults often lasts more than 6 months (chronic ITP) and is resistant to conventional treatment (corticosteroids, intravenous immune globulin, or splenectomy). The goal of medical management is to increase the platelet count to a safe level, without the risks of bacterial infections associated with splenectomy or toxicity from prolonged corticosteroid therapy. Splenectomy increases platelet counts in hours to days in most patients with acute ITP, but nearly 50 percent experience recurrent thrombocytopenia by 5 years postsplenectomy.

**Key Words:** platelets, thrombocytopenia, platelet antibodies, reticuloendothelial system, macrophage Fc receptors, splenectomy, intravenous immune globulin, IV Rh immune globulin, rituximab

**Introduction**

Immune thrombocytopenic purpura (ITP, idiopathic or autoimmune thrombocytopenic purpura) is an acquired bleeding disorder of children and adults that presents with thrombocytopenia as the only significant abnormal laboratory finding. There is neither a specific clinical nor a laboratory finding that reliably establishes a diagnosis of ITP. A diagnosis of ITP is established by excluding other potential causes of thrombocytopenia.

**Classification**

ITP is a heterogeneous disease with a wide range of clinical and laboratory presentations. Typically, patients are classified according to age at the time of diagnosis (ITP in children versus adults), but no one classification system is capable of segregating patients with this highly variable disease into categories without a significant number of exceptions. The goal of classifying patients is to be able to match a newly diagnosed patient with a group of other patients with similar findings for purposes of selecting an appropriate treatment and providing prognostic information.

**Primary versus secondary immune thrombocytopenia**

Conventionally, thrombocytopenias are divided into three major categories: those resulting from (1) abnormally decreased platelet production (e.g., aplastic anemia), (2) platelet sequestration (e.g., hypersplenism), or (3) abnormally increased platelet destruction (e.g., immune destruction). Immune (antibody-mediated) thrombocytopenia may occur as a complication of another disease (secondary thrombocytopenia) (e.g., HIV/AIDS, systemic lupus erythematosus, or a primary immunodeficiency syndrome) or as the only abnormal finding (primary immune thrombocytopenia). In the following review, “ITP” is intended to refer to primary immune thrombocytopenia.

**ITP in children versus in adults**

Typically, children with ITP present with an acute onset of petechiae and diffuse bruising approximately 4 to 8 weeks after a viral illness. As many as 85 percent of affected children experience an uneventful course and spontaneous remission within 6 months. In 2003, the International Childhood ITP Study Group reported the results of a prospective study of 2540 infants and children with newly diagnosed ITP, providing voluminous data on the clinical spectrum of childhood ITP. In this study, the incidence of intracranial hemorrhage, the most feared complication of ITP in
children, was only 0.17% during the first 6 months after diagnosis. In contrast to ITP in children, ITP in adults typically presents with an insidious onset; affects a preponderance of females, as seen in other autoimmune diseases in adults; and progresses to chronic ITP (persistent thrombocytopenia or a requirement for treatment 6 months after onset). This traditional profile of ITP in adults has been challenged by the results of a prospective study reported in 2003 for a population cohort of 245 adults with ITP in the UK. In this study, there were 134 females/111 males (1.2:1.0) and the majority of patients (63.3%) achieved remission (platelet count > 100,000/µL) and an additional 24 percent achieved a partial remission.

Pathophysiology

Harrington’s “thrombocytopenic factor”

While splenectomy has been recognized as an effective treatment for patients with ITP since it was first described in 1913, the modern concept of the pathophysiology of ITP began in 1951 when Harrington et al. reported “a thrombocytopenic factor” in the blood of patients with ITP. Harrington infused himself and seven other nonthrombocytopenic subjects with whole blood or plasma from patients with “idiopathic” thrombocytopenic purpura and observed a rapid decrease in most recipients’ platelet counts. One patient’s plasma was fractioned by Cohn’s method and the thrombocytopenic effect was localized to the globulin fraction. This observation might have justified changing the name from “idiopathic” to “immune” thrombocytopenic purpura more than 50 years ago, but the designation “idiopathic” persists in common usage, even today.

