Annu. Rev. Med. 2005. 56:425–42
doi: 10.1146/annurev.med.56.082103.104644

MANAGEMENT OF ADULT IDIOPATHIC THROMBOCYTOPENIC PURPURA

Douglas B. Cines[1] and Robert McMillan[2]
[1]*Departments of Pathology and Laboratory Medicine and Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104; email: dcines@mail.med.upenn.edu*
[2]*The Scripps Research Institute, La Jolla, California 92037; email: mac.mcmillan@att.net*

Key Words platelets, bleeding, autoantibodies, splenectomy

■ **Abstract** Idiopathic thrombocytopenic purpura (ITP) is a common hematologic disorder manifested by immune-mediated thrombocytopenia. The diagnosis remains one of exclusion, after other thrombocytopenic disorders are ruled out based on history, physical examination, and laboratory evaluation. The goal of treatment is to raise the platelet count into a hemostatically safe range. The disorder is usually chronic, although there is considerable variation in the clinical course and most patients eventually attain safe platelet counts off treatment. However, a subset of patients has severe disease refractory to all treatment modalities, which is associated with considerable morbidity and mortality. This article focuses on the management of primary ITP in adults. We discuss criteria for treatment, the roles of splenectomy and other treatment options along with their side effects, and the management of ITP during pregnancy.

INTRODUCTION

Idiopathic (immune) thrombocytopenic purpura (ITP) is a disorder manifested by immune-mediated thrombocytopenia (1–3). The exact incidence is unknown, but estimates range from 50 to 100 new cases per million persons each year in the United States and Europe, roughly divided between adults and children (2, 4). Childhood ITP differs from adult ITP in pathogenesis, differential diagnosis, and management. Another important distinction is between ITP that occurs as an isolated condition (primary ITP) or in the context of predisposing conditions (secondary ITP). This chapter focuses on the management of primary ITP in adults. The reader is referred elsewhere for comprehensive reviews of ITP in childhood and of secondary ITP (1, 2, 5). Practice guidelines for ITP have been published by the American Society of Hematology (6) and the British Committee for Standards in Haematology General Haematology Task Force (7).

PATHOGENESIS

Platelets from 50%–60% of ITP patients are coated with immunoglobulin G (IgG) antibodies that recognize one or more platelet surface glycoproteins (GP), including GPIIb-IIIa, GPIb-IX, and GPIa-IIa, among others (8). The antibody-coated platelets are recognized by tissue macrophage Fcγ receptors, resulting in their phagocytosis. The fundamental disturbance that leads to the autoantibody production is unknown. T lymphocytes and B lymphocytes that react with platelet autoantigens have been detected in the peripheral blood and spleen of patients with ITP (9, 10), and autoantibody production by cells from the spleen, blood, and bone marrow has been demonstrated (10, 11). Also recognized are a skewing of cytokine production compatible with activation of Th0/Th1 cells (elevated IL-2 and IFNγ, reduced to absent IL-10) and a reduced Th3 response (12–14).

Thrombopoietin levels are normal in ITP, suggesting a normal or increased megakaryocyte mass (15). However, platelet turnover studies in ITP patients often reveal normal or reduced platelet production rather than the increased production that would be expected (16, 17). This suggests either inhibition of platelet production or intramedullary destruction of nascent platelets. Recent in vitro studies, showing reduced megakaryocyte production and maturation in the presence of ITP plasma, provide evidence for autoantibody-induced suppression of megakaryocytopoiesis (18, 19).

The absence of detectable antigen-specific autoantibody on some ITP patients' platelets could indicate autoantibody against other platelet surface proteins, a limitation of assay sensitivity, or the presence of other mechanisms. A recent study suggests that T lymphocyte-induced lysis of platelets may contribute to platelet destruction (20).

PRESENTATION

ITP presents most commonly in women during the second and third decades of life (21), although the disorder can occur in either sex and at any age (4, 22). Patients typically present with petechiae or purpura that develop over several days, accompanied by platelet counts of 1000–20,000/μl, although onset can be insidious. Severe cutaneous bleeding, epistaxis, gingival bleeding, hematuria, or menorrhagia may develop at platelet counts below 10,000/μl. Spontaneous intracranial hemorrhage or bleeding at other internal sites is uncommon in the absence of severe thrombocytopenia (<5000/μl). Individuals with platelet counts of 30,000–50,000/μl may note easy bruising; platelet counts above 50,000/μl are usually discovered incidentally. An occasional patient presents with bleeding symptoms disproportionate to the platelet count because of antibody-induced platelet

dysfunction (23). Most ITP patients are otherwise in their usual state of health, although some complain of fatigue.

DIAGNOSIS

The diagnosis of primary ITP remains one of exclusion. A careful history is important to exclude drugs that can cause thrombocytopenia (22), familial thrombocytopenia (24), post-transfusion purpura, or disorders associated with secondary ITP (see below). The physical examination shows only evidence of bleeding. The presence of adenopathy or splenomegaly suggests another diagnosis. Blood counts are normal except for the platelet count unless there has been significant bleeding or immune hemolysis. Review of the peripheral blood smear is important to exclude pseudothrombocytopenia (25) and other hematologic conditions. Platelets are often large, but platelets approaching the size of red cells or the finding of unusually small platelets should prompt consideration of an inherited thrombocytopenia (24). A bone marrow examination is not required to establish the diagnosis when the presentation is typical, although it is recommended in patients whose findings suggest other hematologic disorders or in older individuals (>60 y of age) (6). When performed, it reveals normal to increased numbers of megakaryocytes with no dysplastic features on light microscopy. No additional diagnostic studies are required to make a diagnosis of ITP in the typical case (6, 7). The response to therapy provides important additional diagnostic information.

Testing for HIV and/or hepatitis C infection is indicated in at-risk populations (26, 27), but the utility of testing for infection with *Helicobacter pylori* remains controversial (see below). ITP may occur in patients with systemic lupus erythematosus, antiphospholipid syndrome, B-cell neoplasms, immune thyroid disorders, or common variable hypogammaglobulinemia, and in patients who have undergone allogeneic or autologous marrow or stem cell transplantation, among others. The presence of these disorders, other than subclinical thyroid disease, is usually evident. Serologic or other testing in the absence of suggestive signs and symptoms is of limited utility, with the possible exception of testing for antiphospholipid antibodies (28). Approximately 1% of patients with ITP have coexisting immune hemolytic anemia (Evans syndrome) and a smaller percentage have immune neutropenia, which confer a less favorable prognosis.

