How I treat idiopathic thrombocytopenic purpura (ITP)

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Introduction

Our goal is to set forth our opinion of the best approach to managing adults with primary idiopathic (autoimmune) thrombocytopenic purpura (ITP), with emphasis on the word “opinion.” The paucity of evidence-based medicine on this topic has been noted. Both the American Society of Hematology and the British Committee for Standards in Haematology have issued “practice guidelines.” These, in large part, proved to be compendia of opinions from panels of experienced physicians who concurred on some matters but not on others. We cite published evidence where we find it compelling and reproducible, but much of what follows rests on our mutual experience treating patients, both on- and off-study, rather than an encyclopedic, heavily referenced review. Many issues remain unresolved, expert opinions differ for good reason, and it is likely that our own approach will change based on emerging data. Comprehensive reviews on pathogenesis, laboratory testing, secondary ITP, ITP in children, and treatment are to be found elsewhere.

Who develops ITP?

Until recently, experience from numerous centers over more than a half-century indicated that the typical adult with ITP is a woman, generally between 18 and 40 years of age. Gender disparity largely disappears among the elderly. Two recent publications have questioned this perception. The first was a survey from a single county in Denmark using International Classification of Disease (ICD) codes at hospital discharge over a 22-year period. The female-male ratio was 1.7, the median age at diagnosis was 56 years, and the incidence of ITP increased with age and increased overall during the period of study. The second was a prospective cohort analysis of newly presenting adults with platelet counts less than 50,000 × 10^9/L in the Northern Health Region of the United Kingdom. The female-male ratio was 1.2 and, again, the age-specific incidence was highest among those older than 60 years. Presenting symptoms, severity of thrombocytopenia, and response to therapy were typical for ITP, so these data do not simply reflect increased detection of mild cases based on automated platelet determinations, or drug-dependent antibodies.

How we diagnose ITP

ITP remains a diagnosis of exclusion. The essential elements include an otherwise healthy individual who presents with isolated thrombocytopenia, an otherwise unremarkable peripheral smear, a physical examination that only shows evidence of bleeding consistent with the platelet count, and the exclusion of other causes of thrombocytopenia if grounds for suspicion exist. These include exposure to drugs, herbs, foods, or other substances (eg, quinine) associated with thrombocytopenia; pseudothrombocytopenia; giant platelets; family history consistent with inherited thrombocytopenia; or symptoms/signs suggestive of an underlying disorder that may cause secondary immune thrombocytopenia. We only perform bone marrow examinations as a matter of routine in otherwise typical patients if they are over 60 years of age when the incidence of MDS becomes significant, in those who do not show a robust response (> 50,000 × 10^9/L) to treatment, and often prior to splenectomy if not previously performed. Response to treatment, especially intravenous immune globulin (IVIG) or intravenous anti-D (IV anti-D), even if transient, is the single best diagnostic test. Conversely, a poor response to treatment may necessitate re-evaluation of the diagnosis, including a bone marrow examination.

Testing for HIV or hepatitis C infection (or both) is indicated in at-risk populations and the latter may occur more widely than previously appreciated. Remissions induced by eradication of asymptomatic Haemophilus pylori infection have been reported in studies from Italy and Japan, but is not our experience. We neither perform the more sensitive breath testing nor treat empirically at presentation, but consider testing in chronic cases and those with gastrointestinal symptoms. Approximately 1% of patients have coexisting immune hemolytic anemia (Evans syndrome) and a smaller percentage have immune neutropenia, which confer a less favorable prognosis. Immunoglobulin levels are measured if there is a history of recurrent infection or allergy, if there is a reaction to IVIG or prior transfusions, or if there is a concern about common variable immunodeficiency or IgA deficiency. Clonality and cytogenetics are assessed as part of the bone marrow evaluation. Disturbances in thyroid function occur with sufficient frequency that we often measure thyroid-stimulating hormone levels if there are complaints of persistent fatigue and prior to splenectomy. We test for antiphospholipid antibodies if there is a history thrombosis, recurrent or second- or third-trimester gestational failure, or a prolonged activated partial thromboplastin time. Up to 5% to 10% of patients eventually meet criteria for systemic lupus erythematosus or another cause of secondary immune thrombocytopenia. Our approach to secondary immune thrombocytopenia,

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including systemic lupus erythematosus, antiphospholipid syndrome, B-cell malignancies (primarily chronic lymphocytic and large granular leukemias), and HIV infection, among others, has been reviewed elsewhere.4

