Review Article

Medical Progress

IMMUNE THROMBOCYTOPENIC PURPURA

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IMMUNE thrombocytopenic purpura is an autoimmune disorder characterized by a low platelet count and mucocutaneous bleeding. The estimated incidence is 100 cases per 1 million persons per year, and about half of these cases occur in children.[1-3] Immune thrombocytopenic purpura is classified as primary or as secondary to an underlying disorder and as acute (of six months or less in duration) or chronic. Adult-onset and childhood-onset immune thrombocytopenic purpura are strikingly different. Affected children are young (peak age, approximately five years) and previously healthy, and they typically present with the sudden onset of petechiae or purpura a few days or weeks after an infectious illness. Boys and girls are equally affected. In more than 70 percent of children, the illness resolves within six months, irrespective of whether they receive therapy. By contrast, immune thrombocytopenic purpura in adults is generally chronic, the onset is often insidious, and approximately twice as many women as men are affected. This review focuses on the diagnosis and management of primary immune thrombocytopenic purpura.

PATHOPHYSIOLOGY

It was long suspected that immune thrombocytopenic purpura is mediated by autoantibodies, since transient thrombocytopenia occurs in neonates born to affected women, and this suspicion was confirmed on the basis of the development of transient thrombocytopenia in healthy recipients after the passive transfer of plasma, including IgG-rich fractions, from patients with immune thrombocytopenic purpura. Platelets coated with IgG autoantibodies undergo accelerated clearance through Fcγ receptors that are expressed by tissue macrophages, predominantly in the spleen and liver. A compensatory increase in platelet production occurs in most patients. In others, platelet production appears to be impaired, as a result of either intramedullary destruction of antibody-coated platelets by macrophages or the inhibition of megakaryocytopoiesis.[4] The level of thrombopoietin is not increased,[5] reflecting the presence of the normal megakaryocyte mass.

A detailed analysis of autoantigen specificity has been published elsewhere.[6] The first antigen to be identified was recognized on the basis of the failure of immune thrombocytopenic purpura antibodies to bind to platelets that were genetically deficient in the glycoprotein IIb/IIIa complex.[7] Antibodies that react with glycoproteins Ib/IX, Ia/IIa, IV, and V and diverse other platelet determinants have since been identified,[8-11] and the presence of antibodies against multiple antigens is typical.[9] The destruction of platelets within antigen-presenting cells — presumably, although not necessarily, initiated by antibody — may generate a succession of neoantigens, resulting in sufficient antibody production to cause thrombocytopenia (Fig. 1).

Naturally occurring antibodies against glycoprotein IIb/IIIa show clonal restriction in light-chain use,[12] and antibodies derived from phage-display libraries show highly constrained V_H gene use.[13,14] Sequencing of the antigen-combining regions of these antibodies suggests that they originate from a limited number of B-cell clones by antigen-driven affinity selection and somatic mutation.[14] Adults with immune thrombocytopenic purpura often have increased numbers of HLA-DR+ T cells, increased numbers of soluble interleukin-2 receptors, and a cytokine profile suggesting the activation of precursor helper T and type 1 helper T cells.[15] In these patients, T cells stimulate the synthesis of antibody after exposure to fragments of glycoprotein IIb/IIIa but not after exposure to native proteins.[16] The derivation of these cryptic epitopes in vivo and the reason for sustained T-cell activation are unknown.

The methods that are currently used to treat immune thrombocytopenic purpura are directed at different aspects of this cycle of antibody production and platelet sensitization, clearance, and production (Fig. 2). The efficacy and side effects of each approach are discussed below.

GENETICS

Immune thrombocytopenic purpura has been diagnosed in monozygotic twins[17] and in several families,[18]

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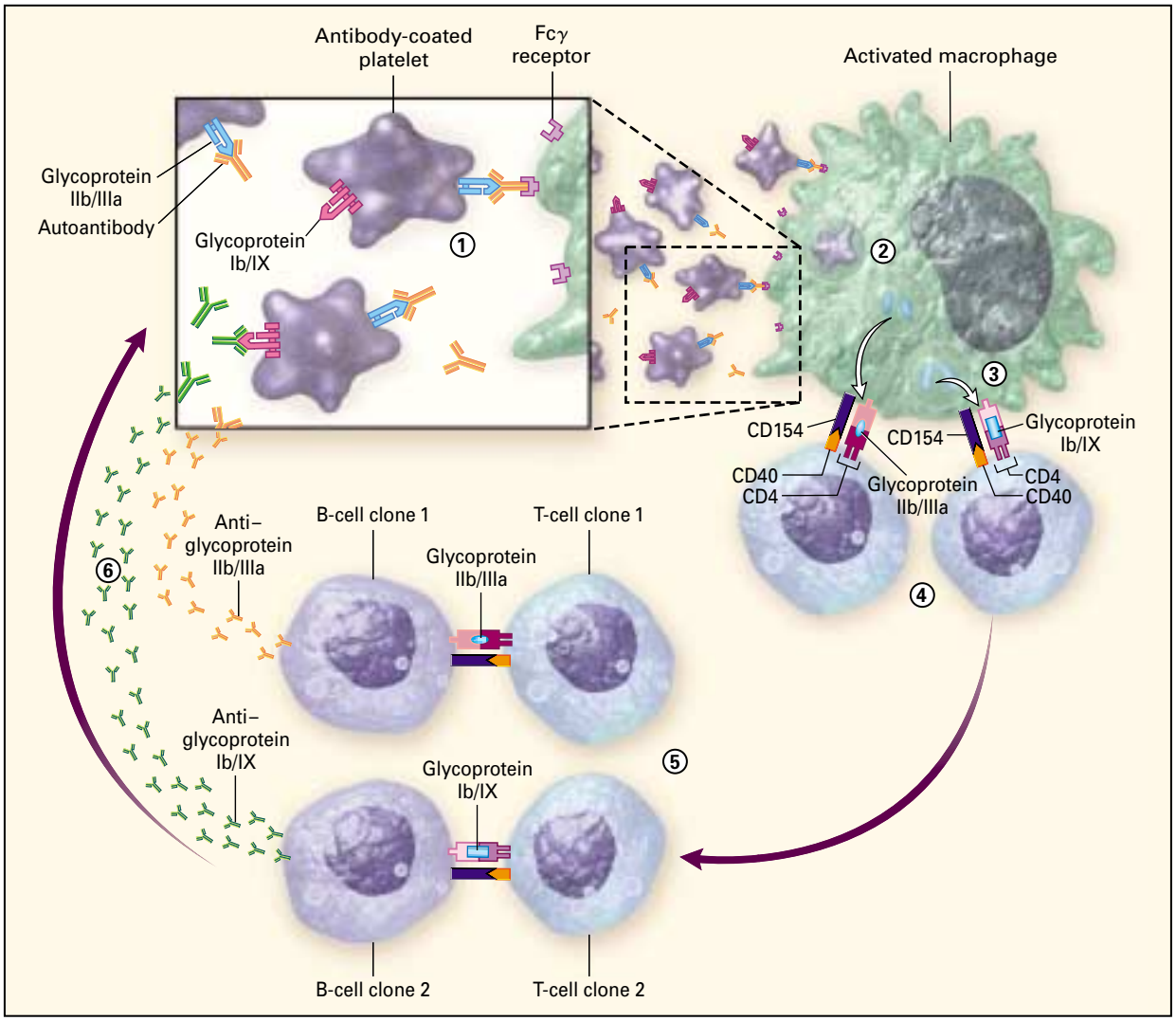


Figure 1. Pathogenesis of Epitope Spread in Immune Thrombocytopenic Purpura.

