Review

Management of Immune Thrombocytopenic Purpura in Adults

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Primary immune thrombocytopenic purpura (ITP), also referred to as idiopathic thrombocytopenic purpura, is an organ-specific autoimmune disorder in which antibody-coated or immune complex–coated platelets are destroyed prematurely by the reticuloendothelial system, resulting in peripheral blood thrombocytopenia. The disease is heterogeneous with regard to its severity and clinical course and is unpredictable in its response to therapy. Although the basic underlying pathophysiology of ITP has been known for more than 50 years, current treatment guidelines are based on expert opinion rather than on evidence because of a lack of high-quality clinical trials and research. The only patients for whom treatment is clearly required are those with severe bleeding and/or extremely low platelet counts (<10 × 10^9/L). Treatment of patients with ITP refractory to corticosteroids and splenectomy requires careful evaluation of disease severity, patient characteristics related to risk of bleeding, and adverse effects associated with treatment. Clinical trials with numerous new agents are under way, which we hope will add more effective and targeted strategies to our therapeutic armamentarium. We describe a logical and structured approach to the clinical management of ITP in adults, based on a literature review and our personal experience.

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ITP = immune thrombocytopenic purpura; IVIg = intravenous immunoglobulin

Primary immune thrombocytopenic purpura (ITP), also known as idiopathic thrombocytopenic purpura, is an immune-mediated disorder in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system. No consistent epidemiological data exist relating to ITP in adults. George et al[1] reviewed the data of several reports and extrapolated an incidence of 66 cases per million persons per year. A Danish survey[2] from 1973 to 1995 estimated the annual incidence of ITP among adults to be 32 cases per million per year, using a lower-threshold platelet count of 50×10^9/L. The incidence rate increased during the study period, primarily because of increased recognition of asymptomatic patients. This study confirmed that, in keeping with other autoimmune disorders, adult ITP is more common in women (female-male ratio, 1.7). However, in contrast to the common belief that ITP is a disorder of younger and middle-aged people, the median age in this study was 56.4 years, and the incidence in people older than 60 years was more than twice that of people younger than 60 years (4.62 vs 1.94 cases per 100,000 per year). Also, the sex bias difference was almost completely eliminated in older patients.

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The results of the Danish study have been confirmed recently in another setting. A British group[3] published the results of a prospective study in a population-based cohort of newly presenting adults (≥16 years of age) with ITP and platelet counts of less than 50×10^9/L. The study took place between January 1, 1993, and December 31, 1999, in the former Northern Health Region in the United Kingdom (population, 3.08 million). The diagnosis of ITP in 245 patients (134 females to 111 males [1.2:1]) was confirmed by bone marrow examination, and the median follow-up was 60 months (range, 6-78 months). The overall incidence was 1.6 cases per 100,000 per year. The absolute incidence was similar for both sexes, with the highest age-specific incidence in those older than 60 years. The median age in this survey was 56 years.

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The clinical features of ITP in adults are different from the clinical features seen in childhood (Table 1[4]). In children, ITP is usually an acute, self-limiting disease, often occurring 2 to 3 weeks after a viral infection (varicella, rubella, mumps, upper respiratory tract infection, gastroenteritis, flu-like illnesses, etc) or immunization. In contrast, ITP in adults typically has an insidious onset, with no preceding viral or other illness, and has a chronic course. Many cases of ITP in adults are diagnosed incidentally after a routine complete blood cell count. In adults, the symptoms and signs are highly variable and range from the fairly common asymptomatic patient with mild bruising and mucosal bleeding (eg, oral or gastrointestinal tract) to frank hemorrhage from any site, the most serious of which is intracranial.

The diagnosis of ITP remains one of exclusion, requiring that all other conditions or factors that can cause thrombocytopenia be ruled out.[4] These causes include collagen vascular diseases, lymphoproliferative disorders, agammaglobulinemia, therapy with certain drugs, alloimmune thrombocytopenia, congenital or hereditary thrombocytopenia, myelodysplasia, von Willebrand disease type IIB, human immunodeficiency virus infection, and other infections. The history and physical examination are aimed at detecting these various causes of thrombocytopenia and are supported by ancillary laboratory tests (Table 2).

Few high-quality studies are available with which to assess the efficacy of ITP treatments; existing guidelines are based more on expert opinion than on evidence.[4,5] Unfortunately, even among experts there is only little to moderate agreement regarding the best treatment for these patients. In this article, we illustrate current treatment options for ITP that are based on a literature review and personal experience.

WHICH PATIENTS WITH ITP SHOULD BE TREATED?

The answer to the seemingly "innocent" question of which patients with ITP should be treated is complex and underlines the heterogeneity of ITP. Disease-related and patient-related factors should be considered and treatment tailored to the individual patient. Considering the chronic nature of the disease, the goal of treatment should be to provide a safe platelet count to prevent major bleeding while minimizing adverse effects.

An understanding of the natural history of untreated ITP provides part of the rationale for deciding which patients should be treated. Although 80% to 90% of children have a spontaneous remission of the disease within 2 to 8 weeks,[6,7] spontaneous remissions in adults are much rarer. However, in many adults presenting with mild and asymptomatic thrombocytopenia, the disease appears to have a stable and benign course without treatment.[8-10] Possibly less than 10% of such patients develop a more severe thrombocytopenia and require treatment at 3- to 7-year follow-up.[8] In our study of 208 adults with chronic ITP, 9% of patients remitted spontaneously or required some form of therapy to support the platelet count.[8] In other series, the incidence of spontaneous remissions may have been underestimated because all patients were treated initially with corticosteroids.[4]

Only a few studies have addressed the mortality risk attributable to ITP. Cohen et al[11] reviewed data from 17 case series involving 1817 patients with ITP and showed that the rate of fatal hemorrhage is between 0.0162 and 0.0389 cases per patient-year at risk (the *time at risk* was defined as the time during which the platelet count is $<30 \times 10^9$/L). The relationship between disease-related and treatment-related mortality was specified by Portielje et al.[10]

Table 1. **Immune Thrombocytopenic Purpura in Children and Adults**

	Children	Adults
Peak age incidence (y)	2-6	>50
Sex incidence (M:F)	1:1	1:1.7
Onset	Acute	Insidious
Preceding infection	Common	Unusual
Platelet count ($\times 10^9$/L)	Often <20	Often >20
Usual duration	2-4 wk	Years
Course* (%)		
Spontaneous remissions	>80	2
Chronic disease	24	43
Response to splenectomy	71	66
Complete recovery	89	64

*Data from George et al.[4]

During the follow-up period, 6 patients died, 2 of hemorrhage and 4 of infections, which were probably treatment related. In another study, 3 of 6 adults died of infections, and only 2 died of hemorrhage.[12] A recent report by Neylon et al[3] indicates that 27 of 245 patients (11%) died during the study period, but only 3 (1.2%) of these deaths were attributable to ITP (bleeding) and only 1 (0.4%) to overwhelming sepsis after splenectomy. The other deaths were apparently unrelated to either ITP or its treatment. Considering these data together, it appears that the treatment of ITP is almost as dangerous as the disease itself and that some patients are clearly overtreated.

The peripheral blood platelet count is obviously the major parameter for predicting the risk of bleeding, but few studies have described the risk of clinically important bleeding at varying levels of thrombocytopenia. A platelet count of greater than 30×10^9/L is usually considered "safe" for people leading a sedentary lifestyle.[4,5] However, only 1 prospective study supports this cut-off level. Cortelazzo et al[9] described 49 untreated patients (of 117 total patients with ITP) with platelet counts greater than 30×10^9/L and no symptomatic bleeding. No adverse events were reported among these 49 patients during a mean follow-up period of 30 months. A recent retrospective study indicated that patients with ITP who achieved platelet counts greater than 30×10^9/L while not being treated or while receiving maintenance therapy had a long-term mortality rate identical to or only slightly greater than that of the general population.[10] Therefore, these studies support the contention that a platelet count of greater than 30×10^9/L is reasonably safe, but they do not indicate whether the critical threshold is 30×10^9/L or a lower value. An early investigation by Lacey and Penner[13] showed that spontaneous major bleeding in adults with ITP is rare (<5% of patients) with platelet counts of greater than 10×10^9/L and occurs in about 40% of patients with platelet counts of less than 10×10^9/L. These findings are in agreement with

Table 2. **Principal Elements of the Initial Work-up in Adult Patients With Suspected Immune Thrombocytopenic Purpura***