We do not rely on measuring antiplatelet antibodies to make or exclude a diagnosis of ITP. Although some argue that current methods to detect platelet antigen-specific antibodies are now sufficiently specific to affirm the diagnosis, antibodies have also been detected in 10% to 20% of patients with certain causes of “nonimmune” thrombocytopenias (eg, chronic liver disease, MDS), the populations in which testing would be most helpful. These assays lack sufficient sensitivity to exclude a diagnosis of ITP and interlaboratory reproducibility is inadequate.24

Who we treat

What is a hemostatic platelet count? Is the platelet count a reasonable surrogate marker for the risk of serious bleeding? In a recent 10-year study of 310 patients in whom treatment was generally used only at platelet counts less than 30,000 × 10⁹/L, only one hemorrhagic death occurred.22 In a meta-analysis of 17 studies, the age-adjusted risk of fatal hemorrhage at platelet counts persistently less than 30,000 × 10⁹/L was estimated to be 0.4%, 1.2%, and 13% per patient per year for those younger than 40, 40 to 60, and older than 60 years of age, respectively. Predicted 5-year mortality ranged from 2.2% to 47.8%.23 Similar mortality rates have been reported by others depending on duration of follow-up.24,25 Major bleeding, including spontaneous intracerebral hemorrhage (ICH), occurs predominantly in patients with platelet counts less than 20,000 × 10⁹/L, generally less than 10,000 × 10⁹/L.24,27 Thus, a compelling case can be made to treat patients with platelet counts below 20,000 × 10⁹/L. Some experts would apply this reasoning to recommendations for splenectomy,28 although we use a higher threshold (see “Splenectomy”).

What is more contentious and requires individualization and considerable judgment is the wisdom of treating patients with platelet counts between 20,000 and 50,000 × 10⁹/L. Although few otherwise healthy, sedentary individuals die of hemorrhage over a 10-year period if they maintain a stable platelet count more than 20,000 × 10⁹/L and though we rarely treat patients with platelet counts more than 30,000 × 10⁹/L in the absence of exculating circumstances that predispose to serious bleeding, no published follow-up is of sufficient length or size to project risk over a life span. Our opinion is that it is as unreasonable to apply a “one-size fits all” threshold as it would be to attempt to normalize platelet counts in all patients. Is 20,000 to 30,000 × 10⁹/L a safe and appropriate platelet count for the 63-year-old man with angina who then suddenly requires clopidogrel and aspirin after a coronary stent is placed? What about the high school student able to afford college only if awarded a football scholarship, the policeman who routinely faces physical confrontation, the 28-year-old hard-hat construction worker, the 19-year-old woman with marked menorrhagia unresponsive to hormonal management, the 26-year-old who feels completely drained of energy unless her platelet count approaches 50,000 × 10⁹/L, or even the extensive traveler. There is room for disagreement in each of these cases, but they illustrate the types of issues confronted in real practice.

Although rare, major bleeding has been reported at platelet counts between 20,000 and 30,000 × 10⁹/L. Furthermore, counts may drop suddenly at any time.24 A worrisome number of patients who developed ICH did so after acute and often unpredictable events such as viral infection or head trauma, or after inadvertently taking medications that impair platelet function.27 We would argue that the goal of therapy must be individualized on the basis of signs and symptoms, tolerance of treatment, lifestyle, and patient preference. Our usual practice is to maintain a somewhat higher platelet count initially (eg, 30,000 × 10⁹/L) while we get to know the patient, with the goal of establishing a track record of bleeding, compliance, and risk management that allows us to modify the threshold for treatment over time.

Treatment at presentation

Principles of management

Patients typically present with petechiae or purpura that develop over several days accompanied by platelet counts less than 20,000 × 10⁹/L, although the onset is often more insidious than previously appreciated.18 Severe cutaneous bleeding, prolonged epistaxis, gingival bleeding, overt hematuria, or menorrhagia may develop at platelet counts less than 10,000 × 10⁹/L. Spontaneous or posttraumatic ICH or bleeding at other internal sites is uncommon, but not without precedence,24 at platelet counts between 10,000 and 20,000 × 10⁹/L. Those with platelet counts between 30,000 and 50,000 × 10⁹/L may note easy bruising, whereas platelet counts above 50,000 × 10⁹/L are usually discovered incidentally. Rarely, do patients present with bleeding disproportionate to the platelet count because of antibody-induced platelet dysfunction.29 Some patients experience untoward and otherwise unexplained fatigue when their platelet count is low.