The factors that initiate autoantibody production are unknown. Most patients have antibodies against several platelet-surface glycoproteins at the time the disease becomes clinically evident. Here, glycoprotein IIb/IIIa is recognized by autoantibody (orange, inset), whereas antibodies that recognize the glycoprotein Ib/IX complex have not been generated at this stage (1). Antibody-coated platelets bind to antigen-presenting cells (macrophages or dendritic cells) through Fcγ receptors and are then internalized and degraded (2). Antigen-presenting cells not only degrade glycoprotein IIb/IIIa (light blue oval), thereby amplifying the initial immune response, but also may generate cryptic epitopes from other platelet glycoproteins (light blue cylinder) (3). Activated antigen-presenting cells (4) express these novel peptides on the cell surface along with costimulatory help (represented in part by the interaction between CD154 and CD40) and the relevant cytokines that facilitate the proliferation of the initiating CD4-positive T-cell clones (T-cell clone 1) and those with additional specificities (T-cell clone 2) (5). B-cell immunoglobulin receptors that recognize additional platelet antigens (B-cell clone 2) are thereby also induced to proliferate and synthesize anti–glycoprotein Ib/IX antibodies (green) in addition to amplifying the production of anti–glycoprotein IIb/IIIa antibodies (orange) by B-cell clone 1 (6).

and a propensity for autoantibody production in family members has been noted.[19] An increased prevalence of HLA-DRw2 and DRB1*0410 alleles was noted in certain ethnic populations. HLA-DR4 and DRB1*0410 alleles have been associated with an unfavorable and favorable response to corticosteroids, respectively, and HLA-DRB1*1501 has been linked with an unfavorable response to splenectomy. However, numerous (albeit small) studies have failed to demonstrate a consistent association between immune thrombocytopenic purpura and specific major-histocompatibility-complex class I or class II polymorphisms.

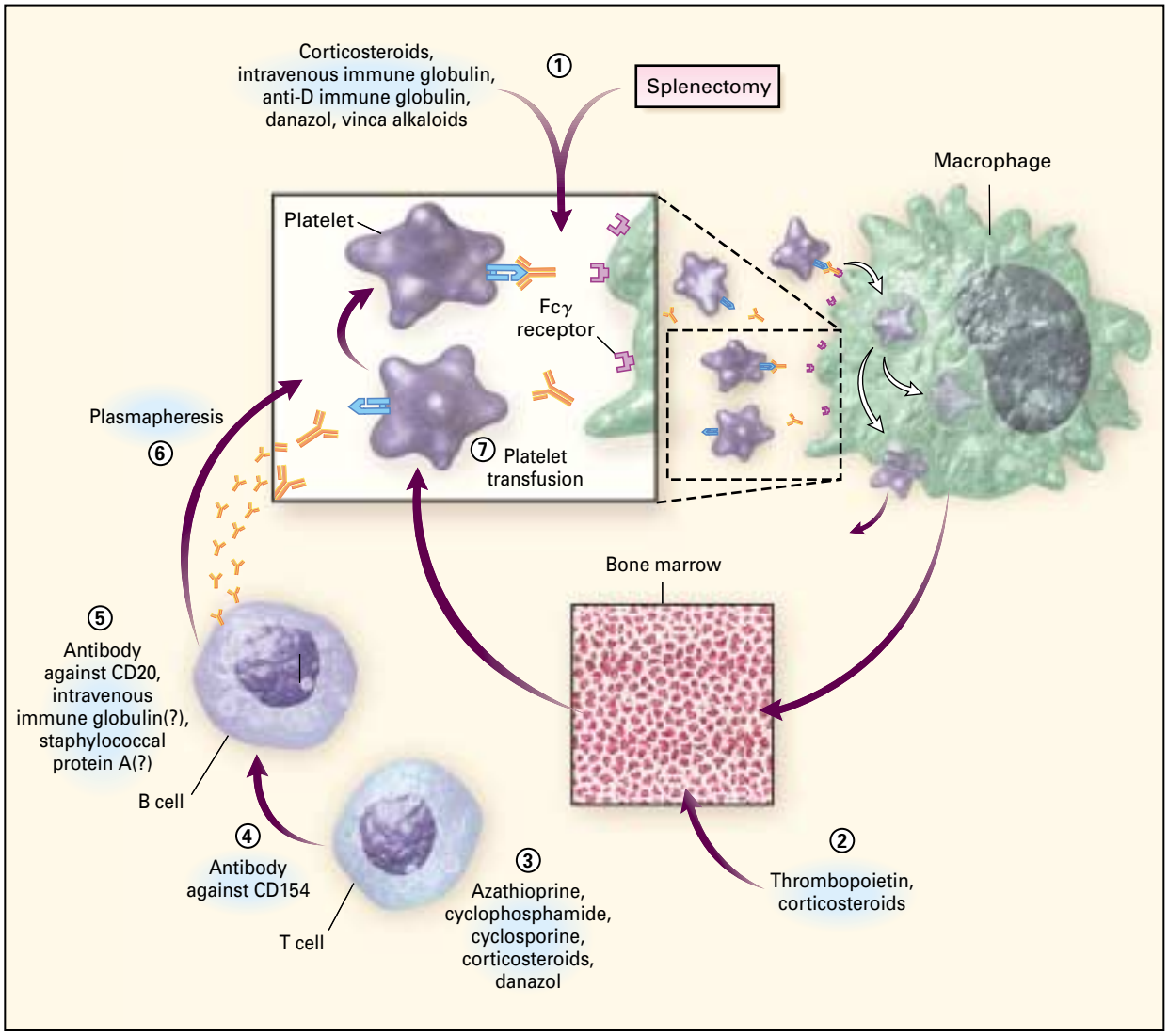


Figure 2. Mechanisms of Action of Therapies for Immune Thrombocytopenic Purpura.