History
Bleeding symptoms
Type of bleeding
Severity of bleeding
Duration of bleeding
Systemic symptoms, including weight loss, fever, headache, and symptoms of autoimmune disorders such as arthralgias, rash, alopecia, and venous thrombosis
Risk factors for HIV infection
Pregnancy status
Medications, including heparin, alcohol, quinidine/quinine, and sulphonamides, which may cause thrombocytopenia, and aspirin, which may exacerbate bleeding
Family history of thrombocytopenia, including bleeding symptoms and symptoms of autoimmune disorders
Comorbid conditions that may increase the risk of bleeding such as gastrointestinal disease, chronic liver diseases, chronic kidney diseases
Physical examination
Bleeding signs
Type of bleeding
Severity of bleeding
Liver, spleen, lymph nodes, and jaundice
Evidence for infection, particularly bacteremia or HIV infection
Evidence for autoimmune disease, such as arthritis, nephritis, or cutaneous vasculitis
Evidence for thrombosis
Neurologic function
Laboratory tests
Necessary and/or appropriate
Repeated hemograms
Peripheral blood smear observation
Bone marrow aspirate (if older than 60 years or another hematologic disorder is suspected, and in patients for whom splenectomy is considered)
HIV test (in patients with risk factors for HIV infection)
Unnecessary, but may be appropriate
Lupus anticoagulant
Platelet antigen-specific antibody
Direct antiglobulin test
Chest x-ray
Mean platelet volume
Reticulocyte count
Urinalysis
Thyroid function tests

*HIV = human immunodeficiency virus.
Adapted from George et al,[4] with permission from The American Society of Hematology.

observations of patients with chemotherapy-induced bone marrow suppression, indicating that clinically important bleeding is less likely with platelet counts of greater than 10×10^9/L unless the patient is febrile or has a serious systemic illness.[14]

The degree of thrombocytopenia per se does not always accurately predict bleeding risk, however, and experienced hematologists are aware that in many patients with ITP, the platelet count appears to have little bearing on the bleeding diathesis. Some individuals with severe ITP (platelets counts of $<10 \times 10^9$/L) do not bleed, whereas others with higher platelet counts bleed excessively. In fact, in the previously mentioned report by Neylon et al,[3] only 1 of the 3 deaths due to bleeding occurred at a platelet count of less than 10×10^9/L.

Older studies have suggested that bleeding manifestations in patients with ITP are expected to be less severe at equivalent platelet counts than in patients with thrombocytopenia due to a hyporegenerative bone marrow.[15] This is likely to be related to the fact that the circulating platelets in patients with ITP are younger because the platelet lifespan is reduced, and these younger platelets possess greater hemostatic activity.[16] Nevertheless, platelet dysfunction in ITP has been well described in the literature, indicating that antiplatelet antibodies can affect platelet function.[17-21] For example, antibodies may bind to adhesion molecules or other receptors on platelets to alter platelet function. They may impair adhesion and aggregation of platelets, inducing features of Glanzmann thrombasthenia[19] or Bernard-Soulier–like syndromes[20] or various other platelet dysfunctions. In contrast, some antibodies may activate platelets, promoting thrombotic complications in ITP.[21]

It is apparent from the results of several studies that factors other than the peripheral blood platelet count influence the risk of bleeding, the most important of which is probably age. In one report, the rates of severe hemorrhagic complications in patients older than 60 years and younger than 40 years were 10.4% and 0.4% per patient per year, respectively.[9] Similar rates of 13.0% and 0.4% per patient per year, respectively, were noted in the previously mentioned meta-analysis by Cohen et al.[11] The presence of conditions such as fever, uremia, or chronic liver disorders is known to be associated with impaired platelet function and an increased risk of bleeding, but specific data for patients with ITP are unavailable.

Safe platelet counts differ between sedentary persons and those with active lifestyles, but to date this finding has not been investigated systematically, and no precise recommendations can be given. We consider a platelet count of 50×10^9/L a reasonable threshold for people engaged in "physical" jobs, such as carpenters and farmers, whereas athletes who perform contact sports probably would require a platelet count of greater than 80×10^9/L. The British Committee for Standards in Haematology[5] has recently suggested the values of the platelet counts that are considered safe for patients who are undergoing procedures likely to induce blood loss, including surgery, dental extraction, or obstetric delivery (Table 3). Once again, note that these recommendations are based on opinion and that many physicians would not agree with them on the basis of their own experience.

In summary, the critical elements in the decision-making process include the presence of active bleeding; platelet

count; patient age; patient's lifestyle related to risk of bleeding; presence of additional risk factors for bleeding, such as uremia, chronic liver diseases, etc; predictable adverse effects of the offered treatment; and patient's preferences (Table 4). Accordingly, we believe that patients with ITP can be grouped into 1 of 4 treatment categories: (1) those who must be treated, which includes all patients with active bleeding; (2) those who should be treated, which includes patients with a platelet count of less than 10×10^9/L and no active bleeding; (3) those who might be treated, which includes patients with platelet counts between 10×10^9/L and 30×10^9/L but with no active bleeding, for whom the decision to treat is made after a thorough evaluation of the patient's characteristics (age, lifestyle, etc) (Table 4); and (4) those for whom treatment is not needed or is required in special circumstances, which includes patients with platelet counts of greater than 30×10^9/L and no bleeding tendency (Table 5).

Although this categorization is widely accepted for the initial treatment of adults, it may not be fully appropriate in patients for whom several treatments have failed and whose platelet counts are persistently less than 10×10^9/L. In some of these patients, particularly in younger individuals who have no bleeding symptoms, a wait-and-see policy may be preferable to avoid the long-term toxicities associated with treatment.

EMERGENCY TREATMENT

Patients with internal or widespread mucocutaneous bleeding or in need of emergency surgery require urgent aggressive therapy. Hospitalization is required, and general measures should be instituted to reduce the risk of bleeding, including avoidance of drugs that inhibit platelet function, control of blood pressure, and other factors. Although no systematic studies have evaluated the efficacy of different regimens, there is general agreement that appropriate interventions should include the following[4,5]:

- Intravenous immunoglobulin (IVIg), 1 g/kg per day for 2 days
- Intravenous methylprednisolone, 1 g/d for 3 days
- Platelet transfusions (either 5 U every 4-6 hours or 2 U/h)

Management of intracranial bleeding should include all these interventions. When the platelet count is greater than 100×10^9/L, craniotomy may be considered. Emergency splenectomy may be considered in individual patients who do not respond and require additional treatment. Although patients with ITP are assumed to have rapid platelet destruction, transfused platelets may provide temporary critical hemostatic support. Platelet transfusions usually are given after IVIg and are often effective in controlling bleeding, irrespective of the increase in platelet counts. Nevertheless, it has been shown that 42% of platelet transfusions result in a platelet increase of at least 20×10^9/L.[22] Aminocaproic acid (5 g initially and then 1 g every 5 hours given orally or intravenously) has been reported to be effective in controlling severe bleeding in ITP after failure of corticosteroids and platelet transfusions.[23] Given the efficacy of these interventions, plasmapheresis has been used rarely in emergency settings but may play a role in refractory cases.[24]

Table 3. **Recommendation for "Safe" Platelet Counts in Adults**

Procedure	Platelet count ($\times 10^9$/L)
Dentistry	≥10
Extractions	≥30
Regional dental block	≥30
Minor surgery	≥50
Major surgery	≥80
Vaginal delivery	≥50
Cesarean section	≥80
Spinal or epidural anesthesia	≥80

From the British Committee for Standards in Haematology General Haematology Task Force,[5] with permission from Blackwell Publishing.

INITIAL TREATMENT

Once the decision to treat a patient with ITP has been made, and provided the patient's situation is not life threatening, corticosteroids are the standard initial treatment.[4] Intravenous immunoglobulins are generally recommended for patients with critical bleeding and for those unresponsive to corticosteroids.[4] The platelet count also can be supported by anti-D immunoglobulin, which is active in the presplenectomy setting.[4] Results of treatments in the major series reported thus far are summarized in Table 6.[8,10,25-41]

Table 4. **Factors That Should Be Considered in Deciding When to Treat Patients With Immune Thrombocytopenic Purpura**

- Presence of active bleeding
- Platelet count
- Age
- Lifestyle (participation in activities that predispose to trauma)
- Additional risk factors for bleeding
  - Uremia
  - Untreated or poorly controlled hypertension
  - Fever
  - Infections
  - Alcoholism
  - Aneurysms
  - History of peptic ulcer disease
  - Chronic liver diseases
- Adverse effects of treatment
- Patient's preferences

Table 5. **Treatment Categories in Immune Thrombocytopenic Purpura**

Category	Indication for treatment
1. Presence of active bleeding Platelet count: any	Yes
2. Platelet count $<10 \times 10^9$/L No active bleeding	Yes
3. Platelet count $10\text{-}30 \times 10^9$/L No active bleeding	Only after evaluation of all the factors in Table 4
4. Platelet count $>30 \times 10^9$/L No active bleeding	No*

*Treatment may be required in special circumstances, eg, in preparation for major surgery or obstetric delivery.