Management is predicated primarily on the severity of thrombocytopenia and bleeding. Drugs that interfere with platelet function are discontinued. Alternatives are substituted for drugs deemed necessary but potentially causal. The initial goal of treatment is to attain a hemostatic platelet count (≥30,000 × 10⁹/L) while minimizing the toxicity of treatment. Figure 1 shows our treatment algorithm for initial management. The reader is referred elsewhere for a more comprehensive tabulation of drug doses, expected response times, and common side effects.30 Therapy is indicated in all patients who present with bleeding and those with platelet counts less than 20,000 × 10⁹/L because fewer than 10% of adults rapidly attain spontaneous remission. Those with platelet counts more than 50,000 × 10⁹/L can almost always be observed, although some (5 of 87 in one series7) require treatment later. In general, immediate therapy is not required for patients with platelet counts between 20,000 and 50,000 × 10⁹/L in the absence of bleeding or predisposing comorbid conditions such as uncontrolled hypertension, active peptic ulcer disease, anticoagulation, recent surgery, or head trauma.23 We recommend maintaining platelet counts above 40,000 to 50,000 × 10⁹/L for patients requiring aspirin, nonsteroidal anti-inflammatory drugs, warfarin, or other antithrombotics.

Hospitalization and emergency therapy

We hospitalize (1) patients with profound mucocutaneous or internal bleeding and (2) those who present with platelet counts of less than 20,000 × 10⁹/L and a history of significant bleeding, those in whom there is a question about compliance, and in some cases, those in whom responsiveness to therapy has not been established—for example, when comorbid factors predisposing to bleeding or complications of therapy are present. All others can be
treated as outpatients. Urgent treatment is initiated with intravenous methylprednisolone (1.0 g/d for 1-3 consecutive days) combined with IVIG (Figure 1). Before splenectomy in Rh + patients, we have combined IVIG and IV anti-D, which act through different IgG-Fc receptors,34-36,63 with vincristine and methylprednisolone,37 and platelet transfusions (bolus followed by continuous infusion as needed) for life- or organ-threatening bleeding or after head trauma.38 Recombinant factor VIIa may be added in patients unresponsive to other modalities if an immediate response is necessary, such as with ICH.39 IVIG is generally well tolerated other than for a postinfusion headache. Rarely, patients develop aseptic meningitis, acute renal failure, pulmonary insufficiency, thrombosis, or hemolysis; dissolving lyophilized preparations in sterile water to lower osmolarity and slowing the infusion rate may lessen these risks. Common toxicities of IV anti-D include fever/chill reactions, which can be ameliorated by pretreatment with corticosteroids, and extravascular hemolysis; intravascular hemolysis and disseminated intravascular coordination are rare33,91 and the risk is lessened by avoiding treatment in those with a positive direct antiglobulin test unless attributable to prior IVIG or IV anti-D therapy. We also initiate general measures to reduce the risk of bleeding, including cessation of drugs that impair platelet function, control of blood pressure, measures to minimize trauma, and measures to reduce mucosal bleeding, such as ε-aminocaproic acid (100 mg/kg loading dose up to a maximum of 5 g given intravenously over 30-60 minutes followed by up to 5 g every 6 hours intravenously or orally [maximum dose = 24 g/day]) and, on occasion, desmopressin acetate (DDAVP; 0.3 μg/kg). We use ε-aminocaproic acid or tranexamic acid swish and swallow to help control oral bleeding, topical thrombin, collagen, and fibrin glue to manage dental extractions, and progestational agents to manage menorrhagia.

**Initial therapy for nonemergent indications**

We treat most patients with prednisone (1.0 mg/kg/day) orally as the initial approach. IV anti-D can be substituted for prednisone in Rh + and direct antiglobulin-negative patients intolerant of corticosteroids or who have contraindications to their use.40,41 Therapy with prednisone can be supplemented with IVIG (1.0 g/kg/d for 1-2 days), IV anti-D (50-75 μg/kg), or IV methylprednisolone (1 g) if platelet counts remain below 20,000 × 10^9/L or if there is another need for a more rapid response. Rapid lasting responses to dexamethasone (40 mg orally daily for 4 d/mo) are reported, although the assertion that this approach increases long-term response compared with prednisone42 requires longer follow-up and confirmation. Proton pump inhibitors should be given when corticosteroids are used for more than a few weeks. We have used aspirin in patients at risk for thrombosis (even in the absence of antiphospholipid antibody) whose platelet counts increase rapidly to more than 600,000 × 10^9/L.16