Platelet autoantibodies

Autoantibodies that react with platelet membrane glycoproteins have been demonstrated in as many as 80 percent of patients with ITP. These antibodies react with glycoproteins IIb/IIIa (α₃β₃), integrin or CD41/CD61, GPIb/IX, and others. As a consequence, autoantibody-coated platelets are phagocytized in the reticuloendothelial system (RES) via Fcγ receptors on mononuclear macrophages. Technically, the name “reticuloendothelial system” is a misnomer, with recognition that RES mononuclear phagocytes are neither reticular nor endothelial cells. However, the traditional concept that the spleen, liver, and bone marrow are functional sites for RES phagocytic activity is useful and is preserved in this review. Intuitively, one might expect that the severity of bleeding in patients with ITP would correlate with the presence of one or more of these antibodies, since their glycoprotein targets are integral to normal platelet function and hemostasis. However, current laboratory assays for platelet antibodies do not demonstrate a convincing correlation between specific glycoprotein targets and disease severity. Neither research-level nor commercially marketed assays for detecting platelet antibodies have sufficient specificity to be useful as diagnostic assays for ITP in clinical practice. An evaluation of the performance of Capture-P (Immucor, Inc., Norcross, GA), a commercially marketed kit for indirect platelet antibody tests, concluded that the method was not useful for establishing or excluding the diagnosis of ITP. This finding is consistent with the American Society of Hematology’s practice guideline, which concluded that current tests for platelet antibodies are neither necessary nor appropriate in the evaluation of ITP in children or adults. Recently, serologic reactivity of ITP autoantibodies has been further localized to epitopes on α₃ or the amino-terminal portions of both GPIbα and GPIIIa. McMillan et al. developed an immunobead assay to detect ITP antibodies reactive to GPIb/IIIa or GPIb/IX that has a minimum specificity of 84.4 percent, raising the possibility that the long-awaited laboratory diagnostic assay for ITP may be forthcoming.

Polymorphic FcγR macrophage receptors

In ITP, autoantibody-coated platelets are removed from the circulation by Fcγ receptors on mononuclear macrophages, principally in the spleen. Among the three families of Fcγ receptors that have been recognized (FcγRI, FcγRII, and FcγRIII), there is considerable diversity of structure and function. FcγRI has a strong affinity for monomeric IgG. FcγRII and FcγRIII bind IgG only when it presents in an immune complex. FcγRII is polymorphic and two codominant alleles have been described, FcγRIIA-H131 and FcγRIIA-R131. In one study, the distribution of FcγRII receptors was skewed toward the FcγRIIA-R131 allotype, suggesting that Fc receptor polymorphisms may have a role in the pathophysiology of ITP or may be responsible for modulating the immune response. In another study, there was no significant difference in the distribution of FcγRIIA genotypes between ITP patients and controls, but there was a correlation between FcγRIIA genotypes and the response to
ITP autoantibodies have been identified in all IgG subclasses. The most prevalent IgG subclass detected among ITP antibodies is IgG1 (77%), but IgG2, IgG3, and IgG4 ITP antibodies have been identified. Further complicating the effort to identify a correlation between diagnosis or prognosis for ITP and a specific laboratory marker (i.e., antibody specificity, FcγR genotype, or the IgG subclass) is the observation that some patients with ITP appear to have oligoclonal platelet antibodies, whereas other patients have polyclonal antibodies.

Selected Treatments for ITP

In many persons with ITP, particularly children, thrombocytopenia resolves without specific treatment after a benign course lasting only a few days to a few weeks. Other persons may have sustained thrombocytopenia with life-threatening hemorrhages and a treatment-resistant clinical course lasting several years. For readers of Immunoheamatology with an interest in reading more than selected aspects of the treatment for ITP, I recommend the March 2002 issue of Blood Reviews, which contains 21 articles focused primarily on clinical management. The following brief comments are intended to address selected aspects of the treatment of ITP that have special relevance to immunohematologists and blood bank serologists.

The goal of current treatments for ITP is to decrease the synthesis of the platelet autoantibodies and/or decrease the rate of splenic destruction of autoantibody-coated platelets.