Corticosteroids

Corticosteroids have not been shown to alter the natural history of ITP; however, they allow the physician to "buy time" to determine which patients have acute ITP (lasting less than 6 months) and which patients will develop chronic ITP and thus potentially need additional therapy. Approximately two thirds of patients achieve a complete or partial response with corticosteroids, and most responses occur within the first week of treatment.[4] The standard practice is to initiate treatment with oral prednisolone or prednisone, 1 to 2 mg/kg per day, given as single or divided doses. However, major variations exist in treatment regimens in reference to the duration of full-dose treatment (2-6 weeks) and the mode of tapering (fast or slow). In our practice, we taper and discontinue prednisone over 4 weeks after achieving a normal platelet count because this period includes the time during which most spontaneous remissions would occur.

To date, only 2 randomized studies have compared conventional with low doses of prednisone as initial therapy.[42,43] There was no difference in the likelihood of remission at 6-month follow-up in either study. However, the larger study observed a trend toward an increased frequency of complete remission (46% vs 35%) in the group given the larger doses of prednisone. Moreover, a faster increase in platelet count was observed in the group receiving the larger dose of prednisone (77% vs 51% having a platelet count greater than 50×10^9/L after 14 days of prednisone). No data were published on the long-term outcome of these 2 studies. One study assessed the efficacy of high-dose methylprednisolone as first-line therapy for 21 adults with severe thrombocytopenia and severe or persistent mucosal or vaginal bleeding; the results were compared with 36 patients with a less severe presentation who were treated with conventional doses of prednisone.[44] Patients treated with high-dose methylprednisolone responded more rapidly (4.7 vs 8.4 days) and had a higher overall response rate (80% vs 53%) despite presenting with more severe disease clinically. However, no difference was shown between the 2 groups in the frequency of complete or persistent remission. Oral dexamethasone at a dosage of 40 mg/d for 4 consecutive days has been used recently as initial treatment in 125 patients with ITP.[25] The response rate was extremely high (85%), and with a median follow-up of 30.5 months, 50% of responders had a continuous complete remission at the time this manuscript was written. Nevertheless, this was not a randomized trial, and whether or not initial high-dose therapy has a positive effect on the rate of sustained remissions is an unresolved issue.

A few studies have evaluated the long-term outcome of patients receiving corticosteroid treatment alone.[8,10,45] These studies indicate that there is a high early relapse rate (within 6 months) and thereafter a slower but continuous relapse rate up to 6 years. Less than 20% of patients were in complete remission at the last follow-up. Various factors for predicting the response (short term and/or long term) to corticosteroid therapy also have been analyzed. A shorter duration of symptoms has been associated with a better response to corticosteroids in 2 studies,[26,45] whereas age of patients older than those in the 45- to 60-year range was associated with a poorer response in another study.[46]

If prednisone is resumed when thrombocytopenia recurs, it is important to avoid the consequences of prolonged corticosteroid therapy. The risk for corticosteroid-induced osteoporosis is of particular concern,[47] and it is generally recommended that patients treated with prednisone for more than 3 months receive calcium and vitamin D supplementation and monitoring of bone mineral density.

Table 6. **Response to First-Line Treatments and Splenectomy***

Reference	Type of treatment	No. of patients	No. (%) of responses	
			Initial	Long-term
8, 25-31	Corticosteroids	1685	1107 (66)	202/1296 (16)
32-36	IVIg	259	193 (75)	NA
37, 38	Anti-D immunoglobulin	165	115 (70)	NA
8, 10, 26-31, 39-41	Splenectomy	1322	1059 (80)	819/1287 (64)

*IVIg = intravenous immunoglobulin; NA = not available.

The mechanisms of action of corticosteroids in ITP have not been completely elucidated. It has been suggested that corticosteroids impair the clearance of antibody-coated platelets by tissue macrophages,[48] inhibit antibody production,[49] and increase platelet production possibly by inhibiting phagocytosis of platelets by bone marrow macrophages.[48] In addition, cutaneous bleeding may resolve before an increase in the platelet count is seen, suggesting a direct effect of corticosteroids on vascular integrity.[50]

Intravenous Pooled Normal Human Immunoglobulin

Intravenous immunoglobulin has been studied primarily in patients who were unresponsive to corticosteroids and other therapies. Intravenous immunoglobulin is effective in elevating the platelet count in approximately 85% of patients, with 65% achieving normal platelet counts ($>100 \times 10^9$/L).[51] Platelet counts may begin to increase after 1 day and usually reach peak levels within 1 week after treatment.[52] However, responses are generally transient, lasting no longer than 3 to 4 weeks, after which the platelet counts decrease to pretreatment levels.[51,52] The dose of IVIg has been the subject of several studies. A single randomized study showed no difference in efficacy between the 2 dosing schedules of 0.4 g/kg per day for 5 days and 1 g/kg per day as a single infusion.[53] A multicenter trial randomly assigned 35 consecutive adult patients with ITP to receive IVIg at an initial total dosage of 0.5 g/kg or 1.0 g/kg over a period of 4 to 12 hours on day 1.[32] Nonresponders received additional IVIg in divided doses on days 4 and 5 to reach a total dose of 2.0 g/kg. This study suggested that initial treatment with 1 g/kg of IVIg appeared to be more effective than 0.5 g/kg and that some adults who did not respond to 1 g/kg responded to a higher dose. On the basis of these studies, the standard regimen for IVIg is now 1 g/kg per day for 1 to 2 days.

Intravenous immunoglobulin is prepared by ethanol precipitation of pooled plasma, followed by techniques to minimize self-aggregation.[54] Preparations of IVIg are stabilized with glucose, maltose, glycine, sucrose, sorbitol, or albumin. At least 90% to 95% of the IVIg preparation is composed of monomeric IgG. The IgG retains normal Fab and Fc functions required for antigen binding and phagocytic cell interaction, respectively. IgG aggregates, IgA, and other contaminants constitute a negligible fraction. Intravenous immunoglobulin has a normal IgG half-life in vivo, with a physiological subclass distribution.[54]

The adverse effects of IVIg are generally mild. Approximately one half of patients have headaches, usually during the first infusion. Occasionally, the headache is severe and associated with nausea and vomiting.[55,56] These symptoms can mimic intracranial hemorrhage, and a computed tomographic scan of the head may be required to determine the diagnosis. A few patients also experience rigidity, drowsiness or lethargy, fever, photophobia, and painful eye movements simulating meningitis.[57] Renal impairment or failure has been reported with some preparations.[58,59] Intravenous immunoglobulin products containing sucrose may present a greater risk for this complication.[59] In fact, a disproportionate amount of renal impairment or failure in patients with ITP (approximately 90%, according to US reports) has been associated with sucrose-containing products,[60] including (1) one product manufactured by the Central Laboratory Blood Transfusion Service, Swiss Red Cross (Bern, Switzerland) (Sandoglobulin, distributed by Novartis, and Panglobulin, distributed by the American Red Cross), and (2) IVIg products manufactured by Centeon L.L.C. (Bradley, Ill) (Gammar-P I.V./Gammar-I.V.b).

To minimize adverse effects, the infusion of IVIg is given slowly over several hours. Particular caution should be exercised in the administration of sucrose-containing IVIg products in patients at increased risk for developing acute renal failure, which includes those with any degree of preexisting renal insufficiency, diabetes mellitus, and age older than 70 years.[61]

The mechanisms of action of IVIg in ITP are complex and not fully elucidated. Some studies suggest blockade of Fc receptors on reticuloendothelial cells[33,62] and suppression of antibody production and binding,[37,63] which may be the result of anti-idiotype antibodies that bind antiplatelet antibodies and modulate immune response.[64]

The relative efficacy of high-dose methylprednisolone (15 mg/kg per day intravenously on days 1 to 3) vs IVIg (0.7 g/kg per day intravenously on days 1 to 3) was studied in a prospective randomized trial of 122 patients with previously untreated severe acute ITP.[38] In a second randomization, patients received either placebo or oral prednisone (1 mg/kg per day) on days 4 to 21. The percentage of patients with a platelet count greater than 50×10^9/L on days 2 and 5 was slightly greater for those receiving IVIg (7% and 79%, respectively) than for those receiving methylprednisolone (2% and 60%; P=.04). The use of prednisone was significantly more effective than placebo for all short-term study end points (eg, days with platelet count of $>50 \times 10^9$/L, highest platelet count, platelet count at 21 days, and time to relapse). However, remission rate at 1 year was not affected by the initial treatment (IVIg vs methylprednisolone).