There is no consensus concerning the optimal duration of corticosteroid treatment. Our practice is to continue full doses for 3 to 4 weeks, until a response is seen or side effects become intolerable. Response rates vary from 50% to 90% depending on intensity and duration of therapy, but only 10% to 30% of patients enter stable remission once therapy is tapered or stopped17,25,41,43,46; even those who enter remission often require additional or alternative therapy, at least initially.47 We taper prednisone slowly, especially once doses of 10 mg/d are reached, to avoid adrenal insufficiency. Failure to respond to prednisone, IV anti-D, and/or IVIG should prompt the diagnosis to be reconsidered and a bone marrow evaluation, including cytogenetics and flow cytometry, to be performed.

**Persistent ITP**

Thrombocytopenia recurs in most patients when corticosteroids are tapered. We treat patients with persistent ITP with the goal of maintaining the platelet count more than 20,000 to 30,000 × 10^9/L while avoiding steroid-induced osteoporosis, cataracts, and other toxicities. The major decision is whether to temporize with medical therapy or to proceed swiftly to splenectomy. For those in whom the former is chosen, our preference is to infuse IV anti-D as needed. In the largest series to date, 25% to 30% of patients showed responses lasting longer than 1 year.47 Alternatives, including anti-CD20 (rituximab) or danazol are discussed (see “First-line therapy” and “Second-line therapy,” respectively). For those whose disease does not abate by 1 year after diagnosis, who do not show a durable response, or who are intolerant of therapy, we recommend splenectomy.

**Splenectomy**

Splenectomy remains the single best option to convert a patient with ITP into a “nonpatient,” that is, one who is unlikely to need frequent monitoring or intervention, and it minimizes interference with a normal lifestyle. The timing of the procedure depends on...
disease severity, responsiveness and side effects of therapy, risk of trauma and of the procedure, and patient and doctor preference. If the patient does not wish to temporize, we recommend splenectomy within 3 to 6 months if any therapy (eg, more than 10 mg prednisone/d) is required to maintain a platelet count greater than 30 000 × 10^9/L. In contrast, some experts recommend a far more protracted period of watchful waiting, with splenectomy reserved for those with a platelet count consistently less than 20 000 × 10^9/L or in the face of difficult-to-control bleeding.\(^7\) Although we might concur with this approach in, for example, a 75-year-old asymptomatic patient with a platelet count of 18 000 × 10^9/L, a life expectancy of 8 to 12 years, and significant risks from surgery, we think the benefits of splenectomy outweigh the risks in the typical active young adult with easy bruising or significant menorrhagia, a platelet count of 20 000 to 30 000 × 10^9/L, and a life expectancy of 50 to 60 years whose disease shows no signs of abating. However, long-term effects of the procedure on the incidence of occlusive cerebrovascular disease remain under study. Thus, the decision must be individualized, and patients are increasingly reluctant to have a healthy organ removed unless they have experienced significant bleeding or morbidity from prior therapy. Such preferences must be respected. This trend has been accelerated by evidence that IV anti-D and anti-CD20 may allow splenectomy to be deferred and possibly avoided.\(^41,47\)

We use IVIG, IV anti-D, or pulse doses of corticosteroids in known responders to boost the platelet count prior to splenectomy. Although splenectomy has been performed safely at exceedingly low platelet counts, nonresponders may experience bleeding problems after the procedure. Prophylactic platelet transfusions are rarely warranted and their routine use should be discouraged. Approximately 85% of patients attain a hemostatic response after splenectomy and two thirds achieve a durable response (for reviews, see Kojouri et al\(^48\) and Schwartz et al\(^49\)). Our experience is consistent with the reported incidence of relapse of 15% to 25% within 10 years.\(^7,25\) In general, responses cannot be predicted through routinely available measures.\(^48\) However, we have found that patients totally refractory to multiple prior treatments appear to fare less well, as do the elderly,\(^50\) patients with secondary forms of ITP,\(^51\) and perhaps those with an hepatic platelet sequestration pattern.\(^25,52\) although we have no direct experience on the latter. Mortality rates for open and laparoscopic splenectomy are 1.0% and 0.2%, respectively.\(^48\) The outcomes of the 2 approaches are comparable,\(^53\) although the former hastens recovery and offers better cosmesis. We reserve splenic irradiation for the rare patient in whom splenectomy is indicated but hazardous or as a diagnostic test.\(^54\)