Many drugs used in the initial treatment of immune thrombocytopenic purpura impair the clearance of antibody-coated platelets (1) by the Fcγ receptors expressed on tissue macrophages (inset). Splenectomy works at least in part by this mechanism but may also impair the T-cell–B-cell interactions involved in the synthesis of antibody in some patients. Corticosteroids may also increase platelet production by impairing the ability of macrophages within the bone marrow to destroy platelets, and thrombopoietin stimulates megakaryocyte progenitors (2). Many nonspecific immunosuppressants, such as azathioprine and cyclosporine, act at the level of the T cell (3). A monoclonal antibody against CD154 that is now in clinical trials targets a costimulatory molecule needed for the optimization of the T-cell–macrophage and T-cell–B-cell interactions involved in antibody production and class switching (4). Intravenous immune globulin may contain antiidiotypic antibodies that impede antibody production. A monoclonal antibody that recognizes CD20 expressed on B cells (5) is also under study. Plasmapheresis may transiently remove antibody from the plasma (6), and platelet transfusions are used in emergencies to treat bleeding (7). The effect of staphylococcal protein A on the antibody repertoire is under study.

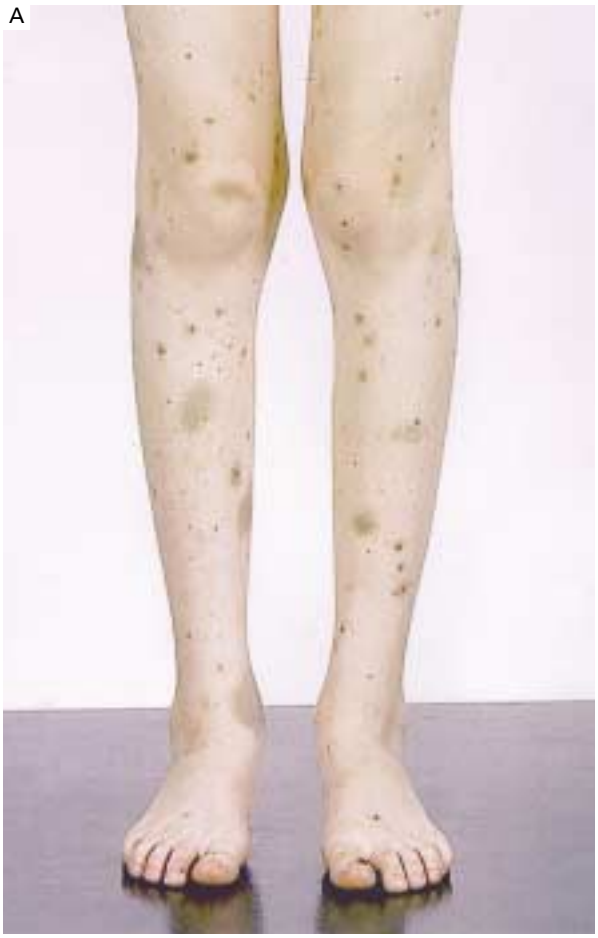
DIAGNOSIS

The diagnosis of immune thrombocytopenic purpura remains one of exclusion. Secondary forms of the disease occur in association with systemic lupus erythematosus, the antiphospholipid syndrome, immunodeficiency states (IgA deficiency and common variable hypogammaglobulinemia), lymphoproliferative disorders (chronic lymphocytic leukemia, large granular lymphocytic leukemia, and lymphoma), infection with human immunodeficiency virus and hepatitis C virus, and therapy with drugs such as heparin and quinidine. In children less than three months of age, passively ac-

quired autoimmune or alloimmune thrombocytopenia must be excluded. Hereditary nonimmune thrombocytopenia can masquerade as immune thrombocytopenic purpura. Anticardiolipin and antinuclear antibodies and positive direct antiglobulin tests are not infrequent but are of little diagnostic or therapeutic importance in the absence of clinical disease,[20,21] although some have reported an increased risk of thrombosis associated with the presence of antiphospholipid antibodies.[22] A few patients have concurrent autoimmune hemolytic anemia, neutropenia, or both, which carry a less favorable prognosis.

The duration of bleeding may help to distinguish acute from chronic immune thrombocytopenic purpura; the absence of systemic symptoms helps clinicians to rule out secondary forms and other diagnoses. It is important to take a careful history of the use of drugs and other substances that can cause thrombocytopenia. The family history is generally unremarkable in patients with immune thrombocytopenic purpura, and the physical examination generally reveals only evidence of platelet-type bleeding (petechiae, purpura, conjunctival hemorrhage, or other types of mucocutaneous bleeding) (Fig. 3). Marked splenomegaly should trigger consideration of an alternative diagnosis; however, a spleen tip is palpable in approximately 10 percent of children. Apart from thrombocytopenia, the blood count should be normal for the patient's age or, if abnormal, readily explained (e.g., by the presence of anemia due to epistaxis). Inspection of a peripheral-blood smear is required to rule out pseudothrombocytopenia, inherited giant platelet syndromes, and other hematologic disorders. Large, immature platelets (megathrombocytes) are often seen. These young reticulated platelets that are detectable by flow cytometry on the basis of their messenger RNA content are presumed to be more metabolically active,[23] offering an explanation for the observation that bleeding in immune thrombocytopenic purpura is typically less pronounced than in states of bone marrow failure at similar platelet counts. Laboratory investigation at the time of presentation should be kept to a minimum if there are no atypical findings.[24]

One of the most contentious issues is the need for bone marrow aspiration. The guidelines of the American Society of Hematology state that a bone marrow examination is not required in adults younger than 60 years of age if the presentation is typical but is appropriate before splenectomy is performed.[24] Our practice is to perform a bone marrow examination in patients over 40 years of age, in patients with atypical features (e.g., those with additional cytopenias), or in patients who do not have a brisk or robust response to therapy. There is consensus, supported by the results of retrospective studies,[25] that bone marrow examination is not necessary in children if management



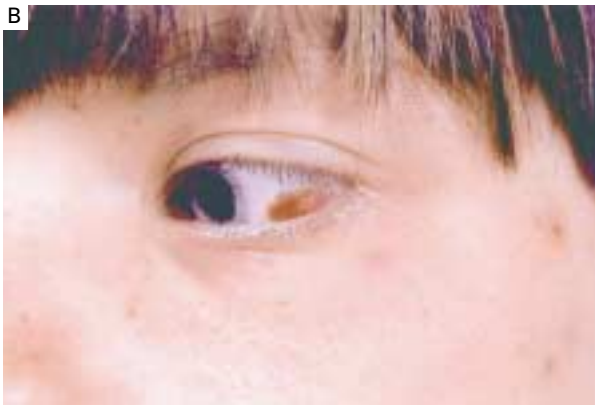
involves observation or intravenous immune globulin. Although it is not mandatory, many pediatric hematologists recommend that an aspiration be performed before starting corticosteroids to rule out the rare case of acute leukemia.[26] A marrow examination is mandatory in patients with atypical cases, such as those with lassitude, protracted fever, bone or joint pain, unexplained macrocytosis, or neutropenia.