Because of its high cost, IVIg generally is used when resistance to corticosteroids develops, when there is a contraindication to the use of corticosteroids, or during pregnancy when potentially teratogenic drugs must be avoided. The rapid nature of the response to treatment makes it an ideal agent for treatment of life-threatening bleeding or

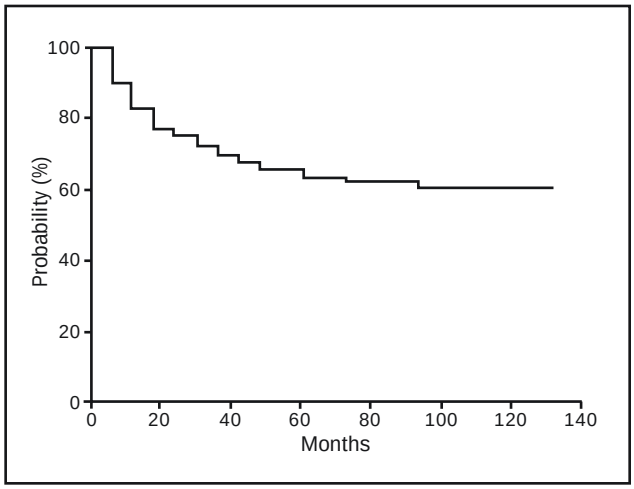


Figure 1. Kaplan-Meier plot of relapse-free survival after splenectomy in patients with immune thrombocytopenic purpura (N=62) who were monitored at our institution.

before surgery, although corticosteroids also may increase the platelet count with sufficient rapidity.

Anti-D Immunoglobulin

The anti-D immunoglobulin is effective only in Rh D-positive nonsplenectomized patients, in whom the antibody binds to the erythrocyte D antigen. The mechanism of action involves immune-mediated clearance of the opsonized erythrocytes via the Fc receptors of the reticuloendothelial system, thereby minimizing removal of antibody-coated platelets.[39] Anti-D can be administered safely by intravenous injection over a few minutes. The response rate in one series was 70%, and the increase in platelet count lasted more than 3 weeks in 50% of the responders.[27] The toxicity profile of anti-D is similar to that of IVIg. The standard dosage of 50 mg/kg per day of intravenous anti-D requires 72 hours to produce a clinically significant platelet increase.[40] Therefore, anti-D has not been recommended as first-line therapy to rapidly elevate the platelet count in patients with severe thrombocytopenia. In a prospective randomized trial, 27 Rh D-positive patients with a diagnosis of ITP in whom initial treatment with corticosteroids had failed and who had platelet counts of 30×10^9/L or less received intermittent treatment with anti-D at a dose of 50 to 75 μg/kg intravenously whenever their platelet count was 30×10^9/L or less.[28] The higher dose resulted in greater median day 1 (43×10^9/L vs 7.5×10^9/L; P=.01) and day 7 (153×10^9/L vs 64.5×10^9/L; P=.001) platelet increases despite no greater hemoglobin decrease. The results also indicated that 68% of patients repeatedly responded to anti-D infusion and that in some patients, splenectomy may have been delayed or completely avoided.[29] The substantial advantages of anti-D compared with IVIg are lower costs (although still much more expensive than corticosteroids) and more convenient administration. The dose-limiting toxicity of anti-D is hemolytic anemia, with a mean decrease in hemoglobin of 1.0 g/dL, occasionally accompanied by chills and nausea. Anti-D appears to have minimal efficacy in splenectomized patients.[40]

SECOND-LINE TREATMENT

The spleen is the organ primarily responsible for the destruction of antibody-sensitized platelets, and splenectomy is traditionally considered to be the second-line treatment in adults with ITP in whom achieving a safe platelet count with initial prednisone therapy has failed. However, there are many uncertainties and controversies regarding the optimal time for performing splenectomy, the prediction of response, the selection of the surgical procedure (standard vs laparoscopic method), and the long-term efficacy of this procedure. No randomized trial has compared the efficacy and risks of drug treatment with splenectomy, and it is unlikely that such a trial will ever be performed. As with other treatment modalities, the decision to recommend splenectomy should be individualized, taking into account the age of the patient, duration of the disease, comorbid conditions, efficacy and adverse effects of corticosteroid treatment, and preferences of the patient.

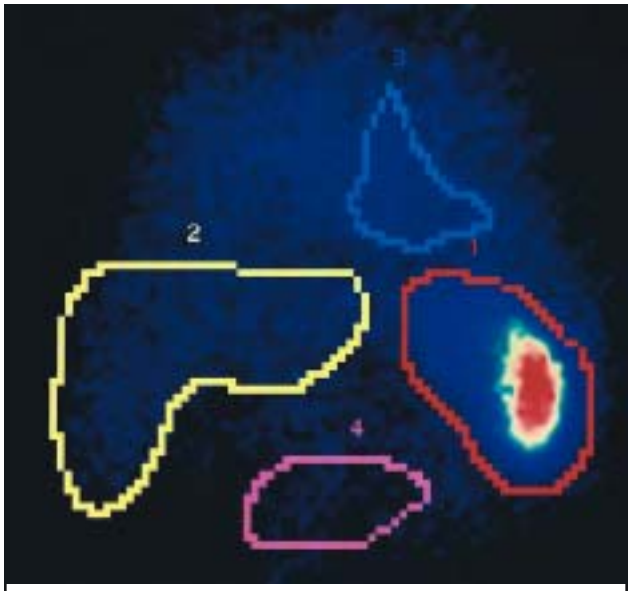
About 75% of patients who undergo splenectomy achieve a complete remission (platelet count of >100-150 $\times$ 10^9/L).[8,30,31,34,65-68] Most relapses occur during the first 2 years after splenectomy, but even after that, a small percentage of patients continue to relapse. In our series, approximately 60% of responders remained in remission at 10 years (Figure 1), which is in keeping with most published reports. However, in another study with a large number of patients and long-term follow-up, most splenectomized patients had relapsed,[41] although the conclusions of this study were not supported by a detailed presentation of primary data. In some patients who relapse after splenectomy, an additional (accessory) spleen may be detected and a second complete remission may be achieved after its removal.[45,69,70] However, there are no studies of accessory splenectomy that document efficacy by long-term complete remissions. Numerous methods can be used to look for an accessory spleen, including computed tomographic scanning, ultrasonography, and radionuclide imaging. If radionuclide methods are used, the intraoperative use of a hand-held isotope detector probe can help locate an accessory spleen during surgery.

Most experts agree that splenectomy should be seriously considered for patients in whom ITP is primarily refractory to corticosteroid treatment, at 4 to 6 weeks after diagnosis, or in patients for whom a daily dose of 10 mg or more of

prednisone is required to keep the platelet count at a "safe" level.[4] In contrast, some suggest that this procedure should be performed only after all other therapeutic modalities have been exhausted and the patient has a platelet count of less than 25×10^9/L and is bleeding.[41] In fact, it appears that the timing of splenectomy is delayed in most medical centers. The median time to splenectomy was 11 months (range, 3-156 months), 3 years (range, 3 weeks to 19 years), and 8 to 51 months in 3 different studies.[8,31,71] The most likely explanation for this observation is that the decision to recommend splenectomy to many patients is difficult because they may do well on low-dose corticosteroids and splenectomy is an invasive procedure with potential risks. For example, in a series of 78 patients who underwent splenectomy, 26 (33%) experienced postoperative complications resulting in prolonged hospitalization or readmission.[10] The risk appeared particularly increased in elderly or obese patients with comorbid conditions. Therefore, identification of patients who may benefit from splenectomy would be helpful when making this decision.