The major known long-term risk of splenectomy is overwhelming bacterial sepsis, which occurs in less than 1% of adults with uncomplicated ITP.\(^55\) We immunize our patients with polyvalent pneumococcal, H influenzae type b, and quadrivalent meningococcal polysaccharide vaccines at least 2 weeks prior to splenectomy if possible,\(^56,57\) although our experience is that most patients respond to vaccination given more than 6 weeks after surgery. We do not recommend lifelong use of phenoxymethylpenicillin (250-500 mg orally twice daily) or erythromycin (500 mg orally twice daily) in otherwise healthy adults, in contrast to others.\(^7\) Revaccination for pneumococcus is recommended every 5 to 10 years. We suggest patients wear a MedAlert bracelet. All febrile illnesses demand careful evaluation and intravenous antibiotics should be provided urgently at the onset of any systemic illness with fever of 38°C (101°F) or higher until bacterial sepsis can be excluded.

### Treatment of chronic ITP

**Principles of treatment**

Approximately 30% to 40% of patients have platelet counts less than 50 000 × 10^9/L after splenectomy because they did not respond or they had a relapse, whereas others are unable or unwilling to undergo the procedure. The goal of therapy in this setting is to attain a hemostatic platelet count rather than to achieve cure, while minimizing drug-induced toxicity (Figure 2). Most patients achieve this goal, although it may take years.\(^25,26\) and therapy can be toxic if not used judiciously.\(^25,26\) There are no randomized trials to support the effectiveness of any specific approach.\(^58\) We concur with several of the recommendations of the British HaematoIogy Task Force\(^3\) concerning platelet counts for minor surgery (≥ 50 000 × 10^9/L) and most major surgery (> 80 000 × 10^9/L); higher counts are advisable for cardiac bypass surgery, neurosurgery, and complex orthopedic or plastic surgery.

- **Platelet counts:** Usually ≥ 50 000 × 10^9/L for minor surgery, 50 000 × 10^9/L for most major surgery, and 80 000 × 10^9/L for cardiac bypass surgery, neurosurgery, and complex orthopedic or plastic surgery.

**First-line therapy**

We treat symptomatic relapses or severe recurrent thrombocytopenia in the same way as at initial presentation, that is, with corticosteroids or IVIG or the emergent measures described (see "Hospitalization and emergency therapy") depending on severity, with the exception that few patients who have undergone splenectomy respond well to IV anti-D.\(^59\) Although some patients who failed to respond to these measures on presentation do so after splenectomy, it is almost always wise to introduce additional medications, because few patients can be managed with chronic low-dose (5-10 mg) or alternate day doses of prednisone or wish to be bound indefinitely to parental therapy with IVIG. However, we often use these agents initially because the other suggested medications may adversely affect comorbid conditions (eg, corticosteroids and bone density or danazol and prostate disease). Elderly patients are more likely to have severe bleeding and to suffer debilitating side effects of therapy.\(^90\) It is our practice to look for an accessory spleen with magnetic resonance imaging or another sensitive scanning method (eg, heat-damaged red cells) if the response to splenectomy was durable.\(^49\)

**Figure 2. Therapy of adult ITP following splenectomy.** (1) The goal of therapy in this population is to maintain a hemostatic platelet count while minimizing drug-induced toxicity; select patients may require somewhat higher platelet counts because of comorbid risk factors as discussed in "Treatment of chronic ITP." (2) Our preference is to use anti-CD20 if not used previously and we consider reuse if a response was seen prior to splenectomy. Alternatively, we combine danazol with either azathioprine or mycophenolate mofetil for a minimum of 4 months, if possible, because of induced toxicity; select patients may require somewhat higher platelet counts than 50 000 × 10^9/L. We suggest lifelong use of phenoxymethylpenicillin (250-500 mg twice daily) or erythromycin (500 mg orally twice daily) in otherwise healthy adults, in contrast to others.\(^7\) Revaccination for pneumococcus is recommended every 5 to 10 years. We suggest patients wear a MedAlert bracelet. All febrile illnesses demand careful evaluation and intravenous antibiotics should be provided urgently at the onset of any systemic illness with fever of 38°C (101°F) or higher until bacterial sepsis can be excluded.