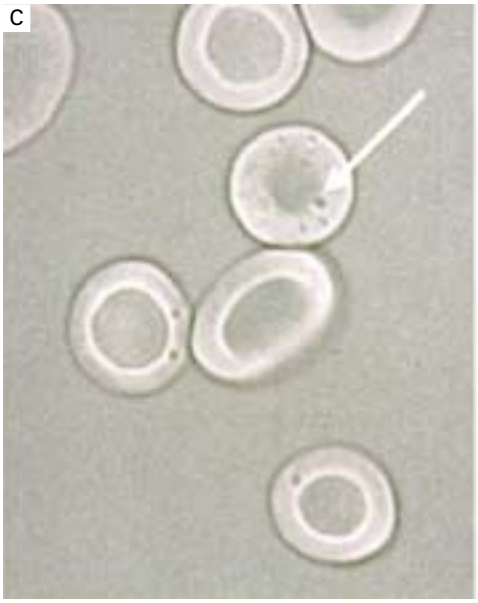
MEASURING PLATELET-ASSOCIATED ANTIBODIES

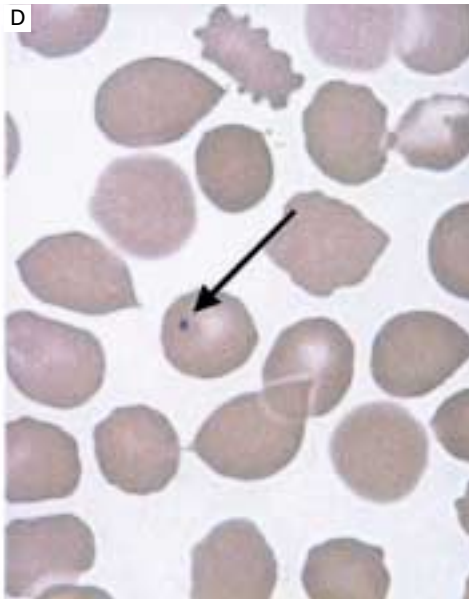
A detailed discussion of the detection of platelet-associated antibody is beyond the scope of this review.[27] The direct assay for the measurement of platelet-bound antibodies (Fig. 4)[28] has an estimated sensitivity of 49 to 66 percent, an estimated specificity of 78 to 92 percent, and an estimated positive predictive value of 80 to 83 percent.[29,30] A negative test cannot be used to rule out the diagnosis.[29,31] The detection of unbound plasma antibody is less useful.

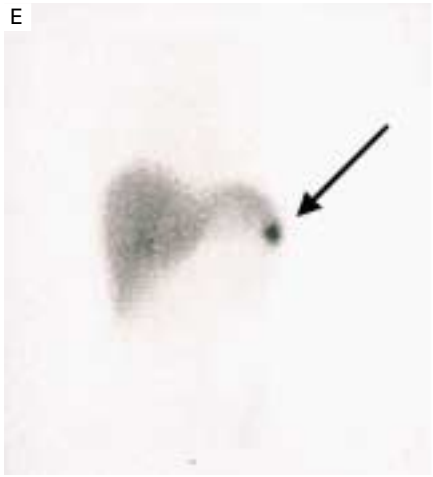
Figure 3. Clinical Features of Immune Thrombocytopenic Purpura.

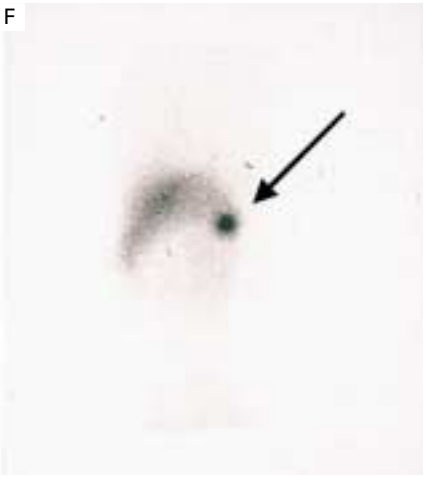
Panel A (facing page) shows extensive petechiae and purpura on the legs of a child with immune thrombocytopenic purpura. Whether children who present with only these features should be treated is controversial. Panel B shows a conjunctival hemorrhage. Extensive mucocutaneous bleeding may be a harbinger of internal bleeding. Typical changes after splenectomy in the erythrocytes (arrow in Panel C) include pitting and Howell–Jolly bodies (arrow in Panel D), which are remnants of nuclear chromatin. Anterior view (Panel E) and left lateral view (Panel F) of scans with technetium Tc 99m–labeled heat-damaged red cells show an accessory spleen (arrows) in a patient who had a relapse of immune thrombocytopenic purpura after splenectomy.











Interlaboratory agreement in the detection of platelet-bound antibody is 55 to 67 percent, but the extent of agreement in the detection of plasma antibody is lower.[32] These favorable operating characteristics depend on the composition of the control population with nonimmune thrombocytopenia; the predictive values are less compelling when the differential diagnosis involves systemic lupus erythematosus, chronic hepatitis, myelodysplasia, and B-cell lymphomas.[33,34] These tests have yet to be shown to distinguish primary from secondary immune thrombocytopenic purpura, or children with a self-limited course from those in whom chronic disease will develop.[35]

INITIAL MANAGEMENT

Adults

Immune thrombocytopenic purpura occurs most commonly between 18 and 40 years of age and is two to three times as common among women as among men,[36] although this pattern has been called into question.[1] In patients with platelet counts above 50,000 per cubic millimeter, immune thrombocytopenic purpura is usually discovered incidentally; those with 30,000 to 50,000 platelets per cubic millimeter may note excessive bruising with minor trauma; petechiae or ecchymoses develop spontaneously when counts are between 10,000 and 30,000 per cubic millimeter; and patients with counts below 10,000 per cubic millimeter are at risk for internal bleeding.[37] In one recent series, half the patients presented with counts below 10,000 per cubic millimeter.[1] Therefore, adults generally require treatment at the time of presentation, typically with oral prednisone (at a dose of 1.0 to 1.5 mg per kilogram of body weight per day). Response rates range from 50 percent to over 75 percent, depending on the intensity and duration of therapy.[24] Most responses occur within the first three weeks,[38,39] but there is no consensus concerning the appropriate

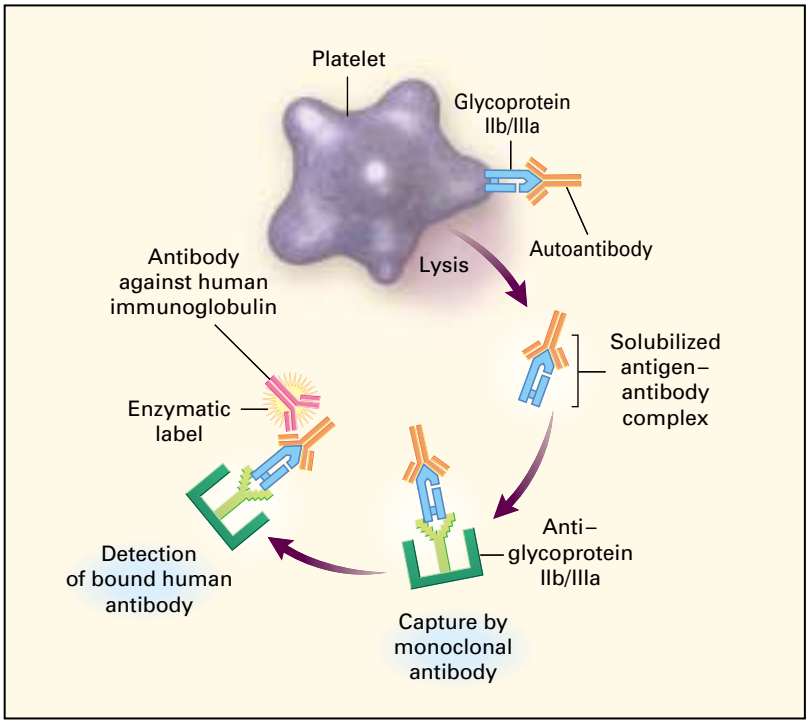


Figure 4. Detection of Platelet-Specific Antibodies with a Monoclonal-Antigen–Capture Assay.