Not unexpectedly, observing splenic sequestration of indium-labeled platelets was a good prognostic factor in many studies in which this scanning method was applied (Figure 2[72]).[35,37,72-75] In the large study by Najean et al,[72] patients with hepatic sequestration had a response rate of only 1%, whereas in other studies,[35,76] the response rate was higher (≥28%). Thus, patients with hepatic sequestration may still respond to splenectomy but to a lesser degree; the likelihood of achieving a complete response is lower than in patients in whom platelet destruction is purely or predominantly splenic. However, platelet sequestration studies are difficult to perform and are available in only a few medical centers. Furthermore, the specificity of the test is not high enough to recommend it routinely for patients in whom splenectomy has been considered.

Although it is generally agreed that increased age is a poor prognostic factor, this has not been reported consistently.[31,35,36,45,72-75] Also, the literature is controversial concerning the prognostic value of the response to IVIg. Law et al[77] reported a 90.5% positive predictive value and a 100% negative predictive value of the response to IVIg. In most subsequent studies, it was confirmed that patients who responded to IVIg had a higher response rate to splenectomy, but the positive and negative predictive values were not as high.[71,73,75,78-82] Thus, patients who do not respond to IVIg still have a good chance of responding to splenectomy. Response to prednisone has been found to be a good prognostic factor in some studies,[26,35,45,73] but not in others.[8,71] There is agreement that the time to splenectomy is not a prognostic factor.[8,26,71,73-75] Presence of platelet antibodies had no prognostic value in 2 studies.[73,83] Taken together, "predictive" factors seem to have only limited



Pattern of uptake	Age, 5-30 y	Age, >30 y
Splenic	96% remission	91%
Mixed (splenic + hepatic)	15% remission	NA

Figure 2. Indium 111–labeled platelet scanning to determine the site of platelet destruction. 1 = spleen; 2 = liver; 3 = heart; 4 = bladder; NA = not available. In this patient with immune thrombocytopenic purpura, intense uptake is seen in the spleen, with no activity in other organs. The probability of achieving response is influenced by the pattern of uptake of the radionuclide.[72]

value when deciding about splenectomy, and of currently available methodology, the indium-labeled platelet study appears to be the most accurate predictor of response to splenectomy.

Splenectomized patients have a small risk for overwhelming infections, with an estimated mortality of 0.73 per 1000 patient-years.[84] The risk for serious postsplenectomy infection is greater in children younger than 5 years, who are therefore treated with prophylactic penicillin after splenectomy. Although there are no data on the efficacy of vaccination, immunizations for *Streptococcus pneumoniae*, *Hemophilus influenzae* B, and *Neisseria meningitides* are generally advised at least 2 weeks before splenectomy.[4] The usefulness of postoperative antibiotic prophylaxis is a matter of controversy, and although it is not the standard of care in the United States, lifelong prophylactic antibiotics are recommended in UK guidelines.[85]

There is no agreement on the minimal platelet count regarded as sufficient to perform splenectomy; in our practice, we recommend a platelet count of at least 50×10^9/L, but often our patients must reach higher counts because surgeons are reluctant to operate on patients with throm-

bocytopenia. No data indicate whether preoperative treatment with corticosteroids or IVIg is more beneficial.

Laparoscopic splenectomy has become popular during the past decade. The technique has the advantage of a reduced risk of postoperative complications (which allows the procedure to be performed in patients who cannot undergo open surgery) and a shorter hospital stay. Potential problems associated with the laparoscopic approach are technical difficulties necessitating conversion to open surgery and the inability to identify additional spleens and bleeding. Furthermore, the operation time with laparoscopic splenectomy is greater than with standard open surgery. No randomized trials have been conducted to compare laparoscopic with conventional open surgery, although numerous studies have shown that laparoscopic splenectomy is safe when performed by a surgeon experienced in this procedure.[86-90] Despite the lack of scientific evidence, it may be the preferred method in patients with a high risk of postoperative complications, such as elderly patients, those with cardiovascular disease, and/or those with a high risk of postoperative infection or thrombosis.

In patients at high risk for surgery, splenic irradiation[91,92] or partial splenic embolization[87-89] have been used with reports of success. Calverley et al[91] reported that of 11 patients with ITP who were treated with splenic irradiation, 8 responded. Three patients had a sustained (>52 weeks) increase in platelet count to safe levels after therapy was discontinued. An additional patient had a sustained response but required intermittent low-dose corticosteroids. Four other patients had increased platelet counts that lasted from 8 to 25 weeks. The total radiation dose was 6 Gy in 6 doses over 3 weeks without renal shielding. In another study, 8 patients with chronic ITP received a radiation dose of 15 Gy.[92] One patient had a good durable response (>1 year); 2 patients had a good transient response; 2 patients had only partial response but required no other treatments for 2 years; and 3 patients had no response. The radiation was administered at a dosage of 1.5 Gy 2 times per week for 5 weeks with left kidney shielding but with 20% to 25% of the splenic volume undertreated. Splenic irradiation may result in the development of adhesions between the spleen and surrounding tissues, complicating splenectomy if it is performed later. Therefore, splenic irradiation should be recommended only for those with contraindications to splenectomy.

Partial splenic embolization was first used by Miyazaki et al,[93] who reported a 35% prolonged response rate in patients with ITP. In a recent study, 20 (51%) of 39 patients responded to the initial embolization (complete response in 11 and partial response in 9).[94] One of the 11 complete responders and 5 of the 9 partial responders relapsed after a median follow-up period of 34 months (range, 15-23 months) and underwent repeated embolization, resulting in complete response in 1 patient, partial response in 4 patients, and no response in 1 patient. However, in 6 of 19 nonresponders, repeated embolization elicited a partial response in only 1 patient. The remission rate of 51% was maintained by means of repeated embolization for a median follow-up period of 76 months after the initial embolization. Because a small accessory spleen can almost certainly cause relapse, leaving a residual quantity of spleen (as in partial splenic embolization) can cause any long-term remission to fail. On the basis of this consideration, Martinez Lagares et al[95] prospectively performed total splenic embolization in 13 patients, of whom 5 were dependent on high doses of corticosteroids to maintain a safe platelet count ($>30 \times 10^9$/L) and 8 were corticosteroid resistant with a sustained low platelet count ($<30 \times 10^9$/L). Complete embolization was achieved in 12 patients, and a partial embolization was achieved in 1 patient with an aberrant splenic artery. Of the 12 patients, 10 had a complete and sustained response (median, 27 months; range, 22-38 months), with peak platelet counts greater than 400×10^9/L between days 8 and 13.

TREATMENT OF PATIENTS IN WHOM SPLENECTOMY FAILS

Patients can be defined as having chronic refractory ITP if splenectomy fails and the patients require additional therapy. About 30% of adult patients with ITP may belong to this category. The goals of therapy for refractory ITP are clearly different from those for patients at initial presentation because the chance of inducing a durable, complete, and unmaintained remission is much lower. Again, the actual necessity for treatment should always be considered, and the risks and adverse effects of treatment should be weighed against the risks of no treatment.

A common strategy is to try treatment with low-dose corticosteroids. In fact, some patients require low doses of prednisone, 5 to 10 mg/d or even less, that are comparable to physiological glucocorticoid secretion, approximately 7.5 mg/d of prednisone. For these patients, experimenting with new drugs does not seem necessary, although even at these low doses, the risk of osteoporotic fractures is increased.[96] However, many other patients require higher doses of prednisone to maintain a safe platelet count. For these patients, alternative approaches are warranted, but no treatments have been shown to be effective in randomized clinical trials assessing outcomes of bleeding and death. Therefore, no algorithm based on evidence can be proposed for standard care of chronic refractory ITP.[97] Many agents, combination therapies, and procedures have been proposed, some of which should be considered experimental (Table 7). The order in which they are cited in this review does not imply a judgment of ranking or efficacy of

these therapies. Figure 3 shows an approach to therapy based on our personal experience.

Eradication of *Helicobacter pylori* Infection

A simple measure that can be adopted before other treatments are initiated is the detection and eventual eradication of *Helicobacter pylori* infection. Recent reports suggest that this infection is associated with the development of autoimmune diseases including ITP and that its eradication may result in clinical responses. Studies describing the prevalence of *H pylori* infection in patients with ITP have generated conflicting results. Prevalences ranged from 21.6% in the American study by Michel et al[98] to 71.4% in the Spanish study by Jarque et al.[99] These discrepancies can be explained perhaps by the different socioeconomic conditions of the patient populations investigated.[100] The results of *H pylori* eradication in ITP have been reviewed recently.[98] Responses were extremely variable (reported range, 7%-100%). In total, 56 (46%) of 122 patients in whom the bacterium had been eradicated experienced substantial improvement of thrombocytopenia. However, only a few of these patients had severe chronic ITP.