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**Treatment of Patients Failing Splenectomy**

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**First-line Therapy**

- IV anti-CD20
- Danazol + either Azathioprine or Mycophenolate mofetil
- Prednisone or IVIG prn

**Second-line Therapy**

- Cyclophosphamide
- IV or oral
- Cyclosporine

**Third-line Therapy**

- Combination chemotherapy
- Stem-cell transplantation

**Experimental Therapy**

- Thrombopoietic factors
treatments typically require weeks to months for their effect to become apparent. Monitoring bone density or prophylactic treatment is indicated to avoid osteoporosis in patients treated chronically (> 6 months) with corticosteroids.

We generally treat patients in whom splenectomy fails with the anti-CD20 monoclonal antibody, rituximab (375 mg/m² intravenously every week for 4 weeks). Responses are usually noted within 4 to 8 weeks after the first infusion but may occur as late as 4 months. A complete or partial remission occurs in 25% to 50% of patients who respond, but many complete responses are durable (> 1 year). Side effects are mostly related to the first infusion (fever, chills, hypotension, bronchospasm, etc). Profound and prolonged peripheral B-cell depletion is universal; but serious infection other than reactivation of hepatitis B in chronic carriers is rare and generally seen only in the context of additional immunosuppression. In our limited experience, patients who responded but had a relapse often respond to subsequent courses. Optimal dosing for ITP and use in combination with other modalities is under investigation. The long-term effect of treatment on immune surveillance is unknown.

Second-line therapy

For patients who do not respond to rituximab, we generally initiate therapy with at least 2 agents to avoid inducing multiple drug resistance genes.65 This approach also permits the more problematic agent to be tapered first. We generally choose danazol and either azathioprine or mycophenolate mofetil. Some patients are intolerant or unwilling to continue danazol because of mood or menstrual changes, hirsutism, rash, myalgias, or transaminase elevations; liver function tests should initially be monitored monthly and then every 1 to 3 months. Treatment must be continued for 4 to 6 months to see its full effect. Once a response is seen, corticosteroids can be tapered and IVIG stopped. Approximately 50% of patients unresponsive to splenectomy but not refractory to other treatments can be managed using either danazol alone or combined with low doses of steroids, but in our experience response rates are higher when danazol is combined with an immunosuppressant.

Our preference is to use azathioprine (2 mg/kg orally every day adjusted to avoid severe neutropenia), preferably in combination with danazol (10-15 mg/kg/d), typically 600-800 mg per day, as the first approach to chronic immunosuppression because the incidence of acute and serious side effects is lower than with cyclophosphamide and the frequency of lasting remissions is comparable (20%-40%). However, responses occur more slowly (typically 3-4 months) and this agent, like danazol, is often stopped prematurely. If a response occurs, therapy should be continued at full doses for at least 12 months and then discontinued gradually. Should relapse occur, the decision to restart azathioprine must be balanced against the theoretical risk of complications from long-term use, which appears low based on experience in renal transplantation. We have less personal experience with the use of mycophenolate mofetil. Treatment is begun with 500 mg orally twice a day and the dose is increased to 1000 to 1500 mg orally twice a day after 2 weeks. In one study responses lasting 1 to 39 months were noted in 15 of 23 patients with minimal toxicity66; the response rate in refractory patients is undoubtedly lower. Once a response is seen, the doses of danazol and the immunosuppressant can be gradually lowered over a period of months, but rarely discontinued entirely. Danazol alone is unlikely to work in patients with profound thrombocytopenia unresponsive to corticosteroids or other measures. Dapsone (75-100 mg orally daily) provides results similar to danazol, but should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency.

An alternative is to use cyclophosphamide either intravenously (2 or 3 courses of 500-1000 mg/m² at 3-4-week intervals)67 or orally (1-2 mg/kg daily adjusted to avoid severe neutropenia). Responses typically require 1 to 3 months. Thrombocytopenia may worsen initially. If a complete response occurs to oral therapy, we give full doses for an additional 3 months and then strongly consider stopping treatment. In the event of relapse, the long-term risks (eg, secondary malignancy, MDS) must be weighed against the potential benefits of resuming therapy. Patients should drink at least 2 L liquids daily to prevent hemorrhagic cystitis, and the blood count should be monitored weekly. The response to cyclophosphamide or azathioprine in patients who did or did not respond to the other agent is unknown. We rarely use vinca alkaloids except as adjunctive therapy because responses are almost always transient and treatment with vincristine is complicated by peripheral neuropathy. Occasionally, patients can be maintained with periodic doses of vinblastine. We have seen rare dramatic responses to ex vivo perfusion of plasma over staphylococcal protein A columns, but its efficacy is far less than reported and its use is limited by potentially severe side effects.