The utility and necessity of measuring platelet antibodies remains an area where opinions differ. The finding of platelet-bound autoantibodies, using antigen-specific assays, has an estimated sensitivity of 49%–66%, a specificity of 78%–92%, and a positive predictive value of 80%–83% (29–31) when patients with ITP are compared to healthy individuals. Inter-laboratory agreement is 55%–67% (32). A positive antigen-specific assay strongly supports the diagnosis of immune thrombocytopenia, but a negative test cannot rule it out (31). No studies have been reported in which results were used to alter diagnosis or to engineer therapy.

TREATMENT

Management is predicated largely on the severity of bleeding. The goal of treatment is to attain a hemostatic platelet count (>20,000–30,000/μl) while minimizing drug toxicity. Figure 1 shows a treatment algorithm for management of adult chronic

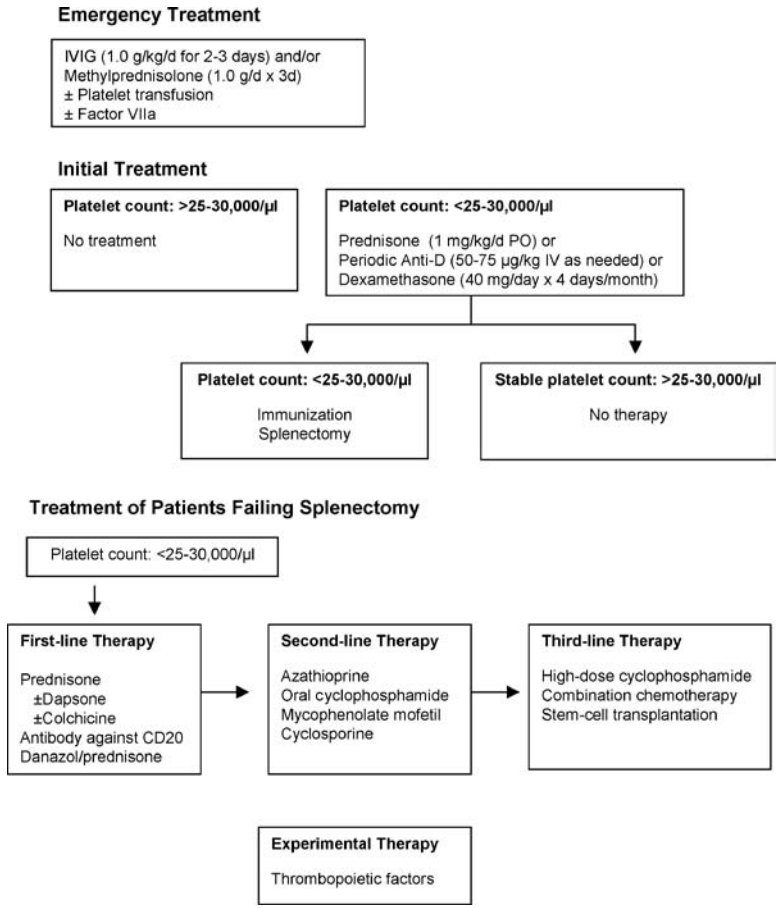

Figure 1 Therapy of adult chronic idiopathic thrombocytopenic purpura in adults (other forms of this disease are treated differently, hence the need for the qualifiers). Emergency treatment is given as needed for extremely low platelet counts (5000–10,000/μl) or for active bleeding. Initial treatment is usually started with prednisone although some physicians prefer periodic anti-D (antibody against erythrocyte RhD antigen) or pulsed dexamethasone. Treatment of refractory patients usually proceeds in the order shown; experimental therapy can be given at any time, depending on the toxicity of the treatment relative to that of the standard therapies.

ITP, and Table 1 lists the drug doses, expected response times, and commonly encountered side effects.

Hospitalization and Emergency Therapy

Hospitalization should be considered for any of the following: (*a*) patients who present for the first time with platelet counts <10,000–20,000/μl in whom responsiveness to therapy has not been established, (*b*) those with previously diagnosed ITP who have extremely low platelet counts (<5000/μl), or (*c*) any patient with profound mucocutaneous, internal, or CNS bleeding. Therapy includes general measures to reduce the risk of bleeding, such as avoidance of drugs that impair platelet function, control of blood pressure, measures to minimize trauma, and local treatments where indicated (e.g., ε-aminocaprioic acid for epistaxis, progesterone for vaginal bleeding). Treatment is initiated immediately with intravenous IgG (IVIG) at a dose of 1.0 g/kg/d for 1–3 consecutive days, and/or intravenous methylprednisolone (1–2 g/d for 1–3 consecutive days) until the platelet count exceeds 50,000/μl (1, 33, 34). IVIG is generally well tolerated but occasional patients develop aseptic meningitis, acute renal failure, pulmonary insufficiency, or hemolysis. Anti-D, at a dose of 75 μg/kg, has been suggested as an alternative to IVIG, although experience with this agent in the emergency setting is limited (35). Platelet transfusions are given as needed for life- or organ-threatening bleeding (36). Recombinant Factor VIIa may be efficacious in unresponsive patients (37).

Initial Therapy

Most patients are treated initially with prednisone (1.0 mg/kg/d). Anti-D (50–75 μg/kg/IV) can be used in Rh^+ individuals who are intolerant to corticosteroids or have contraindications to their use (35, 38). Anti-D causes a mild hemolytic anemia that is generally well tolerated, although rare cases of severe intravascular hemolysis have been reported (39). Supplemental therapy with IVIG (1.0 g/kg/d for 2 days) should be added if platelet counts remain below 20,000–30,000/μl despite several days of corticosteroids or if bleeding is excessive. In some cases, the addition of IV methylprednisolone (30 mg/kg up to 1 g) may be warranted. Therapy is generally not required at platelet counts above 30,000/μl in the absence of bleeding or predisposing comorbid conditions such as uncontrolled hypertension, active peptic ulcer disease, recent surgery, or head trauma (6).