High-Dose Corticosteroids

Oral or intravenous dexamethasone, at a dosage of 40 mg/d for 4 days and repeated every 4 weeks, has been used since the publication of an uncontrolled series of 10 patients. Splenectomy had failed in 6 of these patients.[101] All 10 patients in this series experienced a complete, durable response. However, subsequent studies have not produced such favorable results in terms of response rate, with sustained responses achieved only in sporadic cases.[102-105]

One study reported on 9 adult patients with platelet counts of less than 50×10^9/L who were all treated initially with oral corticosteroids (prednisolone or prednisone at 1 mg/kg per day). Methylprednisolone was given at 30 mg/kg per day for 3 days, 20 mg/kg per day for 4 days, and then 5, 2, and 1 mg/kg per day each for 1 week. Platelet counts returned to normal within 3.5 days in all patients, although in 7, the response lasted only a few weeks before decreasing to pretreatment levels.[106]

Danazol

Danazol, an attenuated androgen initially formulated for the treatment of endometriosis, can be used in male patients and nonpregnant female patients with ITP. Ahn and Horstman[107] recently reviewed 25 publications about danazol therapy in chronic ITP. Favorable outcomes were reported in 21 and negative outcomes in 4. Pooled data show that danazol produces a sustained platelet increase in 30% of patients. The platelet counts of an additional 10% of patients increased to 50×10^9/L to 100×10^9/L. However, a detailed analysis of the data reveals that extremely few patients with severe chronic refractory ITP responded to this agent. In most negative studies, danazol was used in a small number of patients as a single agent and was discontinued after 2 to 4 months. However, in some patients, response was delayed for as long as 10 months. Therefore, therapy should be continued for at least 6 months, preferably for 1 year, if no serious adverse effects occur. Remissions induced by long-term danazol can last for years, even after discontinuation of the drug.[107] Pharmacokinetic studies indicate that danazol concentrations in plasma and in blood cell membranes are extremely variable.[108,109] Some patients in whom standard dosage (400-800 mg/d) failed responded to a low dose (50 mg/d),[110] suggesting that excessively high blood concentrations may have adverse effects on platelets. The mechanisms of action of danazol are unclear but involve impairment of macrophage-mediated clearance of antibody-coated platelets via decreased Fc receptor expression.[111] Danazol is generally well tolerated; the most frequent adverse effects include headache, nausea, breast tenderness, maculopapular rash, weight gain, hair loss, myalgia, amenorrhea, and liver dysfunction. Long-term study of patients with angioneurotic edema have shown the safety of danazol therapy given over a 10-year period.[112] Rare cases of hepatic peliosis and hepatomas have been reported.[107]

Table 7. **Treatment Options for Patients With Chronic Refractory Immune Thrombocytopenic Purpura**

Type of treatment	Adverse effects
Conventional agents	
Oral dexamethasone	Osteoporosis, psychosis, avascular necrosis of femoral head (idiosyncratic)
Intravenous methylprednisolone	Diabetes, fluid retention
Danazol	Weight gain, hirsutism, liver function disturbances
Azathioprine	Immunosuppression, neutropenia, liver function disturbances
Intravenous cyclophosphamide	Leukemia, cytopenia, teratogenicity
Vinca alkaloids	Neuropathy
Combination chemotherapy	Leukemia, cytopenia, teratogenicity
Cyclosporin A	Nephrotoxicity, immunosuppression
Dapsone	Hemolysis, nausea, abdominal pain
Staphylococcal protein A column	Acute hypersensitivity-type reaction, vasculitis
Interferon α	Flu-like syndrome, fatigue, neuropathy
Experimental therapies	
Rituximab	First-infusion reactions
Campath-1H	Rigors, fever, lymphopenia
Mycophenolate mofetil	Nausea, abdominal pain
Megakaryocyte growth and development factor	Hypertension, vomiting, headache
Autologous stem cell transplantation	Hemorrhagic cystitis, vaginal bleeding, gastrointestinal bleeding, epistaxis, febrile neutropenia

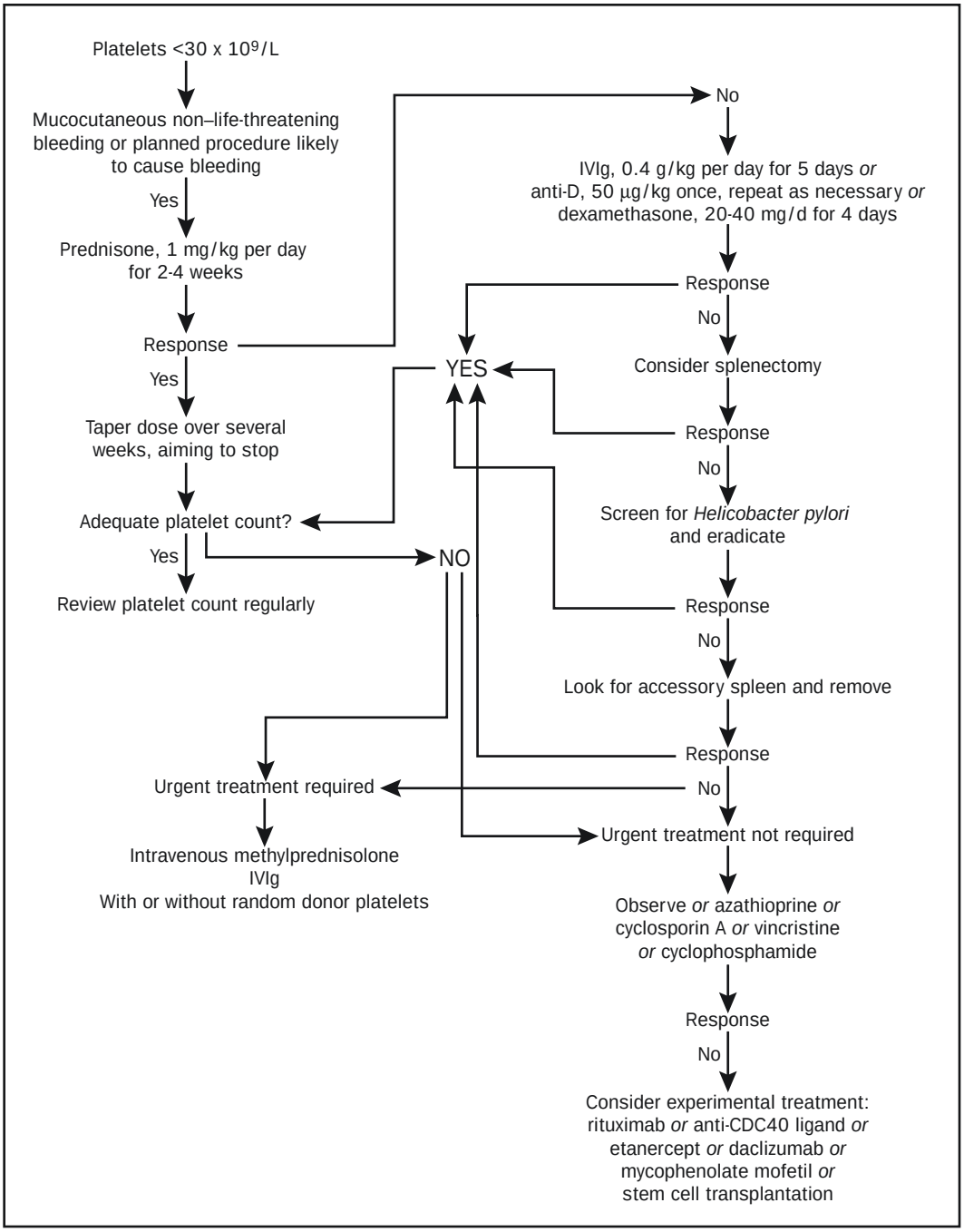


Figure 3. Treatment options in adults with severe refractory immune thrombocytopenic purpura. IVIg = intravenous immunoglobulin.