In this test, platelets from a patient suspected of having immune thrombocytopenic purpura are coated with an autoantibody — in this case, an autoantibody against the glycoprotein IIb/IIIa complex (orange). Platelets from the patient or control platelets are lysed, releasing solubilized antigen–antibody complexes (orange and light blue). These are captured by immobilized murine monoclonal antibody against glycoprotein IIb/IIIa (green). An antibody against human immunoglobulin (pink) labeled with an enzyme (yellow) is added to detect human IgG bound to the plate, which is measured by enzyme-linked immunosorbent assay. Normal platelets preincubated with plasma from the patient or control plasma are studied in a similar manner in order to detect circulating antibodies.

duration of treatment.[37] The incidence of continuous remission ranges from less than 5 percent to over 30 percent,[24] depending on the duration of the disorder,[40] response criteria, and duration of follow-up.[36,38,39] Anti-D immune globulin (75 μg per kilogram) is equally efficacious in Rh-positive patients at presentation, but is considerably more expensive and is generally less toxic.[41]

Intravenous immune globulin (1 g per kilogram per day for two to three consecutive days) is used to treat internal bleeding, when the platelet count remains below 5000 per cubic millimeter despite treatment for several days with corticosteroids or when extensive or progressive purpura are present. Approximately 80 percent of patients have a response, but sustained remission is infrequent,[42] and the cost of using intravenous immune globulin is considerable. Renal failure and pulmonary insufficiency may occur, and anaphylaxis may occur in recipients who have a congenital deficiency of IgA.

Decisions about splenectomy depend on the severity of the disease, tolerance of corticosteroids, and the patient's preferences with regard to surgery. Many hematologists recommend splenectomy within three to six months if more than 10 to 20 mg of prednisone per day is required to maintain a platelet count above 30,000 per cubic millimeter, although emerging data may support an approach of watchful waiting.

Children

The initial treatment of children with typical acute immune thrombocytopenic purpura remains controversial,[43,44] in part because the outcome is so favorable without treatment. The decision whether to treat such children is driven by fear of intracranial hemorrhage and untoward restrictions on physical activity. The actual incidence of intracranial hemorrhage is between 0.2 and 1 percent.[2] Almost all intracranial hemorrhages occur at platelet counts below 20,000 per cubic millimeter, and generally below 10,000 per cubic millimeter. Contributing risk factors include head trauma and exposure to antiplatelet drugs. Most intracranial hemorrhages occur within four weeks after presentation with immune thrombocytopenic purpura, often within the first week.[2,45] Such hemorrhages are too infrequent to allow a direct assessment of the effect of therapy. Therefore, the decision to treat a child with immune thrombocytopenic purpura is based on the unproven assumption that shortening the duration of severe thrombocytopenia affords protection.[46]

The case for observation is that most children with typical acute immune thrombocytopenic purpura recover completely within a few weeks without treatment and that there is no proof that therapy prevents intracranial hemorrhage.[43,44,47] Indeed, immune thrombocytopenic purpura in many children — certainly those without hemorrhage — is managed on an outpatient basis with minimal investigation, short-term therapy in select cases,[48] and the avoidance of activities that predispose the patient to trauma and of medications that impair platelet function.[49]

Randomized clinical trials have demonstrated that therapy with intravenous immune globulin shortens the duration of severe thrombocytopenia (defined as a platelet count below 20,000 per cubic millimeter).[50] Adverse reactions are generally transient and related to the rate of infusion; these include headache, fever, nausea, and rarely, aseptic meningitis that may arouse concern about the possibility of intracranial hemorrhage.[51] The response to intravenous immune globulin is more rapid than the response to intravenous anti-D immune globulin given at a dose of 25 μg per kilogram per day for two consecutive days[52,53]; however, a larger dose of anti-D immune globulin (75 μg per kilogram) evokes a response similar to intravenous immune globulin.[41] The average decrease in the hemoglobin level is 1.3 g per deciliter,[54] and intravascular hemolysis is rare.[55] The short-term benefit of oral corticosteroids in traditional doses (1 to 2 mg of prednisone per kilogram per day) is uncertain,[56] but platelet counts increase more rapidly with higher doses.[48] Behavioral changes, weight gain, osteopenia, and glycosuria can occur during even brief courses of high-dose corticosteroids. The relative efficacy of intravenous immune globulin as compared with high-dose corticosteroids is unresolved.[57,58]

In the absence of data showing improved clinical outcome, treatment decisions are based on the assessment of the physician. If treatment is recommended, the minimal therapy required to achieve a platelet count that is sufficient to sustain hemostasis should be used. A single dose of intravenous immune globulin (0.8 g per kilogram) is generally effective.[52] Excellent early responses to oral prednisone (4 mg per kilogram per day for four consecutive days) have also been reported in an uncontrolled prospective study.[48] Parents should be advised about the risks and benefits of observation alone, including the small risk of intracranial hemorrhage and the remote risk of transfusion-transmitted illnesses from intravenous immune globulin or anti-D immune globulin.[59]

Urgent Treatment

Neurologic symptoms, internal bleeding, or emergency surgery demands immediate intervention.[24] Methylprednisolone (30 mg per kilogram per day; maximum, 1.0 g per day for two to three days) should be administered intravenously over a period of 20 to 30 minutes[60,61] together with intravenous immune globulin (1 g per kilogram per day for two to three days) and an infusion of platelets that is two to three times the usual amount infused[37]; vincristine may

be considered as part of combination therapy. Splenectomy should be considered if it has not yet been performed. Plasmapheresis is of limited benefit. Antifibrinolytic therapy (e.g., aminocaproic acid) may reduce mucosal bleeding, and recombinant factor VIIa[62] should be considered. For severe persistent bleeding, the course of high-dose intravenous immune globulin can be extended to five days, along with continuous infusion of platelets (1 unit per hour).[37]

MANAGEMENT OF FIRST RELAPSE

Adults

Most adults with immune thrombocytopenic purpura have one or more relapses when doses of corticosteroids are tapered or when they have not had a response to corticosteroids and require intravenous immune globulin or anti-D immune globulin (Fig. 5). No treatment is required for asymptomatic patients in whom platelet counts above 30,000 per cubic millimeter are maintained, unless it is indicated because of coexisting conditions or preference (e.g., for those whose vocations necessitate exposure to trauma). In some patients, remission occurs without additional treatment.[63] Splenectomy is the appropriate next step for most adults who have a relapse or have not had a response to corticosteroids, intravenous immune globulin, or anti-D immune globulin.