There is no consensus as to the optimal duration of treatment. We generally continue treatment with corticosteroids for a minimum of 3–4 weeks or until a response occurs. Response rates of 50%–90% are reported depending on the intensity and duration of therapy, but only 20%–30% of patients enter a stable remission once a course of steroids has been completed (6, 40–42). Recent reports that a higher proportion of patients will attain a long-term response if treated initially with dexamathasone (40 mg/d for 4 d/mo) (43) or anti-D (44) than if treated with prednisone require confirmation and longer follow-up. Most patients relapse as the dose of prednisone is lowered, and many of these will require

TABLE 1 Characteristics of the treatments used in refractory chronic idiopathic thrombocytopenic purpura

Therapy	Dose[a]	Response time	Common side effects
Prednisone	1–1.5 mg/kg PO qd	1–4 weeks	Hypokalemia, gastric upset, sodium and fluid retention, hyperglycemia, hypertension, myopathy, osteoporosis, infection risk, psychosis
Dexamethasone	40 mg PO qd × q4 weeks	1–4 weeks	Same as for prednisone
Rituximab	375 mg/M^2 IV q4 weeks × 4	3–4 weeks	Infusional symptoms: fever, chills, headache, bronchospasm Severe B cell reduction and potential for infection
Danazol	200 mg PO qid	3–6 months	Weight gain, fluid retention, seborrhea, hirsutism, vocal changes, amenorrhea, acne, headache, liver toxicity, thrombocytopenia
Colchicine	0.6 mg PO tid	4–8 weeks	Diarrhea (may limit therapy), nausea, vomiting
Dapsone	75–100 mg PO qd	4–8 weeks	Hemolysis, agranulocytosis, aplastic anemia, exfoliative dermatitis, toxic hepatitis, choleostatic jaundice, peripheral neuropathy
Cyclophosphamide	150 mg PO qd	6–8 weeks	Cytopenias, hemorrhagic cystitis, GI symptoms, sterility, secondary malignancies[b]
Azathioprine	150 mg PO qd	2–10 months	Cytopenias, GI symptoms, secondary malignancies[b]
Cyclosporine	1.25–2.5 mg/kg PO bid	Variable	Renal insufficiency, hepatotoxicity, hypertension, tremor, hirsutism, gum hyperplasia, hypomagnesemia, secondary malignancies[b]
Mycophenolate mofetil	0.5–1.0 g PO bid	3–4 weeks	Diarrhea, leukopenia, headache, secondary malignancies[b]
High-dose cyclophosphamide	1.0–1.5 g/M^2 IV q 4 weeks	1–4 weeks	Cytopenias, hemorrhagic cystitis, GI symptoms, alopecia, sterility, cardiomyopathy, secondary malignancies[b]
Combination chemotherapy	Several combinations (64)	1–4 weeks	Cytopenias, hemorrhagic cystitis, alopecia, dermatitis, anaphylaxis, GI symptoms, sterility, cardiomyopathy, mucositis, secondary malignancies[b]

(*Continued*)

TABLE 1 (*Continued*)

Therapy	Dose[a]	Response time	Common side effects
Vincristine	1–2 mg IV/week	7–10 days	Peripheral neuropathy, alopecia, constipation, local corrosive effects if extravasated
Vinblastine	5–10 mg IV/week	7–10 days	Leukopenia, alopecia, constipation, local corrosive effects if extravasated
Staph A column	6 treatments	1–2 weeks	Generalized pain, fever, chills, rash, nausea, vomiting, respiratory distress, localized vasculitis

[a]Abbreviations: PO, by mouth; IV, intravenous; SC, subcutaneously; qd, daily; bid, 2 times daily; tid, 3 times daily; qid, 4 times daily; GI, gastrointestinal.

[b]Lymphoproliferative disorders or acute leukemia have occurred in patients with other disorders receiving these drugs.

alternative therapy. Failure to respond to prednisone, anti-D, and IVIG should prompt reconsideration of the diagnosis, and a bone marrow evaluation should be performed if not done previously.

Role of *Helicobacter pylori*

Early studies from Italy and Japan (45, 46) reported an increased incidence of *H. pylori* infection in ITP patients and persistent partial or complete remissions in many patients upon its eradication. However, a recent prospective study in the United States showed no increased incidence of *H. pylori* in ITP patients and no platelet response after its eradication (47). A multi-institutional prospective randomized study is planned, which should help define the role of *H. pylori* in ITP. In the meantime, no evidence-based recommendations can be made about *H. pylori* testing and/or treatment in chronic ITP.

Splenectomy

Splenectomy remains the mainstay of subsequent therapy in adults. The timing of the procedure depends on disease severity, side effects of prior therapy, extent of physical activity, and patient preference. Most hematologists recommend splenectomy within 3–6 months if >10–20 mg of prednisone per day is required, although others recommend a more protracted period of watchful waiting. IVIG, anti-D, or pulse doses of corticosteroids are used to boost the platelet count prior to surgery, although splenectomy has been performed safely at exceedingly low platelet counts. Prophylactic platelet transfusions are generally unnecessary. Approximately 75%–85% of patients attain an initial hemostatic response after splenectomy (6, 40, 48, 49); of these, 25%–40% will relapse within 5–10 y (40, 50). Responses cannot be predicted through routinely available measures, but patients totally refractory to

prior treatment fare less well, as do the elderly (48), patients with secondary forms of ITP (5), and perhaps those with an hepatic sequestration pattern of platelet clearance (51). The outcomes of laparascopic and conventional transabdominal approaches are comparable (52), although laparascopic surgery hastens recovery. Splenic irradiation is reserved for those in whom splenectomy is indicated but hazardous (53).