Azathioprine

Azathioprine is one of the most commonly used immunosuppressive agents. Approximately 20% of patients may achieve a normal platelet count with this agent. Responses may be sustained for several months to years and, at least in some patients, persist after treatment is discontinued. An additional 30% to 40% may have partial responses.[1] Median time to response ranges between 2 and 4 months, and treatment should be continued for up to 6 months before being deemed a failure. Azathioprine may be given orally at a dosage of 1 to 4 mg/kg per day, which should be modified according to the leukocyte count. A major con-

cern, particularly in younger patients, is the risk of developing a malignancy. Kyle and Gertz[113] reported the occurrence of acute leukemias and myelodysplastic syndromes in 30 patients treated with azathioprine. The teratogenic risk of azathioprine has not been documented.

Cyclophosphamide

Cyclophosphamide can be given as a daily oral dose or an intermittent (usually every 3-4 weeks) intravenous pulse dose (1.0-1.5 g/m^2). Oral cyclophosphamide is usually initiated at a dosage of 1 to 2 mg/kg per day and should be adjusted with the aim of maintaining mild neutropenia. Responses occur within 2 to 10 weeks and, as with azathioprine, can persist after therapy is stopped.[114] In an uncontrolled case series of 20 patients, the intermittent intravenous regimen produced 65% complete responses and 20% partial responses.[115] Five of the 13 responders relapsed at 4 months to 3 years. Responses occurred within 1 to 6 months after treatment. Adverse effects of cyclophosphamide include bone marrow suppression, hemorrhagic cystitis, infertility, teratogenicity, and development of secondary malignancy. Therefore, the use of this agent should be carefully evaluated among younger patients.

Vinca Alkaloids

Both vincristine and vinblastine have been used for refractory ITP, and the response appears to be independent of the agent used and the mode of delivery (intravenous bolus or a more prolonged infusion).[116] Responses have been described in 50% to 70% of patients. However, only a few patients have a sustained remission, and most require maintenance injections. A common regimen for vincristine is 2 mg/wk intravenously for several weeks. Adverse effects include peripheral neuropathy, which is common and may be persistent, and constipation. The mechanism of action of the vinca alkaloids is uncertain but may be related to inhibition of phagocytic cell function.

Combination Chemotherapy

The use of aggressive lymphomalike chemotherapy regimens for chronic refractory ITP has been reported in one series.[117,118] Immune thrombocytopenic purpura was associated with Hodgkin disease in one case and with chronic lymphocytic leukemia in another. All 12 patients had prior treatment with corticosteroids, and all had undergone splenectomy. The duration of thrombocytopenia ranged from 5 to 110 months, and all patients had platelet counts of less than 5×10^9/L unless they were receiving some form of platelet-enhancing therapy. The chemotherapy regimen consisted of up to 6 cycles of cyclophosphamide and prednisone plus 1 or more other agents (vincristine, procarbazine, and/or etoposide). Seven patients had a complete response, which was sustained in 4 patients for 60 to 150 months, and 2 had a partial response.

Cyclosporin A

Cyclosporin A has been shown to increase platelet counts when given either alone or with prednisolone. Emilia et al[119] reported 12 patients with chronic ITP treated with cyclosporin A (2.5-3.0 mg/kg per day). Complete responses were seen in 9 patients and a partial response in 1. Adverse effects were moderate but transient. Most patients had a sustained response after treatment was discontinued. In another study, 20 patients with ITP refractory to corticosteroids, half of whom had undergone splenectomy, were treated with cyclosporin A for at least 4 weeks.[120] The dosage was reduced by 50 mg/d every 2 weeks in those showing responses. Five patients remained in complete remission for at least 2 years after discontinuing cyclosporin A, and another 6 showed partial responses. Cyclosporin A was discontinued in 6 patients because of adverse effects.

Rituximab

Several small studies have investigated the use of rituximab, a monoclonal antibody directed against the B-cell antigen CD20.[121-123] The regimen used was identical to that used in follicular lymphomas, ie, 375 mg/m^2 weekly for 4 consecutive weeks. The results were variable, but when the data were combined, the overall response rate was slightly greater than 50%, with 25% to 30% sustained complete responses. Responses were observed both early during treatment and several weeks after the last rituximab infusion. Splenectomized and nonsplenectomized patients responded equally well. The toxicity profile of rituximab appears favorable, and most adverse effects are grade 1 to 2 first-infusion reactions. The mechanisms of action of rituximab have not been investigated thoroughly. Rituximab induces a profound B-cell depletion that may involve the autoreactive B-cell clone. However, a mechanism of macrophage blockade by opsonized B cells also has been proposed, which may account for the early responses.

Campath-1H

Campath-1H is a humanized monoclonal antibody against CD52, a molecule expressed by both B and T lymphocytes. Lim et al[124] treated 6 patients with refractory ITP (3 patients had an underlying lymphoproliferative disease). A response was seen in 4 of 5 evaluable patients, and in 3 of these, the response lasted more than 4.9 months. In most patients, between 4 and 6 weeks were needed for a response to occur. Adverse effects were notable and included rigors and fever during the infusion and marked lymphopenia ($<0.1 \times 10^9$/L) in all patients treated. Worsen-

ing of thrombocytopenia was noted in 2 patients during therapy. A more recent study has investigated the use of Campath-1H in patients with various cytopenias. A response was obtained in 15 and maintained in 6 patients at the expense of notable adverse effects.[125]

Autologous Hematopoietic Stem Cell Transplantation

In recent years, autologous peripheral blood stem cell transplantation has been used for severe unresponsive autoimmune disorders. The results of a clinical trial using high-dose cyclophosphamide followed by autologous lymphocyte-depleted peripheral blood stem cell transplantation have been reported by investigators at the National Institutes of Health Clinical Center in Bethesda, Md.[126] The patient group comprised 14 adults with chronic refractory ITP, including 5 patients who had Evans syndrome (autoimmune hemolytic anemia in addition to autoimmune thrombocytopenic purpura). At a median follow-up of 42 months, durable complete remissions were observed in 6 patients, durable partial responses in 2, and no response in 6; there were no transplant-related deaths. This trial has been extended to recruit other patients. Another ongoing trial at Fairview University Medical Center, Minneapolis, Minn, is evaluating the combination of timed plasmapheresis, high-dose cyclophosphamide and total lymphoid irradiation, and posttransplantation immunosuppression with cyclosporin A (http://www.clinicaltrials.gov).

Thrombopoietin and Thrombopoietin-like Agents

An alternative to increasingly intensive immunosuppression may be to stimulate platelet production with thrombopoietin or its analogues. In fact, in addition to markedly shortened platelet survival, impaired platelet production may be responsible for thrombocytopenia in ITP.[127] The pathogenetic mechanisms of this phenomenon probably involve autoantibodies that affect megakaryocyte development. On the basis of these observations, it has been postulated that stimulation by thrombopoietin may result in safe platelet counts. A report involving 4 patients documented increased platelet counts in 3 patients, with thrombocytosis resulting in platelet counts of up to approximately 800×10^9/L in 2 patients.[128]

Other Treatments

Several other therapies have been used in chronic ITP, including dapsone,[129,130] interferon α,[131,132] colchicine,[133] ascorbic acid,[134] low-molecular-weight heparin,[135] mycophenolate mofetil,[136,137] 2-chlorodeoxyadenosine,[138] and liposomal doxorubicin.[139] The number of patients in all these studies was small, and the responses were mostly unimpressive, inconsistent, and transient, often occurring in patients with less severe ITP.

In one study, staphylococcal protein A immunoadsorption was reported to be a highly effective method of improving platelet count. Snyder et al[140] reported the effects of this treatment in 72 patients with chronic ITP. Forty-nine patients had undergone splenectomy, and most had received other platelet-enhancing therapies. All 72 patients were treated with an initial regimen of 6 immunoadsorption treatments for 2 to 3 weeks. Twenty-nine patients continued taking concomitant low-dose corticosteroids (<30 mg/d), 9 of whom also received other platelet-enhancing medications. Twenty-five percent of patients had good responses (platelet counts of $>100 \times 10^9$/L), 21% had fair responses (platelet counts of $>50\text{-}100 \times 10^9$/L and at least double the baseline count), and 54% had poor responses. In 36% of patients, responses were maintained for 2 months or longer. Other studies have documented much less favorable results and considerably greater toxicity.[141,142] The mechanisms of this therapy are unknown, but reduction in platelet-binding immunoglobulin and in circulating immune complex levels has been the postulated mechanism by which protein A immunoadsorption elicits its clinical effects. Protein A immunoadsorption may decrease platelet activation, and this may be an additional mechanism underlying its efficacy.[142] Approximately one third of the patients developed an acute hypersensitivity-type reaction. A few cases of severe vasculitis also have been reported.[141,142]

INVESTIGATIONAL THERAPIES

Clinical trials with numerous new agents are under way. More specific information about these trials can be found at the Web sites http://www.clinicaltrials.gov and http://www.itppeople.com/clinical.htm. Preliminary results for most of these studies are either unavailable or have been published only in abstract form.