Children

Approximately 25 percent of children with immune thrombocytopenic purpura have a relapse after initial treatment.[50,52] Given the lack of evidence that medical therapy favorably alters the long-term outcome, the goal is to maintain a safe platelet count.[47] Splenectomy is deferred as long as possible[64] because one third of children have spontaneous remission[24] and only 5 percent still have severe thrombocytopenia requiring therapy one year after diagnosis.[65] The risk of death due to overwhelming bacterial sepsis is highest in very young children and persists throughout life. Guidelines from the American Society of Hematology recommend that splenectomy be considered for children who have had immune thrombocytopenic purpura for at least one year with symptomatic, severe thrombocytopenia[24]; practice guidelines in the United Kingdom are similar.[64] In Rh-positive children, anti-D immune globulin, if clinically effective, is preferred to intravenous immune globulin because of its ease of administration, similar efficacy, and lower cost. Response rates of approximately 70 percent are seen, and responses often last at least three weeks.[54] Long-term corticosteroid therapy causes unacceptable adverse effects, and the frequency of durable responses to pulses of oral dexamethasone is disappointing.[66]

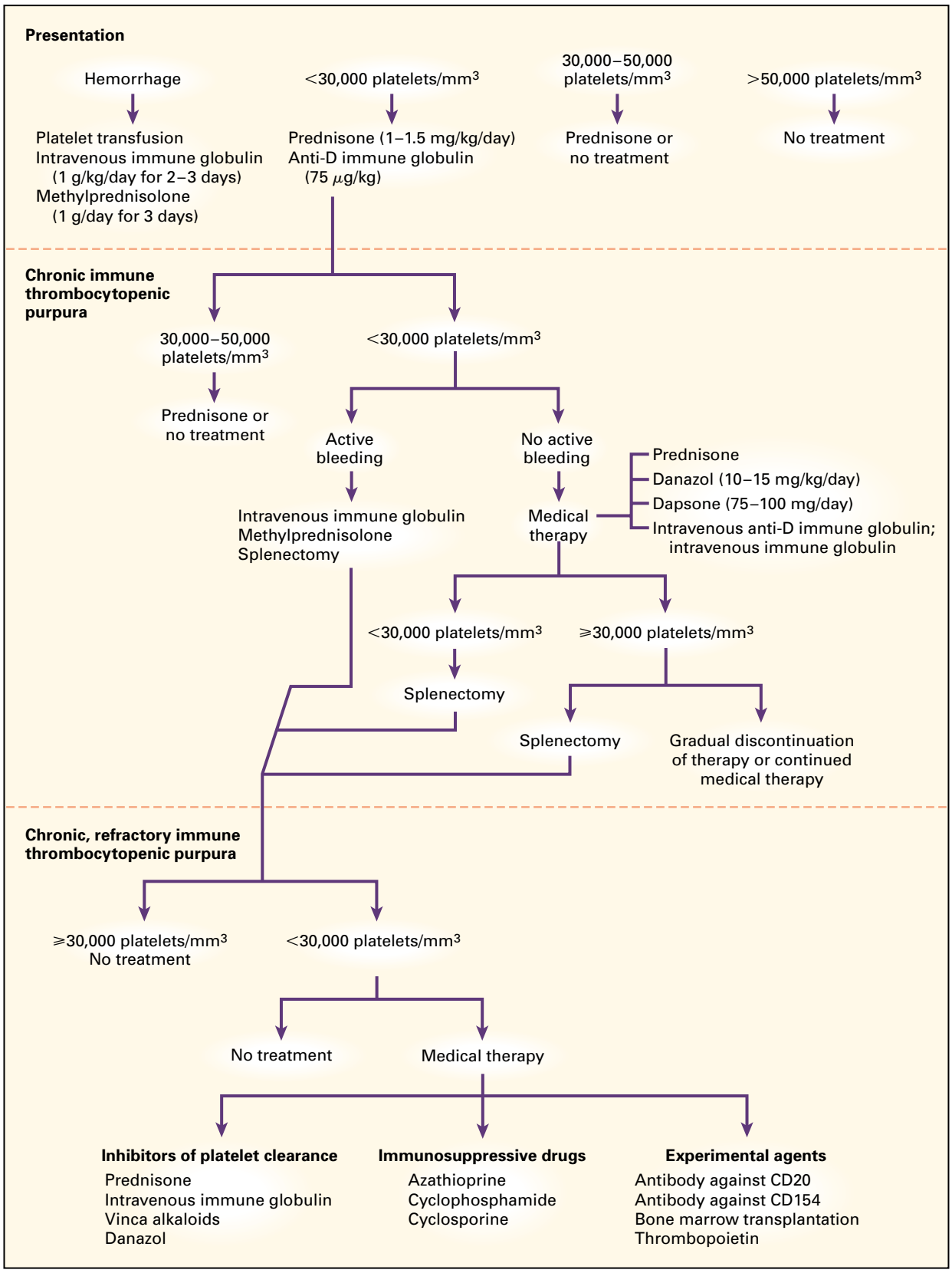
SPLENECTOMY

Adults

There is no means of predicting an individual patient's response to splenectomy. Results of numerous studies indicate that approximately two thirds of patients have a response, generally within days.[24,37,67] Patients with platelet counts below 50,000 per cubic millimeter may require corticosteroids, intravenous immune globulin, or anti-D immune globulin before surgery. However, splenectomy can often be performed, if necessary, without additional therapy, even in patients with low platelet counts.[37] In experienced hands, laparoscopic splenectomy appears to have short-term and long-term benefits and complications that are similar to those associated with open splenectomy,

Figure 5 (facing page). Management of Adult-Onset Immune Thrombocytopenic Purpura.