The major risk of splenectomy is overwhelming bacterial sepsis, which occurs in $<1\%$ of adults with uncomplicated ITP (54). Immunization with polyvalent pneumoccocal, *Hemophilus influenzae* Type B, and quadrivalent meningococcal polysaccharide vaccines, depending on age and immunization history, should be given at least two weeks prior to splenectomy (55, 56). Life-long use of phenoyxmethylpenicillin (250–500 mg PO bid) or erythromycin (500 mg PO bid) has been recommended in a recent guideline from the United Kingdom (7) but is not used routinely in the United States. Revaccination for pneumococcus every 5–10 y is recommended. Some argue for the availability of fresh antibiotics at home and the use of a MedAlert bracelet. At the least, all febrile illnesses demand careful evaluation, and prophylactic IV antibiotics should be strongly considered at the onset of any systemic illness with fever $\geq 101^{\circ}$F until sepsis is ruled out.

Management of Patients Refractory to Splenectomy

About 40%–50% of ITP patients are characterized as refractory, either because they do not respond to splenectomy or because they relapse after an initial response and require additional treatment. Refractory patients often respond slowly to subsequent treatment, have significant morbidity due to ITP and its therapy, and have a mortality rate of $\sim$8%–16% at last follow-up (57–59). As reported recently (60), there are few randomized, controlled trials to support the effectiveness of any therapy for refractory ITP patients; treatment recommendations are based on small, uncontrolled studies and the authors' experience.

A recent study (59), which reported the long-term outcome of 105 refractory adult ITP patients (median follow-up 110 months), showed that 75 patients eventually attained a stable remission. Stable remission was defined as a platelet count $>30{,}000/\mu$l either off all therapy (51 patients) or on maintenance therapy (24 patients). Whether these remissions were due to therapy or reflect the natural history of the disease cannot be determined. On average, remissions occurred slowly with a mean time to remission of $\sim$4 y.

CRITERIA FOR THERAPY In general, sedentary patients with stable platelet counts $>25{,}000$–$30{,}000/\mu$l require no treatment; patients with an active life style may require higher counts. Treatment is necessary for those with lower platelet counts or active bleeding. Therapy should be individualized, depending on the patient's level of activity and comorbid risk factors that predispose to bleeding, and may need to be altered in response to other clinical situations. For example, alkylating agents should be avoided, if possible, in younger adults and those wishing to have

children, and other medications may adversely affect comorbid conditions (bone, cardiac or prostate disease, etc.). Elderly patients are more likely to have severe bleeding and suffer debilitating side effects of therapy. Prior to initiating additional treatment, refractory patients should be evaluated for the presence of an accessory spleen with either magnetic resonance imaging or with a sensitive scanning method (e.g., scan using radiolabeled heat-damaged red cells). If an accessory spleen is present, its removal should be seriously considered, although durable response rates are <25%.

TREATMENT APPROACH The risk from the patient's disease must be weighed against the risk of therapy and its likelihood of success. The presence of severe mucosal, CNS, or other internal bleeding will require concurrent emergency therapy (see above) that may be repeated as often as needed until the thrombocytopenia is controlled with specific forms of therapy. The following treatment progression is recommended, although the individual clinical situation may call for modifications. Most treatments require the concomitant use of corticosteroids to stabilize the platelet count during the early phases of therapy. References concerning the individual treatments can be obtained from published reviews (1, 6, 40).

FIRST-LINE THERAPY First-line therapeutic agents include prednisone, rituximab, and danazol. These agents have moderate risk and should be used in the order described below.

Prednisone (1.0 mg/kg/d) is the drug of choice in refractory patients if safe platelet counts can be maintained on doses acceptable for long-term use ($\leq$10 mg/d). Some patients who require small doses of prednisone to maintain safe platelet counts can be switched successfully to colchicine (0.6 mg PO bid or tid) (61) or dapsone (75 mg/d PO) (62) to avoid the side effects of corticosteroids. These drugs are given initially with prednisone and the latter is then tapered slowly and discontinued. Patients should be screened for erythrocyte glucose-6-phosphate dehydrogenase deficiency prior to initiating dapsone to avoid the risk of severe hemolysis. Some physicians have used pulsed dexamethasone (40 mg/d $\times$ 4 d every 4 weeks for 4–6 cycles) as an alternative to prednisone (63). Responses are usually quicker, but side effects are more prominent.

Rituximab, a chimeric anti-CD20 monoclonal antibody, is indicated for patients who fail corticosteroids or require doses unacceptable for long-term use. Responses to rituximab (375 mg/m^2 IV q week $\times$ 4) are usually noted within 3–4 weeks after the first infusion but may occur as late as 3–4 months. A stable complete or partial remission occurs in about one third of treated patients, although long-term follow-up is not yet available (64). Most side effects are infusion-related and usually occur during the first infusion (fever, chills, hypotension, bronchospasm, etc.). Profound and prolonged peripheral B-cell depletion is universal, but serious infection is rare. Severe side effects, including death from the side effects of infusion, have occurred during the treatment of patients with other disorders. Preliminary experience suggests that patients who relapse after

rituximab therapy will often respond to subsequent courses. The long-term effect of treatment on immune surveillance, if any, is unknown.

Danazol (200 mg PO qid) is given initially with full-dose prednisone (1 mg/kg/d) (65). Responses occur slowly, and therapy should be continued for 3–6 months before it is abandoned. In responding patients, prednisone is gradually tapered and, if possible, stopped. Danazol should be continued at full doses for at least 1 y and then tapered slowly by 50 mg/d every 4 months. Liver function should be monitored monthly, at least initially. Some patients require continuous therapy, with or without low-dose prednisone, to maintain their remission.

SECOND-LINE THERAPY Oral cyclophosphamide or azathioprine should be used next. Responses to cyclophosphamide are more rapid but the risk of serious side effects is greater. Therefore, drug selection depends on the urgency of the clinical situation because the overall response rates are similar (20%–40%). Cyclosporine and mycophenolate mofetil may also be used, although only a few patients have been studied.

The starting dose for cyclophosphamide is 150 mg PO qd adjusted to maintain mild neutropenia (reviewed in Reference 12). Responses occur within 8–12 weeks, and if the count normalizes, full doses are given for 3 additional months before treatment is stopped. In the event of relapse, the long-term risks (e.g., secondary malignancy, myelodysplasia) must be weighed against the potential benefits of resuming therapy. Patients should drink at least 2 liters of liquid daily to prevent hemorrhagic cystitis, and the blood count should be monitored each week.