A response to etanercept, a recombinant fusion protein of the extracellular portion of the P75 tumor necrosis factor α receptor and the Fc portion of human IgG1, has been documented in 3 patients with severe, chronic, refractory ITP.[143] A clinical trial to evaluate the efficacy and toxicity of this agent in children and adults with chronic ITP is ongoing.

A humanized monoclonal antibody to FcγRI receptors on monocytes and macrophages, MDX-33, has been investigated in a multicenter phase 2 study by Terjanian et al.[144] A dose-dependent transient response in 30 patients with mild adverse effects was recorded.

A humanized monoclonal antibody to CD40 ligand has been used in 2 groups of patients with ITP. This agent binds specifically to CD40 ligand (expressed by T cells) and blocks its ability to bind to CD40, thus preventing stimulation of the B lymphocytes and inhibiting antibody production. Of 29 patients treated, 7 showed an increase in platelet

count to greater than 30×10^9/L; at least 2 of these patients have since relapsed. Three additional patients with ITP, with extremely low platelet counts and clinical bleeding, received the highest dose initially (rather than by dose escalation) and all responded.[145] However, this trial was stopped because of adverse thrombotic events. Another multicenter trial with a different humanized monoclonal antibody to CD40 ligand is ongoing.[146]

Daclizumab, a humanized monoclonal antibody directed against CD25 (interleukin 2 receptor), which has been used primarily to prevent rejection of solid organ transplants, is being tested at the Warren Grant Magnuson Clinical Center of Bethesda, Md, in patients with ITP who do not respond to initial prednisone treatment.[147-150]

A phase 1/2 open-label dose-escalation clinical trial to evaluate the safety and efficacy of cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (CTLA-4-Ig) in patients with refractory ITP has been launched in the United Kingdom. The fusion immunoglobulin CTLA-4-Ig combines the first extracellular domain of human CD152 and the Fc portion of human IgG1; CTLA-4-Ig probably blocks T-cell activation by competing for the costimulatory molecules.[151]

ITP IN PREGNANCY

Mild to moderate thrombocytopenia is common in healthy women with an apparently normal pregnancy.[152] Most of these women have gestational thrombocytopenia, a benign self-limiting condition with no notable bleeding risk to either mother or infant.[4,5] Gestational thrombocytopenia is characterized by mild thrombocytopenia (platelets rarely decrease to less than 80×10^9/L), occurrence in healthy women with otherwise normal blood counts, normal platelet counts before and after pregnancy, and no association with fetal or neonatal thrombocytopenia. However, distinguishing gestational thrombocytopenia from ITP may be difficult or impossible when the thrombocytopenia is identified for the first time during pregnancy and no previous platelet counts have been documented.[4,5]

Proper management of ITP in pregnancy requires consideration of both the mother and the fetus because IgG antiplatelet antibodies cross the placenta and may produce profound thrombocytopenia in the neonate. No high-quality prospective studies or randomized clinical trials exist about preferred treatment of the mother or neonate or about optimal delivery procedure. The decision to treat the pregnant woman with ITP is based on assessment of the risk of hemorrhage. The platelet count usually decreases as pregnancy progresses, the greatest rate of decline and nadir occurring in the third trimester.[153] Therefore, careful planning is required to ensure a safe platelet count at the time of delivery. Asymptomatic patients with platelet counts of greater than 20×10^9/L do not require treatment until delivery is imminent but should be carefully monitored, both clinically and hematologically.[154]

Although a consensus has not been reached, most experts agree that platelet counts of greater than 50×10^9/L are safe for normal vaginal delivery and are safe for cesarean section, whereas epidural anesthesia is used only when platelet counts are greater than 80×10^9/L because of the potential risk of hematoma formation and neurologic damage.[4]

The major treatment options for maternal ITP are corticosteroids or IVIg. Vinca alkaloids, androgens, and most immunosuppressive drugs should not be used during pregnancy, although azathioprine has been used safely in patients who underwent transplantation. If the duration of treatment is likely to be short, ie, starting in the third trimester, corticosteroids are a cost-effective option. An initial dosage of 1 mg/kg per day (based on prepregnancy weight) is recommended[153,154] and should be tapered subsequently to the minimum hemostatically effective dose. Patients must be monitored carefully for major adverse effects such as hypertension, hyperglycemia, osteoporosis, excessive weight gain, and psychosis. Because 90% of the administered dose of prednisone is metabolized in the placenta, serious fetal adverse effects such as adrenal suppression are unlikely. If corticosteroid therapy is likely to be prolonged, or notable adverse effects occur, or an unacceptably high maintenance dosage is required (>10 mg/d of prednisone), IVIg therapy should be considered.[5] The response rate (80%) and duration of response (2-3 weeks) to IVIg is similar to those of nonpregnant patients.

The ability of maternal IVIg therapy to improve fetal platelet counts remains controversial.[155] Intravenous immunoglobulin has the same potential risks and adverse effects as in the nonpregnant patient, and the financial cost is much higher than that of corticosteroids. Therapeutic options for women with severely symptomatic ITP refractory to oral corticosteroids or IVIg include high-dose intravenous methylprednisolone (1 g), alone or combined with IVIg or azathioprine,[154] which, from available data, appears to cause no serious problems to either mother or fetus.[156] Splenectomy during pregnancy is performed rarely; if absolutely essential, it is best carried out in the second trimester and may be successfully performed laparoscopically, although this may be technically difficult after 20 weeks' gestation. More recently, intravenous anti-D has been shown to be both effective and safe during pregnancy with no adverse effects experienced by either the mother or fetus.[157]

The major concern is at delivery because the incidence of fetal thrombocytopenia with platelet counts of less than 50×10^9/L is approximately 10% to 15% and with platelet counts of less than 20×10^9/L is approximately 5%.[158-163]

No accurate, risk-free method of determining fetal platelet count is currently available, and both cordocentesis and fetal scalp blood sampling are rarely used in the treatment of ITP during pregnancy. The only characteristics that have been consistently correlated with an increased incidence of fetal thrombocytopenia are prior splenectomy and thrombocytopenia in the first or preceding sibling.[160,161,164] In one series of 64 pregnant women with chronic ITP, the incidence of severe neonatal thrombocytopenia (platelet count of $<50 \times 10^9$/L) was 57% when mothers had prior splenectomy and a gestational platelet count of less than 50×10^9/L; the incidence was 0% when mothers had neither of these 2 findings.[164]

It has been postulated that trauma during vaginal delivery may precipitate central nervous system bleeding in the neonate and that cesarean section may obviate this problem; however, this hypothesis has been questioned.[162] In fact, the incidence of fetal hemorrhage is less than 1%, and there are no differences in the rate of complications with cesarean section compared with vaginal delivery. Thus, it is now generally agreed that the mode of delivery in ITP should be determined purely by obstetric indications.

After delivery, the infant's platelet count often declines during the first week and should be monitored carefully.[165] For severe thrombocytopenia or mucosal bleeding in the neonate, intravenous IVIg is the treatment of choice. Platelet transfusions that are cytomegalovirus negative and irradiated can be added in the event of severe bleeding.[5]

CONCLUSIONS

Because of the general lack of randomized studies, management options for ITP are not based on evidence but on a rational approach to the individual patient that includes assessment of disease severity, patient's characteristics related to risk of bleeding, and the risks and adverse effects of treatment. The toxicity profiles of many of the newer treatments underline the need for appropriate choices and for trials designed to incorporate end points such as quality-of-life measures and economic analyses. Real evidence-based guidelines for this disease are not likely to be developed soon. Considering the low incidence of mortality and major morbidity of ITP, prospective trials probably would require the enrollment of several hundred patients to show the superiority of a particular agent or management protocol. The availability of a biological surrogate marker, such as the detection of autoreactive B-cell clones, would obviously be a major step forward. Unfortunately, such markers have not yet been identified. Basic research needs to be intensified to unravel the pathogenetic mechanisms underlying ITP, which we hope would lead to more individualized, targeted, and possibly less toxic treatment regimens. Meanwhile, a stronger methodology of clinical reports, which should describe consecutive patients with clear inclusion and exclusion criteria as well as long follow-up data to document clinical outcomes and platelet responses, could help clinicians to delineate more precise treatment strategies.

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