Some specialists advocate the use of 20,000 rather than 30,000 platelets per cubic millimeter as the threshold for therapy in patients who present with immune thrombocytopenic purpura. There is no consensus as to the appropriate duration of corticosteroid therapy. The use of anti-D immune globulin as initial therapy is under study and is appropriate only for Rh-positive patients. Whether to use intravenous immune globulin or anti-D immune globulin as initial therapy depends on the severity of thrombocytopenia and the extent of mucocutaneous bleeding. The decision whether to treat patients who present with a platelet count of 30,000 to 50,000 per cubic millimeter depends on whether there are coexisting risk factors for bleeding and whether there is a high risk of trauma. A platelet count of more than 50,000 per cubic millimeter may be appropriate before surgery or after trauma in some patients. In patients with chronic immune thrombocytopenic purpura and a platelet count of less than 30,000 per cubic millimeter, intravenous immune globulin or methylprednisolone may help to increase the platelet count immediately before splenectomy. The medications listed for the treatment of chronic immune thrombocytopenic purpura in patients with less than 30,000 platelets per cubic millimeter can be used individually, but either danazol or dapsone is often combined with the lowest dose of prednisone required to attain a hemostatic platelet count. Intravenous immune globulin and anti-D immune globulin are generally reserved for severe thrombocytopenia that is unresponsive to oral agents. The decision whether to perform a splenectomy, to continue medical therapy, or to taper doses and eventually discontinue therapy in patients with chronic immune thrombocytopenic purpura and a platelet count of 30,000 per cubic millimeter or higher depends on the intensity of therapy that is required, tolerance of side effects, the risk associated with surgery, and the preference of the patient. The decision whether to treat patients with chronic, refractory immune thrombocytopenic purpura involves weighing the risk of hemorrhage against the side effects of each form of therapy. Drugs are often used in combination. Patients who are receiving protracted courses of corticosteroids should be monitored for osteopenia and cataracts. This algorithm represents a synthesis of the published literature, expert opinion, American Society of Hematology guidelines, and the authors' experience.



although the duration of follow-up in patients who have undergone laparoscopic splenectomy has been short.[68] The use of laparoscopic surgery also speeds recovery and shortens hospitalization. Splenic radiation has been used as short-term treatment in patients who are too frail to undergo surgery.[69]

Children

In children, the rate of complete remission after splenectomy is approximately 70 to 80 percent.[24] Laparoscopic splenectomy appears to be preferable to open splenectomy, provided that it is performed by an experienced surgeon.

Sepsis after Splenectomy

The risk of overwhelming bacterial sepsis is substantially increased in patients who have undergone splenectomy. At least two weeks before undergoing splenectomy, patients should be immunized with *Haemophilus influenzae* type b and pneumococcal vaccines, depending on their age and immunization history[70,71]; meningococcal vaccine is also recommended. Because the protection provided by vaccines is incomplete, daily prophylaxis with penicillin (or an equivalent drug if the child is allergic to penicillin) is recommended for patients up to five years of age and for at least one year after splenectomy.[72] Some — for example, physicians in the United Kingdom — recommend continuing prophylaxis into adulthood. All febrile episodes should be carefully assessed, and the urgent use of parenteral antibiotics should be considered. An explanatory letter, a supply of antibiotics, and a Medic Alert bracelet may be helpful to patients when they are traveling.

CHRONIC REFRACTORY IMMUNE THROMBOCYTOPENIC PURPURA

Adults

Approximately 30 to 40 percent of adults do not have a response to splenectomy or have a relapse sometime after undergoing splenectomy. These patients are unlikely to be cured and are at the greatest risk for death, although spontaneous remissions sometimes occur.[73] The cornerstone of management involves minimizing therapy while maintaining a safe platelet count, taking into account coexisting risk factors for bleeding (including requirements for medication that impair platelet function), the patient's level of acceptance of modifications in lifestyle, tolerance or lack of tolerance of treatment, and the potential toxic effects of each intervention. Elderly patients are both more likely to have severe bleeding[74] and to suffer debilitating side effects from treatment. American Society of Hematology guidelines state that a platelet count of 30,000 to 50,000 per cubic millimeter in a patient without other risk factors is generally an appropriate surrogate end point[24] that provides a sufficient margin to minimize the risk of spontaneous hemorrhage.[63,74]

No single treatment algorithm is suitable for all patients.[37,75] Published case series generally include few severely affected patients; the criteria for response involve arbitrary increases in the platelet count of undocumented clinical import; and the effect on survival and morbidity cannot be assessed because of the small numbers of patients and the short follow-up.[37,75] Thus, therapy must be individualized, and published success rates should be viewed as optimistic. The benefit of treating asymptomatic patients is unproved.[76]

Patients who have a relapse are generally treated again with prednisone, but few can be treated for the long term at acceptably low doses or with alternate-day regimens. Steps should be taken to retard osteoporosis when long-term use of corticosteroids is contemplated. The presence of an accessory spleen may be suspected if the typical changes in blood smears are not evident after splenectomy (Fig. 3). Residual splenic tissue can be detected with magnetic resonance imaging or with sensitive scanning techniques (e.g., labeled heat-damaged red cells), but long-term response to surgical removal of an accessory spleen is uncommon.[77] Repeated infusions of intravenous immune globulin are often lifesaving, but it is not unusual for refractoriness to develop.[78]

The next approach in patients requiring additional therapy generally involves agents that impede platelet clearance (Fig. 5) as a corticosteroid-sparing measure. Danazol (10 to 15 mg per kilogram per day) is beneficial in 20 to 40 percent of patients and occasionally induces remission if given for three to six months.[79] Normal platelet counts can be sustained at doses as low as 50 mg daily in some patients. Response is infrequent in patients whose condition has been refractory to treatment with corticosteroids. Side effects include hepatotoxicity, rash, and masculinization. Dapsone (75 mg per day) has been used successfully in 40 to 50 percent of patients with a relapse,[80,81] but response is rare in patients with refractory immune thrombocytopenic purpura. Vinca alkaloids are now used infrequently because the response rate in patients with refractory immune thrombocytopenic purpura is low (3 to 30 percent), and responses are transient and are often complicated by neuropathy.[82] Patients who have undergone splenectomy should not be treated with anti-D immune globulin. Occasional responses occur with ex vivo perfusion of plasma over a staphylococcal protein A column,[83] but severe side effects have been reported.

Immunosuppression is typically reserved for patients with platelet counts below 20,000 per cubic millimeter who have had no response to the abovementioned measures or are intolerant of them. Responses occur in 20 to 40 percent of patients who are

treated for two to six months with azathioprine[40,84] (1 to 4 mg per kilogram orally daily) or cyclophosphamide[40,85] (1 to 2 mg per kilogram orally daily), with the dose adjusted to cause mild neutropenia. Cyclophosphamide has been given as an intravenous bolus alone (1.0 to 1.5 g per square meter of body-surface area every four weeks for one to five doses) or together with some combination of the following: prednisone, a vinca alkaloid, and other agents.[86] Liver function should be monitored in patients treated with azathioprine, which is generally well tolerated; the potential risk of carcinogenicity should be discussed, but azathioprine is not known to have caused cancer in patients with immune thrombocytopenic purpura. Cyclophosphamide can cause marrow suppression, hemorrhagic cystitis, fibrosis of the bladder, alopecia, infertility, and myeloid leukemia and can be teratogenic. There is anecdotal evidence of responses to cyclosporine alone or in combination with cyclophosphamide. Combinations of agents, such as azathioprine, danazol, and prednisone, may be especially useful.