The typical starting dose for azathioprine is 150 mg PO qd adjusted to maintain mild neutropenia (reviewed in Reference 12). Responses to azathioprine occur slowly, over 3–6 months, and this agent is often stopped prematurely. If a response occurs, therapy should be continued at full doses for 18 months and then gradually discontinued. Should relapse occur, the decision to restart azathioprine must be balanced against the theoretical risk of complications from long-term use. The response to cyclophosphamide or azathioprine in patients who did not respond to the other agent is unknown.

The suggested dose for cyclosporine is 1.25–2.5 mg/kg PO bid; doses are adjusted based on cyclosporine and creatinine levels. The authors of one study noted 5 complete and 5 partial remissions among 18 post-splenectomy patients; 30% of patients discontinued treatment due to side effects (hypertension, myalgias and headaches) (68).

Mycophenolate mofetil (69) has also been used, but few patients have been studied. In one study, responses were noted in 15 of 23 patients with durations ranging from 1 to 39 months. Treatment is begun with 500 mg PO bid and the dose is increased to 1000 mg PO bid after 2 weeks. Minimal side effects have been noted.

THIRD-LINE THERAPY High-dose cyclophosphamide and combination chemotherapy are third-line treatments that should be reserved for patients who are refractory

to the above treatments and who have life-threatening symptoms or extremely low platelet counts ($<10{,}000/\mu l$). High-dose cyclophosphamide should be given first because it is easier to administer and costs less. If severe neutropenia occurs (neutrophils $<0.5 \times 10^3/\mu l$), prophylactic antibiotics should be given until the counts reach safe levels.

High-dose cyclophosphamide therapy (70) is given at a dose of 1.0–1.5 g/m^2 at 4-week intervals. Therapy should be stopped if there is no response after two courses, and responding patients should receive at least three courses even if the platelet count has normalized. A high fluid intake is mandatory (3–4 liters daily, either orally or intravenously, during therapy and for at least 3 d afterwards). Frequent blood counts are required during the first two weeks and at least weekly thereafter because neutropenia is common.

Various combinations of chemotherapeutic agents have been used successfully, although only small numbers of patients have been treated (71). In one study, the long-term outcome of 12 patients (follow-up 35–150 months) included 5 complete remissions and 1 partial remission (72). As with pulsed cyclophosphamide, at least 2 liters of fluid should be given daily for 3–4 d after treatment. Frequent blood counts are necessary to monitor neutropenia.

EXPERIMENTAL THERAPY Potential treatment approaches now being investigated include the use of growth factors, stem cell transplantation, and additonal modes of immunosuppression.

In one study, 2 of 4 patients developed temporary thrombocytosis after receiving marrow growth and development factor, a nonglycosylated, truncated form of human thrombopoietin (73). This agent is no longer used clinically owing to unacceptable side effects (thrombocytopenia in normal recipients and patients with malignancies). A recent dose-finding study using AMG 531, a molecule that activates the thrombopoietin receptor, showed a temporary increase in the platelet count in 8 of 12 ITP patients (5 splenectomy failures) at a dose of ≥ 3.0 $\mu g/kg$ (74).

One group has reported results of stem cell transplantation in 14 patients with refractory ITP whose course has been monitored for at least 6 months (75). Of these, 6 patients attained stable platelet counts $>100{,}000/\mu l$ and 2 had partial responses (follow-up 9–42 months). There were no deaths associated with the procedure and no major complications.

Initial trials of immunosuppression using a humanized monoclonal antibody to CD154 that blocks B-cell costimulatory activity. The trials showed efficacy (66, 67), but were temporarily discontinued because of thrombosis in some patients receiving treatment for other disorders.

OTHER TREATMENTS Vinca alkaloids are now used infrequently because responses are almost always transient and because treatment with vincristine is complicated by peripheral neuropathy. Occasionally, patients can be maintained with periodic doses of vinblastine, which is less likely to cause neuropathy. Responses are

sometimes noted with ex vivo perfusion of plasma over staphylococcal protein A columns, but their use is limited by occasional severe side effects.

NONSPECIFIC MEASURES TO CONTROL BLEEDING ε–aminocaproic acid is used to control mucosal hemorrhage. A loading dose of 0.1 g/kg is given over 30–60 min followed by 6 g every 6 h. Despite many potential side effects, few were noted in two studies and the response was impressive (76). Tranexamic acid mouthwash has been used successfully in some patients with oral bleeding, and progestational agents may be of use in patients with menorrhagia.

IDIOPATHIC THROMBOCYTOPENIC PURPURA AND PREGNANCY

ITP occurs in 0.1–1/1000 pregnancies and accounts for ~3% of cases of thrombocytopenia in pregnant women at delivery (77). Pregnancy is generally not discouraged in women with ITP although maternal and fetal complications do occur and additional monitoring and therapy may be needed. Several comprehensive reviews have been published (7, 78, 79). In addition to the differential diagnosis common to all patients with possible ITP, consideration should be given to causes of thrombocytopenia that are confined to or more common during pregnancy, including pregnancy-induced hypertension and related conditions such as HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet count), obstetrical causes of disseminated intravascular coagulation, microangiopathic hemolytic processes, and gestational thrombocytopenia (80). The latter, also referred to as incidental or benign thrombocytopenia of pregnancy, is found in 5%–8% of healthy women with an uneventful pregnancy and accounts for ~75% of all cases of thrombocytopenia at term (81). Thrombocytopenia is generally mild (platelet counts >70,000/μl in 95% of cases), and there is no impact on the health of the mother or fetus. Platelet counts generally return to normal within 2 months postpartum. ITP should be suspected if severe isolated thrombocytopenia is detected early in pregnancy, but the distinction from gestational thrombocytopenia may be problematic in the absence of a prenatal platelet count because both entities are diagnoses of exclusion.