Treatment of chronic refractory ITP

Approximately 5% of patients have chronic refractory ITP, defined as the failure of any modality to keep the platelet count above 20 000 × 10⁹/L for an appreciable time without unacceptable toxicity.25 Although many patients tolerate extremely low platelet counts for years without serious bleeding even without treatment, others suddenly develop ICH or other serious bleeding after infection or incidental trauma. Options are limited, alternative therapies are toxic, the minority of patients respond, and morbidity and mortality are considerable, approaching 10% to 15% in some series.62-66 We generally reserve the treatments we describe for patients who are clearly refractory to previously mentioned modalities (ie, splenectomy, danazol, rituximab, or immunosuppressants) and who have had serious morbidity or have extremely low platelet counts (eg, less than 10 000 × 10⁹/L).

If the decision is made to treat, the next step depends in part on the urgency of the situation. If there is sufficient time, one option is cyclosporine (1.25-2.5 mg/kg/dose orally every 12 hours, adjusted based on drug and creatinine levels); in one study, 5 complete and 5 partial remissions were noted in 18 patients who had undergone splenectomy, but 30% of patients discontinued treatment due to side effects (hypertension, myalgias, and headaches).68 High-dose cyclophosphamide (1.0-1.5 g/m² intravenously) given at 4-week intervals may act more rapidly.69 A high fluid intake (3-4 L daily either orally or intravenously during and for at least 3 days after therapy) and frequent blood counts are necessary. The platelet count may fall before a response is seen and granulocyte colony-stimulating factor and prophylactic antibiotics may be needed. Various combinations of chemotherapeutic agents have been used successfully in small numbers of heavily pretreated patients.69 In one study, the long-term outcome of 12 patients (follow-up 35-150 months) included 5 complete and 1 partial remission.70 Therapy should be stopped if there is no response after 2 courses and the literature is based on treating responders with at least 3 or more courses even if the platelet count has normalized. These recommendations may soon require modification based on the success of thrombopoietic agents (see “Experimental therapy”).
Experimental therapy

A new approach is the use of thrombopoietic factors. In one study, 2 of 4 patients developed temporary thrombocytopenia after receiving marrow growth and development factor, a nonglycosylated, truncated form of human thrombopoietin. In recently published phase 2 placebo-controlled trials of AMG 531, a molecule that activates the thrombopoietin receptor, 8 of 12 patients in one study and 7 of 8 in the other showed temporary but substantial increases in platelet counts at a dose of 3.0 μg/kg or higher. We have used autologous stem cell transplantation as a measure of last resort in young patients with recurrent life-threatening bleeding. The largest reported experience involves 14 patients with refractory ITP who were more than 6 months after transplantation at the time of publication. Of these, 6 attained stable platelet counts that were greater than 100 000 × 10^9/L and 2 had partial responses (follow-up 9–42 months). There were no procedural deaths, but sepsis was common and 2 of the 6 complete responders died within a year. Studies of anti–tumor necrosis factor α receptor and anti–interleukin 2 receptor antagonists are too preliminary to evaluate.

ITP and pregnancy

Women with ITP may consult their physician as to the safety of becoming pregnant or the diagnosis may be considered for the first time during pregnancy because years may have passed since a complete blood count was performed. Several comprehensive reviews have been published. ITP occurs in 1 per 1000 to 1 per 10 000 pregnancies, accounting for approximately 3% of women who are thrombocytopenic at delivery. In addition to the differential diagnosis common to all patients with possible ITP, consideration should be given to causes of thrombocytopenia confined to or more common during pregnancy, including pregnancy-induced hypertension and related conditions such as hemolysis, elevated liver enzymes, and low platelet count (HELLP), obstetric causes of disseminated intravascular coagulation, microangiopathic hemolytic processes, and gestational thrombocytopenia, among others (for a review, see McCrave et al). The latter, also referred to as incidental or benign thrombocytopenia of pregnancy, is found in 5% to 8% of healthy women with an uneventful pregnancy and accounts for at least 75% of all cases of thrombocytopenia at term. Thrombocytopenia is generally mild (platelet counts > 70 000 × 10^9/L in 95% of cases) and there seems to be no impact on maternal or fetal health. Platelet counts generally return to normal within 2 months after delivery. ITP should be suspected any time during pregnancy if isolated thrombocytopenia of less than 50 000 × 10^9/L is detected, especially during the first 2 trimesters, but the distinction from gestational thrombocytopenia may occasionally be problematic in the absence of a prenatal platelet count as both entities are diagnoses of exclusion.