Splenectomy

The rationale for splenectomy in ITP is supported by studies that show elimination of both the white pulp (immune function) and red pulp (phagocytic function) are beneficial. Following splenectomy in ITP, antiplatelet antibodies decrease. This finding is not unexpected, since cultured splenic cells isolated from ITP patients synthesize IgG platelet antibodies. Also, splenectomy removes those mononuclear macrophages most likely to be responsible for destroying ITP autoantibody-coated platelets.

IVIG

A single infusion of a standard dose of IVIG (1 gram/kg) causes broad perturbations of both humoral and cellular immune function. However, the preponderance of evidence supports Imbach’s original explanation that the principal mechanism of IVIG’s beneficial effect in ITP is a consequence of “overloading and blocking of the reticuloendothelial system by IgG catabolism.” Fehr et al. showed that increased platelet counts following infusions of IVIG in four patients with ITP correlated with decreased clearance of IgG-coated RBCs, providing experimental evidence supporting Imbach’s hypothesis.

A single infusion of IVIG (1 gm/kg) is likely to be highly effective (> 85%) for increasing the platelet count by at least 30,000/μL in a previously untreated child or adult with ITP. Typically, the beneficial effect will last for 2 to 4 weeks, when a repeat infusion is needed to sustain the beneficial effect. However, if thrombocytopenia persists, the inconvenience of long infusions (3 to 5 hours), higher cost compared to IV Rh immune globulin (see below), and acute side effects (headache, flulike symptoms) often cause patients and physicians to consider alternative treatment programs.

Anti-D (IV Rh immune globulin)

In 1983, Salama et al. reported that microgram doses of anti-D (IV Rh immune globulin, IV RhIG) in D+ patients with ITP increased platelet counts in ITP to levels comparable to those reported after infusing gram doses of IVIG. Whereas IVIG-induced Fcγ receptor block results from random IgG molecules binding to mononuclear macrophages’ Fcγ receptors, IV RhIG-induced Fcγ receptor block in D+ patients leverages the larger and more numerous anti-D-coated D+ RBCs to compete with smaller and fewer autoantibody-coated platelets for Fcγ receptor binding. Assuming a representative platelet count of 10,000/μL and a normal RBC count of 5,000,000/μL in a patient with ITP, the competition of approximately 500 anti-D-coated D+ RBCs versus one autoantibody-coated platelet (500:1) favors phagocytosis of the RBCs and “RES blockade” of platelet sequestration and destruction. The efficacy of IV RhIG for increasing platelet counts in ITP has been confirmed by several studies (summarized in reference 22). In North America, treatment of patients with ITP with IV RhIG is increasingly popular compared to IVIG, because of the availability of an FDA-approved IV Rh immune globulin (WinRhode® SDF, Nabi, Boca Raton, FL), and its lower cost, ease of administration, and fewer acute side effects. WinRhode is neither effective nor FDA-approved for treatment of ITP in D− patients. D− patients with ITP (approximately 15% of Caucasians are D−) may be treated with IVIG. Rarely, recipients of a standard dose have experienced acute intravascular hemolysis, with hemoglobinemia and hemoglobinuria.
No specific factor has been identified that predicts an acute hemolytic reaction, nor is there an explanation for the variable clinical responses observed after treatment with IV RhoG, raising the possibility that WinRho may have a variable avidity for different Rh phenotypes, reflecting the number of D antigen sites on the RBC membrane (dosage effect). This hypothesis was investigated using WinRho-coated RBCs of selected Rh phenotypes in direct hemagglutination and monocyte monolayer assays (MMAs), but neither serologic dosage effect nor differentiating reactivity of MMAs for RBCs with a double dose of D antigen was demonstrated. Readers are reminded that while WinRho is commonly called “anti-D,” it is manufactured from pools of plasma collected from alloimmunized D- persons and different production lots may contain, in addition to anti-D, variable concentrations of anti-E, -C, -G and/or other alloantibodies. When WinRho is infused intravenously to treat ITP in a D+ patient, the IV bolus (50–75 µg/kg) is approximately 10 times the conventional intramuscular dose used for Rh immunoprophylaxis in D- women (300 µg, total dose). Therefore, serologic testing shortly after an infusion may detect multiple passively infused blood group alloantibodies, as well as the expected positive DAT. The presence of anti-D in the plasma of D+ ITP patients after an infusion of WinRho often raises the question, “Should D+ or D- RBCs be selected for transfusion, if required?” In this author’s opinion, the decision should be based on the immediate clinical priority. For example, if RBCs are required to treat anemia secondary to menorrhagia in a woman with newly diagnosed ITP who remains thrombocytopenic, I favor transfusing D+ RBCs to react with any circulating WinRho and contribute to the immediate goal of increasing the platelet count. In contrast, if a patient is anemic, but no longer thrombocytopenic after an infusion of WinRho, I favor transfusing D- RBCs to support the immediate goal of correcting the anemia.