Platelet counts fall during normal pregnancy. In women with ITP, counts should be monitored at least monthly through the first two trimesters, biweekly in the third, and weekly as term approaches. Corticosteroids can exacerbate gestational diabetes, bone loss, hypertension, and perhaps abruption and prematurity (78). Splenectomy should be avoided if possible, and deferred to the second trimester when necessary, to avoid abortion. Danazol, cyclophosphamide, vinca alkaloids, and other potentially teratogenic agents (with the possible exception of azathioprine) are also to be avoided. Anti-D appears to be safe and effective, although experience is limited (82). IVIG tends to be used more commonly than in nonparous patients. Ideally, maternal platelet counts should be maintained above 30,000/μl throughout pregnancy and above 50,000/μl near term to minimize the need for platelet transfusions in the event a cesarean section is required (6, 7, 83).

Postpartum bleeding is uncommon after vaginal delivery, even in women with severe thrombocytopenia (78, 79). Blood loss during cesarean section varies inversely with platelet counts below 50,000/μl (78). Opinions vary as to the minimal platelet count (50,000–100,000/μl) required for epidural anesthesia (7, 84). Criteria for the use of heparin prophylaxis after cesarean section have been reviewed (7). ITP is not a contraindication to breast-feeding.

Approximately 4% of the neonates are born with profound thrombocytopenia (platelets $<$20,000/μl), but few have platelet counts below 5000/μl unless alloantibodies are also present (85). Marked discrepancies between the neonatal and maternal platelet count are not usual. No antenatal measurements reliably predict the neonatal platelet count, and maternal response to treatment does not guarantee a favorable neonatal outcome. Only prior neonatal outcome provides a useful predictor of the neonatal platelet count in subsequent pregnancies (86). The risk of intracranial hemorrhage is estimated at $<$1%, which is probably lower than that of percutaneous umbilical vein sampling in severely affected neonates (7, 77). There is no evidence that this risk can be reduced by cesarean section (87) or maternal therapy. Current practice is to base the mode of delivery solely on obstetrical considerations (7, 77). A cord platelet count should be measured in all newborns, and serial platelet counts should be obtained during the first week postpartum because the onset of severe thrombocytopenia may be delayed. A CNS sonogram should be considered in all neonates born with profound thrombocytopenia, even in the absence of symptoms.

The *Annual Review of Medicine* is online at http://med.annualreviews.org

LITERATURE CITED

1. Cines DB, Blanchette VS. 2002. Immune thrombocytopenic purpura. *N. Engl. J. Med.* 346:995–1008
2. George JN, El-Harake MA, Aster RH. 1995. Thrombocytopenia due to enhanced platelet destruction by immunologic mechanisms. In *Williams Hematology*, ed. E Beutler, MA Lichtman, BS Coller, TJ Kipps, pp. 1315–55. New York: McGraw-Hill
3. McMillan R, Imbach P. 2003. Immune thrombocytopenic purpura. In *Thrombosis and Hemorrhage*, ed. J Loscalzo, AI Schafer, pp. 476–95. Philadelphia: Lippincott Williams & Wilkins
4. Frederiksen H, Schmidt K. 1999. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. *Blood* 94:909–13
5. Bussel J, Cines DB. 2000. Idiopathic thrombocytopenic purpura, neonatal alloimmune thrombocytopenia, and post-transfusion purpura. In *Hematology: Basic Principles and Practice*, ed. R Hoffman, EJ Benz Jr, SJ Shattil, et al., pp. 2096–114. Philadelphia: Churchill Livingstone
6. George JN, Woolf SH, Raskob GE, et al. 1996. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 88:3–40
7. Provan D, Newland A, Bolton-Maggs P. 2003. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br. J. Haematol.* 120:574–96
8. McMillan R. 2000. Autoantibodies and

autoantigens in chronic immune thrombocytopenic purpura. *Semin. Hematol.* 37: 239–48

9. Kuwana K, Kaburaki J, Ikeda Y. 1998. Autoreactive T cells to platelet GPIIb-IIIa in immune thrombocytopenic purpura. Role in production of anti-platelet autoantibody. *J. Clin. Invest.* 102:1393–402
10. Kuwana M, Okazaki Y, Kaburaki J, et al. 2003. Spleen is the primary site for activation of platelet-reactive T and B cells in patients with immune thrombocytopenic purpura. *J. Immunol.* 168:3675–82
11. McMillan R, Yelenosky RJ, Longmire RL. 1976. Antiplatelet antibody production by the spleen and bone marrow in immune thrombocytopenic purpura. In *Immunoaspects of the Spleen*, ed. JR Battisto, JW Streinlein, pp. 227–37. Amsterdam: North Holland Biomed.
12. Andersson P-O, Olsson A, Wadenvik H. 2002. Reduced transforming growth factor-β1 production by mononuclear cells from patients with active chronic idiopathic thrombocytopenic purpura. *Br. J. Haematol.* 116:862–67
13. Semple JW, Milev Y, Cosgrave D, et al. 1996. Differences in serum cytokine levels in acute and chronic autoimmune thrombocytopenic purpura: relationship to platelet phenotype and antiplatelet T-cell reactivity. *Blood* 87:4245–54
14. Mouzaki A, Theodoropoulou M, Gianakopoulos I, et al. 2002. Expression patterns of Th1 and Th2 cytokine genes in childhood idiopathic thrombocytopenic purpura (ITP) at presentation and their modulation by intravenous immunoglobulin G (IVIg) treatment: their role in prognosis. *Blood* 100:1774–79
15. Emmons RVB, Reid DM, Cohen RL, et al. 1996. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased destruction. *Blood* 87:4068–71
16. Stoll D, Cines DB, Aster RH, et al. 1985. Platelet kinetics in patients with idiopathic thrombocytopenic purpura and moderate thrombocytopenia. *Blood* 65:584–88
17. Heyns AP, Badenhorst PN, Lotter MG, et al. 1986. Platelet turnover and kinetics in immune thrombocytopenic purpura: results with autologous 111-In-labeled and homologous 51-Cr-labeled platelets differ. *Blood* 67:86–92
18. Chang M, Nakagawa PA, Williams SA, et al. 2003. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis *in vitro*. *Blood* 102:887–95
19. McMillan R, Wang L, Tomer A, et al. 2004. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult chronic ITP patients. *Blood* 103:1364–69
20. Olsson B, Andersson P, Jernas M, et al. 2003. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat. Med.* 9:1123–24
21. Doan CA, Bouroncle BA, Wiseman BK. 1960. Idiopathic and secondary thrombocytopenic purpura: clinical study and evaluation of 381 cases over a period of 28 years. *Ann. Intern. Med.* 53:861–76
22. Neylon AJ, Saunders PWG, Howard MR, et al. 2003. Clinically significant newly presented autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br. J. Haematol.* 122:966–74
23. Deckmyn H, De Reys S. 1995. Functional effects of human antiplatelet antibodies. *Semin. Thromb. Hemost.* 21:46–59
24. Drachman JG. 2004. Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood* 103:390–98
25. Bizzao N. 1995. EDTA-dependent pseudothrombocytopenia: a clinical and epidemiological study of 112 cases, with 10 year followup. *Am. J. Hematol.* 50:103–9
26. Hoxie JA. 2000. Hematologic manifestations of HIV infection. In *Hematology: Basic Principles and Practice*, ed. R Hoffman, EJ Benz Jr, SJ Shattil, et al., pp. 2430–58. Philadelphia: Churchill Livingstone