We rarely, if ever, discourage pregnancy in women with known ITP, but we explain that maternal and fetal complications may occur and additional monitoring and therapy may be needed. We explain that platelet counts commonly fall even during normal pregnancy, and a woman with ITP may start from a lower baseline. However, it is also important to point out that precipitous falls are seen on occasion and demand more intensive therapy with its attendant complications.

In the absence of symptoms or treatment, we monitor platelet counts at least monthly through the first 2 trimesters, biweekly in the third, weekly as term approaches and more often, if indicated. Ideally, maternal platelet counts should be maintained above 20 000 × 10^9/L throughout pregnancy and above 50 000 × 10^9/L in the third trimester to minimize the need for platelet transfusions in the event an emergency cesarean section is required, but a higher platelet count may be required for epidural anesthesia. We generally use corticosteroids as initial therapy, but this can induce or exacerbate gestational diabetes, bone loss, hypertension, and perhaps abruptio and prematurity. For this reason, we tend to rely more on IVIG together with low-dose prednisone (20 mg every day) than in nonparous patients. We have recently found IV anti-D to be safe (including for the newborn) and effective, although experience is limited, caution is indicated, and close monitoring of the fetus with sonograms and the newborn with hemoglobin and bilirubin determinations is warranted. Splenectomy should be avoided if possible, and deferred to the second trimester when necessary, to avoid abortion. We do not use danazol, cyclophosphamide, anti-CD20, vinca alkaloids, and other potentially teratogenic therapy (with the possible exception of azathioprine for which a registry exists for renal transplant recipients). There is limited experience with chemotherapy for neoplastic diseases in pregnant women that may be helpful in managing the truly exceptional case (for reviews, see Koren et al and Weisz et al).

The mode of delivery is based almost entirely on obstetric considerations. Postpartum bleeding is uncommon after vaginal delivery, even in women with severe thrombocytopenia. Blood loss during cesarean section varies inversely with platelet counts. Although we think that a platelet count of 50 000 × 10^9/L is generally sufficient for epidural anesthesia, we find practice patterns are set by obstetricians and anesthetologists. Criteria for heparin prophylaxis after cesarean section have been reviewed. ITP is not a contraindication to breast-feeding.

Approximately 4% of ITP neonates are born with severe thrombocytopenia (platelet counts < 20 000 × 10^9/L), but importantly few have platelet counts that are less than 5000 × 10^9/L unless alloantibodies are also present. The severity of neonatal thrombocytopenia is often most marked 1 to 3 days after birth. Marked discrepancies between the neonatal and maternal platelet count are not uncommon. The patient should be informed that no antenatal maternal measurements reliably predict the neonatal platelet count, nor does the maternal response to treatment guarantee a favorable neonatal outcome; conversely, women requiring considerable therapy to manage their platelet count should not assume their neonate has an inordinate risk of bleeding. Only prior neonatal outcome provides a useful predictor of neonatal platelet count in subsequent pregnancies. However, 4 of 6 women who previously delivered severely thrombocytopenic infants treated with IVIG weekly for the last 6 weeks of pregnancy delivered less affected neonates (J.B.B., unpublished data, 2005). The risk of ICH is estimated to be less than 1%, which we think is less than that of percutaneous umbilical vein sampling in severely thrombocytopenic fetuses. We are not aware of evidence that the risk of ICH can be reduced by cesarean section. We measure cord platelet counts in all newborns and serial platelet counts should be obtained during the first week postpartum because the onset of severe thrombocytopenia may be delayed. Sonography, computed tomography scanning, or magnetic resonance imaging of the head should be performed in all neonates born with platelet counts less than 50 000 × 10^9/L even in the absence of symptoms; finding a “silent” ICH demands immediate management and has implications for subsequent pregnancies.
References


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