infection, whereas thrombocytopenia in more advanced stages of HIV infection is often caused by bone marrow failure resulting from megakaryocyte infection with HIV, mycobacterial infection of the bone marrow, and nutritional deficiencies of end-stage HIV disease.

ITP occurs in patients with autoimmune disorders such as systemic lupus erythematosus, inflammatory bowel disease, and nonviral hepatitis. In some patients, ITP is accompanied by autoimmune hemolytic anemia, also called *Evans' syndrome*. The direct Coombs test is usually positive, indicating a warm-reactive autoantibody against erythrocytes. Initial treatment may not be significantly different from that for ITP alone, but chronic Evans' syndrome is thought to respond poorly to splenectomy, unlike ITP alone.

In the setting of systemic lupus erythematosus, ITP may result from factors associated with the autoimmune disease itself, including immune complex deposition on the platelet surface and active vasculitis, both of which may lead to increased platelet clearance and low counts. Therapy for ITP and the underlying autoimmune disorder is usually complementary. When the lupus anticoagulant or anticardiolipin antibody is associated with systemic lupus erythematosus and thrombocytopenia, the diagnosis of secondary antiphospholipid antibody syndrome is made, and this entity most commonly has thromboembolic complications (see Chapter 54).

The first-line treatment of acute ITP in adults is steroids, usually 1 to 2 mg/kg of prednisone per day. Studies have suggested that high-dose dexamethasone given in pulses every 14 or 28 days for six to eight doses may result in superior control of disease. Platelet transfusions typically are not used in ITP because transfused-platelet survival is brief and bleeding complications are uncommon. However, in patients with significant bleeding or who require surgery, platelet transfusions have been safely used and may transiently increase the platelet count, although usually for less than 24 hours.

In patients with acute ITP with severe thrombocytopenia (<5000/μL) or with life-threatening bleeding, high-dose methylprednisolone (1 g/day for 3 days) may be administered alone or in combination with IVIG (1-2 g/kg in divided doses over 2 to 5 days) and platelet transfusion. For recurrent ITP, chronic steroid treatment is often necessary but is usually accompanied by significant side effects. High-dose pulse dexamethasone given for 4 days every 2 weeks is associated with prolonged responses in about two thirds of patients with chronic ITP.

Children and adults with chronic ITP who initially respond to IVIG therapy usually respond well to splenectomy, whereas those who do not respond to IVIG are less likely to have disease remission after splenectomy. More than 50% of chronic ITP patients have some degree of disease remission after splenectomy. If ITP does recur after splenectomy, an accessory spleen must be ruled out, usually by liver and spleen scanning, because Howell-Jolly bodies may still be found.

Recurrent disease often is episodic, especially after viral infections, and these patients can be treated with IVIG. Alternatively, patients who are positive for the blood group Rh(D) antigen can be treated with Rh immunoglobulin (RhoGAM), a preparation of IgG class anti-Rh(D) antibodies. Anti-D induces red cell hemolysis (usually mild), presumably causing Fc receptor blockade of the RES and decreased platelet uptake by the spleen and liver.

Some patients with ITP, especially those with HIV infection, have significant, even fatal, hemoglobinemia or hemoglobinuria after anti-Rh(D) therapy, which should be carefully monitored. Rh immunoglobulin is usually ineffective in patients who have undergone splenectomy. In patients who fail to respond to splenectomy, steroid administration may be avoided by the addition of a combination of IVIG, vincristine, and anti-Rh(D) with danazol and immunosuppressive therapy (e.g., azathioprine).

Some patients with chronic ITP have responded to infusions of the anti-CD20 monoclonal antibody rituximab. Chronic ITP with normal marrow cellularity can respond to stimulation of thrombopoiesis using thrombopoietin mimetics and agonist antibodies, which have shown promise in experimental trials and clinical practice. However, because many patients with chronic ITP never achieve normal platelet counts, the goal for therapy is often to keep platelet counts higher than 30,000/μL to avoid significant bleeding. About 5% of adults with ITP die of chronic, refractory disease and the complications of its therapy.

Drug-Induced Platelet Destruction

Immune-mediated platelet destruction associated with specific drugs is an often overlooked cause of thrombocytopenia. Unlike some of the drugs mentioned earlier (e.g., chemotherapeutic agents) that act by directly suppressing megakaryocyte production, drugs in this category of thrombocytopenia induce an immune response against platelet antigens.

Drugs may induce an autoimmune response by several mechanisms. One is the development of an antibody response against soluble drug molecules. When soluble drugs bind to the platelet membrane, drug-induced antibodies act to destroy circulating platelets through the RES. Other mechanisms of drug-induced thrombocytopenia include formation of an immunogenic neoantigen through drug-platelet interactions (hapten response) with autoantibodies directed against drugs that cross-react with platelet antigens. Occasionally, immune complexes that include the drug and circulating platelets are formed.

Historically, quinidine or quinine-based formulations were among the first classes of drugs to be associated with platelet antibodies. The antibodies can be detected by tests using a drug coupled to a carrier protein. As awareness of drug-induced thrombocytopenia has grown, scores of drugs, including antibiotics, anticonvulsants, psychotropic drugs, and antiplatelet agents, have been reported to mediate platelet destruction (Table 51-2).

Heparin also induces thrombocytopenia, but unlike other drugs, this reaction paradoxically leads to a prothrombotic state. The mechanism of heparin-induced thrombocytopenia and its prothrombotic effects are discussed in greater detail in Chapter 54.

When eliciting the medical history from patients with acute-onset thrombocytopenia, a careful review of all medications, particularly those initiated just before the development of low platelet counts, may help to deduce the cause and reverse the platelet count decline. Regardless of the mechanism of induction, development of thrombocytopenia is temporally related to exposure to the drug and is usually rapid. Discontinuation of the