27. Zhang L, Li H, Zhoa H, et al. 2004. Hepatitis C virus-related adult chronic idiopathic thrombocytopenic purpura: experience from a single Chinese center. *Eur. J. Haematol.* 70:196–97
28. Diz-Kucukkaya R, Hacihanefioglu A, Yenerl M, et al. 2001. Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytopenic purpura: a prospective cohort study. *Blood* 98:1760–64
29. Brighton TA, Evans S, Castaldi PA, et al. 1996. Prospective evaluation of the clinical usefulness of an antigen-specific assay (MAIPA) in idiopathic thrombocytopenic purpura and other immune thrombocytopenias. *Blood* 88:194–201
30. Warner MN, Moore JC, Warkentin TE, et al. 1999. A prospective study of protein-specific assays used to investigate idiopathic thrombocytopenic purpura. *Br. J. Haematol.* 104:442–47
31. McMillan R, Wang L, Tani P. 2003. Prospective evaluation of the immunobead assay for the diagnosis of adult chronic immune thrombocytopenic purpura (ITP). *J. Thombos. Haemostas.* 1:485–91
32. Berchtold P, Muller D, Beardsley D, et al. 1997. International study to compare antigen-specific methods used for the measurement of antiplatelet autoantibodies. *Br. J. Haematol.* 96:477–83
33. Godeau B, Chevret S, Varet B, et al. 2002. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomized multicenter trial. *Lancet* 359: 23–29
34. von dem Borne AEG, Vos JJE, Pegels JG, et al. 1988. High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. *BMJ* 296:249–50
35. Newman GC, Novoa MV, Fodero EM, et al. 2001. A dose of 75 μg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 μg/kg/d in adults with immune thrombocytopenic purpura. *Br. J. Haematol.* 112:1076–78
36. Baumann MA, Menitove JE, Aster RH, et al. 1986. Urgent treatment of idiopathic thrombocytopenic purpura with single-dose gammaglobulin infusion followed by platelet transfusion. *Ann. Intern. Med.* 104: 808
37. Culic S. 2003. Recombinant factor VIIa for refractory hemorrhage in autoimmune idiopathic thrombocytopenic purpura. *Br. J. Haematol.* 120:909–10
38. Scaradavou A, Woo B, Woloski BMR, et al. 1997. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood* 89:2689–700
39. Gaines AR. 2000. Acute onset hemoglobinemia and/or hemoglobinuria and sequelae following Rho(D) immune globulin intravenous administration in immune thrombocytopenic purpura patients. *Blood* 95:2523–29
40. McMillan R. 1997. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann. Intern. Med.* 126: 307–14
41. DiFino SM, Lachant NA, Kirshner JJ, et al. 1980. Adult idiopathic thrombocytopenic purpura. Clinical findings and response to therapy. *Am. J. Med.* 69:430–42
42. Den Ottolander GJ, Gratama JW, de Koning J, et al. 1984. Long term follow-up study of 168 patients with immune thrombocytopenia. Implications for therapy. *Scand. J. Haematol.* 32:101–10
43. Cheng Y, Wong RSM, Soo YOY, et al. 2003. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N. Engl. J. Med.* 349:831–36
44. Cooper N, Woloski BMR, Fodero EM, et al. 2002. Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy? *Blood* 99:1922–27 (Abstr.)
45. Emilia G, Longo G, Luppi M, et al. 2001. *Helicobacter pylori* eradication can induce