**Rituximab**

Rituximab (Rituxan, Genentech, Inc., San Francisco, CA; and Biogen Idec, Inc., Cambridge, MA) is a humanized IgG1/κ monoclonal anti-CD20 that is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive B-cell non-Hodgkin lymphoma. Typically, an infusion of rituximab is followed by a rapid decrease in B-lymphocytes with less myelosuppression than usually is observed with other immunosuppressive agents. As a consequence, rituximab is used increasingly “off label” to treat adults and children with chronic or refractory ITP. Reports of sustained remissions in many patients, together with the relatively selective B-cell immunosuppression, suggest that rituximab is likely to have an increasingly important role in the future management of ITP.

**Treating Helicobacter pylori infection**

In 1998, Gasbarrini et al. reported that eradication of *Helicobacter pylori* (*H. pylori*) in eight Italian adults with ITP and *H. pylori* gastric infections resulted in significantly increased platelet counts. This finding was supported subsequently by studies of *H. pylori*-infected persons with ITP in Italy and Japan. In contrast, in a carefully controlled study of *H. pylori*-infected ITP patients in New York, only one of 15 patients whose *H. pylori* infection had been eradicated experienced an increased platelet count, and that response was transient. Similarly, in a study in Spain, no significant improvements in platelet counts were observed in 56 patients with chronic ITP after eradication of *H. pylori* infection. The discrepancy in treatment outcomes remains unexplained and has resulted in divergent recommendations concerning the role of screening for *H. pylori* infection in patients with ITP. As one might anticipate, the authors of the study in Spain concluded that “there is insufficient evidence to include a search for *H. pylori* in the initial work-up of ITP patients.” Responding to this opinion, the authors of one of the studies in Italy wrote that “the data acquired to date still prompt us to consider the investigation and eradication of *H. pylori* in ITP patients as a simple, inexpensive tool in early management of the chronic disease. Even though the percentage of patients who are responsive to eradication treatment will be small, it should be mandatory [italics added] for the physicians to avoid the toxicity and discomfort that accompany long-term prednisone and other immunosuppressive treatments, also splenectomy.” In an editorial reviewing these diverse findings, McCrae concluded, “Should patients with ITP be routinely screened for *H. pylori*? At this point, probably not.”

For immunohematologists, a more intriguing question may be whether antibodies to *H. pylori* crossreact with antigens on platelets, causing ITP-like immune destruction. As one hypothesis to explain the inconsistent association of ITP and *H. pylori* infection, Michel et al. suggested that “the expression of various Lewis (Le) antigens by *H. pylori* isolates, and the
subsequent production of anti-Le antibodies, could play a role in ITP pathogenesis since platelets may adsorb Lewis antigens from the plasma. In fact, there are significant data to support this hypothesis, since Le\(^b\) functions as a receptor for \(H. pylori\) in the gastric mucosa\(^{39–41}\) and Le\(^b\) may be adsorbed from plasma by platelet membranes.\(^{42}\) At the 1982 annual meeting of the American Association of Blood Banks, McGinniss reviewed the “ubiquitous nature of human blood group antigens” that are shared between RBCs, bacteria, viruses, and parasites.\(^{43}\) The relationship between Lewis antigens, RBCs, gastric mucosa, platelets, and \(H. pylori\) was not recognized at that time. However, the \(H. pylori\)–ITP issue would appear to present yet one more example of antigens that are shared among human blood cells and the diverse microbial agents that infect us.

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