Investigational approaches for patients with severe immune thrombocytopenic purpura that is refractory to conventional measures include humanized monoclonal antibodies against CD20[87] and CD154. Trials of thrombopoietin are under way. Regression of immune thrombocytopenic purpura has been reported after the eradication of *Helicobacter pylori* infection.[88] The National Institutes of Health recently found that high-dose immunosuppression followed by autologous bone marrow transplantation resulted in complete remission in 4 of 14 patients who could be evaluated and partial remission in 4 of these 14.[89]

Children

A challenge is posed by the occasional symptomatic child in whom splenectomy fails or is contraindicated and in whom the platelet count cannot be sustained with acceptable doses of corticosteroids, anti-D immune globulin, or intravenous immune globulin.[90] American Society of Hematology guidelines recommend treatment for such children if they have symptomatic thrombocytopenia and platelet counts of less than 30,000 per cubic millimeter.[24] No regimen is universally effective. We recommend using azathioprine (2 to 3 mg per kilogram orally daily, with the dose adjusted to cause mild neutropenia) at the lowest dose that sustains hemostasis[84]; azathioprine may be used alone or in combination with prednisone. A dose of 0.02 mg of vincristine per kilogram (maximum dose, 2 mg) or 0.1 mg of vinblastine per kilogram (maximum dose, 10 mg) given by bolus injection at intervals of five to seven days for a maximum of three courses may provide transient benefit. In refractory cases, a trial of pulsed intravenous cyclophosphamide (two to four doses of 1.5 g per square meter at four-week intervals), cyclosporine, or combination chemotherapy[86] may be useful. Complex cases in children that require second-line therapies merit referral to a hematologist with expertise in immune thrombocytopenic purpura.

IMMUNE THROMBOCYTOPENIC PURPURA DURING PREGNANCY

It is estimated that immune thrombocytopenic purpura occurs in 1 to 2 of every 1000 pregnancies, accounting for approximately 3 percent of women who have thrombocytopenia at the time of delivery.[91] Although pregnancy is not discouraged in women with preexisting immune thrombocytopenic purpura, maternal and fetal complications can occur, and additional monitoring and therapy may be needed. The diagnosis of immune thrombocytopenic purpura first suspected during pregnancy continues to pose dilemmas, and a uniform approach to management, although emerging, has not been achieved.[92] There may be marked disparities between the maternal and fetal platelet counts. No antenatal measures reliably predict neonatal status, and maternal response to intervention does not guarantee a favorable neonatal outcome. Only previous neonatal outcome provides a useful predictor of the neonatal platelet count in the subsequent pregnancy.[93]

The differential diagnosis of thrombocytopenia during pregnancy includes pregnancy-induced hypertension and related conditions such as the syndrome of hemolysis with elevated liver enzymes and a low platelet count (HELLP), microangiopathic hemolytic processes, and hereditary thrombocytopenias, as well as gestational thrombocytopenia[94] (also referred to as incidental or benign thrombocytopenia of pregnancy), which accounts for approximately 75 percent of cases of thrombocytopenia at term in healthy women who have had an uneventful pregnancy.[95] Characteristic features include mild thrombocytopenia (platelet counts of more than 70,000 per cubic millimeter in 95 percent of cases) and normalization of platelet counts within two months after delivery. There is no effect on the health of the mother or the fetus or infant. Immune thrombocytopenic purpura should be suspected if severe isolated thrombocytopenia is detected early in pregnancy.

Platelet counts in women with immune thrombocytopenic purpura may decrease during pregnancy. Platelet counts should be monitored at least monthly through the first two trimesters, every other week during the third trimester, and weekly as term approaches. Corticosteroid therapy can exacerbate gestational diabetes, bone loss, and hypertension. Splenectomy should be avoided, if at all possible, and should be deferred to the second trimester in order to avoid abortion. Danazol, cyclophosphamide, vin-

ca alkaloids, and other potentially teratogenic agents (with the possible exception of azathioprine) should be avoided. Experience with anti-D immune globulin in pregnant women is limited, so intravenous immune globulin tends to be used more commonly in pregnant women. Ideally, maternal platelet counts should be maintained above 30,000 per cubic millimeter throughout pregnancy and above 50,000 per cubic millimeter near term to minimize the need for platelet transfusions.[96]

Although 10 percent of infants born to women with immune thrombocytopenic purpura are born with platelet counts below 50,000 per cubic millimeter,[91] and counts often decrease during the first few days of life, only 4 percent are born with counts below 20,000 per cubic millimeter.[97] Consequently, the risk of intracranial hemorrhage or other major bleeding complications is less than 1 percent, but this risk is higher than that among the infants of healthy women.[91] The risk is enhanced if alloantibodies are also present.[98] There are no studies showing that the risk of intracranial hemorrhage is reduced by the use of cesarean section,[99] and current practice is not to alter the mode of delivery. Opinions vary concerning the minimal platelet count (50,000 to 100,000 per cubic millimeter) required for epidural anesthesia.[96,100]

Although the fetal platelet count may be accurately determined by percutaneous umbilical-vein sampling, most agree that the risk associated with the procedure outweighs the risk of intracranial hemorrhage due to immune thrombocytopenic purpura.[91] The platelet count should be measured at birth in every neonate born to a woman with immune thrombocytopenic purpura, and this measurement should be repeated during the first few days of life; ultrasonography of the head should be performed to rule out intracranial hemorrhage in infants with thrombocytopenia. Intravenous immune globulin, high-dose corticosteroids, or both should be considered for neonates with platelet counts of less than 30,000 per cubic millimeter at birth. Platelet transfusions should be considered in the face of life-threatening hemorrhage or for severe thrombocytopenia if other risk factors for bleeding are present. Exchange transfusion is reserved for severe, refractory cases. Thrombocytopenia generally resolves within weeks. Immune thrombocytopenic purpura is not a contraindication to breast-feeding.

MORTALITY

The major cause of fatal bleeding in patients with immune thrombocytopenic purpura is intracranial hemorrhage.[1,24,63] The risk is greatest in the elderly, those with a history of bleeding, and those who have no response to therapy.[74,101] In the small subgroup of patients with severe thrombocytopenia, predicted five-year mortality rates from bleeding range from 2.2 percent for those younger than 40 years of age to 47.8 percent for those over 60 years of age,[102] indicating a need for persistent therapy for severe disease.

THE PATIENT'S PERSPECTIVE

Patients may view their disease from a different perspective than their physicians do. Many are relieved to learn that immune thrombocytopenic purpura is treatable but are distressed that the cause is unknown. Fear of bleeding dominates the thinking of many adult patients, whereas adolescents are often more perturbed by restrictions on lifestyle. Some dread alterations in body image and the other side effects of corticosteroid therapy, whereas others fear splenectomy and sepsis.[103] The Internet has become both a source of quixotic remedies and an important resource enabling patients to find expert care and to receive support from other patients.

THE PHYSICIAN'S PERSPECTIVE

Immune thrombocytopenic purpura is a common disorder affecting children and adults. Fundamental questions relating to pathogenesis and management remain. Some physicians place an undue emphasis on normalizing the platelet count as a guide to therapy. Continued research — including well-designed clinical trials that incorporate clinically relevant end points (e.g., the severity of bleeding), quality-of-life measures, and economic analyses — is needed to improve management.

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