platelet recovery in idiopathic thrombocytopenic purpura. *Blood* 97:812–14
46. Kohda K, Kuga T, Kogawa K, et al. 2002. Effect of *Helicobacter pylori* eradication on platelet recovery in Japanese patients with chronic idiopathic thrombocytopenic purpura and secondary autoimmune thrombocytopenic purpura. *Br. J. Haematol.* 118:584–88
47. Michel M, Cooper N, Frissora JC, et al. 2003. Does *Helicobacter pylori* initiate or perpetuate immune thrombocytopenic purpura? *Blood* 103:890–96
48. Fabris F, Tassan T, Ramon R, et al. 2001. Age as the major predictive factor of long-term response to splenectomy in immune thrombocytopenic purpura. *Br. J. Haematol.* 112:637–40
49. Radaelli F, Faccini P, Goldaniga M, et al. 2002. Factors predicting response to splenectomy in adult patients with idiopathic thrombocytopenic purpura. *Haematologica* 85:1040–44
50. Stasi R, Stipa E, Masi M, et al. 1995. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. *Am. J. Med.* 98:436–42
51. Najean Y, Rain J-D, Billotey C. 1997. The site of destruction of autologous ^{111}In-labelled platelets and the efficiency of splenectomy in children and adults with idiopathic thrombocytopenic purpura: a study of 568 patients with 268 splenectomies. *Br. J. Haematol.* 97:547–50
52. Marcaccio MJ. 2000. Laparoscopic splenectomy in chronic idiopathic thrombocytopenic purpura. *Semin. Hematol.* 37: 267–74
53. Calverley DC, Jones GW, Kelton JG. 1992. Splenic radiation for corticosteroid-resistant immune thrombocytopenia. *Ann. Intern. Med.* 116:977–81
54. Lorton JE. 1993. Management of asplenic patients. *Br. J. Haematol.* 84:566–69
55. 1993. Recommendations of the advisory committee on immunization practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. *Morbid. Mortal. Wkly. Rep.* 42:1–11
56. American Academy of Pediatrics, Committee on Infectious Diseases. 2000. Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine and antibiotic prophylaxis. *Pediatrics* 106:362–66
57. Berchtold P, McMillan R. 1989. Therapy of chronic idiopathic thrombocytopenic purpura in adults. *Blood* 74:2309–17
58. Bourgeois E, Caulier MT, Delarozee C, et al. 2003. Long-term follow-up of chronic autoimmune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. *Br. J. Haematol.* 120:1079–88
59. McMillan R, Durette C. 2004. The long-term outcome of adult chronic ITP patients who fail splenectomy. *Blood* 104:956–60
60. Vesely SK, Perdue JJ, Rizvi MA, et al. 2004. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy. *Ann. Intern. Med.* 140:112–20
61. Strother SV, Zuckerman KS, Lo Buglio AF. 1984. Colchicine therapy for refractory idiopathic thrombocytopenic purpura. *Arch. Intern. Med.* 144:2198–200
62. Godeau B, Durand J-M, Roudot-Thoraval F, et al. 1997. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. *Br. J. Haematol.* 97:336–39
63. Caulier MT, Rose C, Roussel MT, et al. 1995. Pulsed high-dose dexamethasone in refractory chronic idiopathic thrombocytopenic purpura: a report on 10 cases. *Br. J. Haematol.* 91:477–79
64. Cooper N, Heddle NM, Haas M, et al. 2004. Intravenous (IV) anti-D and IV immunoglobulin achieve acute platelet increases by different mechanisms: modulation of cytokine and platelet responses to IV anti-D by FcgammaRIIa and FcgammaRIIIa polymorphisms. *Br. J. Haematol.* 124:511–18

65. Ahn YS, Rocha R, Mylvaganam R, et al. 1989. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. *Ann. Intern. Med.* 111: 723–29
66. Vincent J. 1999. http://www.prnewswire.com. Nov. 2
67. Kuwana M, Kawakami Y, Ikeda Y. 2003. Suppression of autoreactive T-cell response to glycoprotein IIb/IIIa by blockade of CD40/CD154 interaction: implication for treatment of immune thrombocytopenic purpura. *Blood* 101:621–23
68. Kappers-Klunne MC, van't Veer MB. 2001. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. *Br. J. Haematol.* 114:121–25
69. Howard J, Hoffbrand AV, Prentice HG, et al. 2002. Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anemia and auto-immune thrombocytopenia purpura. *Br. J. Haematol.* 117:712–15
70. Reiner A, Gernsheimer T, Slichter SJ. 1995. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. *Blood* 85:351–58
71. Figueroa M, Gehlsen J, Hammond D, et al. 1993. Combination chemotherapy in refractory immune thrombocytopenic purpura. *N. Engl. J. Med.* 328:1226–29
72. McMillan R. 2001. Long-term outcomes after treatment for refractory immune thrombocytopenic purpura. *N. Engl. J. Med.* 344:1402–3
73. Nomura S, Dan K, Hotta T, et al. 2001. Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. *Blood* 100:728–30
74. Bussel JB, George JN, Kuter DJ, et al. 2003. An open-label, dose-finding study evaluating the safety and platelet response of a novel thrombopoietic protein (AMG 531) in thrombocytopenic adult patients with immune thrombocytopenic purpura (ITP). *Blood* 102:86a (Abstr.)
75. Huhn RD, Fogarty PF, Nakamura R, et al. 2002. High-dose cyclophosphamide with autologous lymphocyte-depleted peripheral blood stem cell (PBSC) support for treatment of refractory chronic autoimmune thrombocytopenia. *Blood* 101:71–77
76. Bartholomew JR, Salgia R, Bell WR. 1989. Control of bleeding in patients with immune and nonimmune thrombocytopenia with aminocaproic acid. *Arch. Intern. Med.* 149:1959–61
77. Gill KK, Kelton JG. 2000. Management of idiopathic thrombocytopenic purpura in pregnancy. *Semin. Hematol.* 37:275–89
78. Fujimura K, Harada Y, Fujimoto T. 2001. Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates. *Int. J. Hematol.* 75:426–33
79. Webert K, Mittal R, Sigouin C, et al. 2003. A retrospective, 11-year analysis of obstetrical patients with idiopathic thrombocytopenic purpura. *Blood* 4306–11
80. McCrae KR, Samuels P, Schreiber AD. 1992. Pregnancy-associated thrombocytopenia: pathogenesis and management. *Blood* 80:2697–714
81. Burrows RF, Kelton JG. 1993. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N. Engl. J. Med.* 329:1463–66
82. Michel M, Novoa MV, Bussel JB. 2003. Intravenous anti-D as a treatment for immune thrombocytopenic purpura (ITP) during pregnancy. *Br. J. Haematol.* 123:142–46
83. Letsky EA, Greaves M. 1996. Guidelines on the investigation and management of thrombocytopenia in pregnancy and neonatal alloimmune thrombocytopenia. *Br. J. Haematol.* 95:21–26
84. Beilin Y, Zahn J, Comerford M. 1997. Safe epidural analgesia in thirty parturients

with platelet counts between 69,000 and 98,000 mm^3. *Anesth. Analg.* 85:385–88

85. Burrows RF, Kelton JG. 1993. Pregnancy in patients with idiopathic thrombocytopenic purpura: assessing the risks for the infant at delivery. *Obstet. Gynecol. Surv.* 48:781–88
86. Christiaens GCML, Niewenhuis HK, Bussel JB. 1997. Comparison of platelet counts in first and second newborns of mothers with immune thrombocytopenic purpura. *Obstet. Gynecol.* 97:893–98
87. Payne SD, Resnick R, Moore TR, et al. 1997. Maternal characteristics and risk of severe neonatal thrombocytopenia and intracranial hemorrhage in pregnancies complicated by autoimmune thrombocytopenia. *Am. J. Obstet. Gynecol.* 177:149–55

Annual Review of Medicine
Volume 56, 2005

CONTENTS