Some patients do not have reticulocytosis; in them, the antibody may be destroying both reticulocytes and mature erythrocytes.

The mainstay of therapy for AIHA is corticosteroids. Patients are usually treated with 1 to 2 mg/kg of prednisone, and in responding patients, doses are tapered slowly over several months. Patients who fail to respond to prednisone or cannot be tapered off the prednisone can be treated with other immunosuppressive agents, such as cyclophosphamide, azathioprine, chlorambucil, or rituximab. Some patient respond to intravenous immunoglobulin. Splenectomy is effective in many patients who are steroid refractory or steroid resistant, and it is associated with greater sustained response rates than other immunosuppressive therapies in steroid-resistant patients. However, patients who do not respond and who have ongoing hemolysis after splenectomy are at high risk for secondary thromboembolic events.

Warm antibodies mediate *drug-induced hemolysis.* Several mechanisms exist through which drugs may induce AIHA (Table 47-6). Penicillin produces hemolysis by binding to erythrocytes and acting as a hapten; the antibody is directed against the drug, and hemolysis occurs only in the presence of the drug. Type 2 hemolysis is caused by the formation of an antibody-drug complex that binds to the erythrocyte membrane and activates complement. Drugs associated with this type of hemolysis include quinidine, quinine, and rifampin. Still other drugs, including methyldopa and procainamide, cause hemolysis by inducing the production of *true* antierythrocyte antibodies directed against Rh and other RBC antigens. Antibody may persist in the absence of the drug, but not all patients with a positive Coombs test have evidence of hemolysis.

IgM-Mediated (Cold) Hemolytic Anemia

Cold-type immune hemolysis is usually postinfectious. The most common associated infectious agents are *Mycoplasma pneumoniae* and Epstein-Barr virus (EBV). IgM antibodies are produced that are directed against the RBC antigen I *(Mycoplasma)* or i (EBV). The antibodies bind at lower temperatures, present in fingers and toes, and bind complement. During the return to the central circulation, the IgM falls off the RBC, leaving complement bound. The Coombs test is negative for IgG and IgM but positive for complement. Hemolysis is self-limited, is rarely severe, and resolves with supportive therapy. In cases of severe hemolysis requiring transfusion, the patient should be kept warm, and blood should be administered through a blood warmer to minimize further hemolysis.

Cold agglutinin disease is a chronic IgM antibody–mediated hemolysis that is usually seen in association with lymphoproliferative disease. Hemolysis is usually low grade; if severe, it responds poorly to steroids and splenectomy. Acute severe IgM-mediated hemolysis may respond to plasmapheresis. Supportive therapy includes avoidance of exposure to the cold. In the setting of lymphoproliferative disease, patients may respond to immunotherapy with rituximab.

Hemolysis from Causes Extrinsic to the Erythrocyte

Microangiopathic Hemolysis

Microangiopathic hemolytic anemia (MAHA) is caused by traumatic destruction of RBCs as they pass through small vessels. The leading causes of MAHA include thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome (TTP/HUS) (see Table 47-5 and Fig. 47-1). Other causes include pregnancy-related syndromes such as preeclampsia, eclampsia, and the HELLP syndrome (*h*emolysis, *e*levated *l*iver enzyme levels, and *l*ow *p*latelet count); drugs; and metastatic cancers. A similar hemolytic picture can be seen in traumatic hemolysis on a damaged cardiac valve.

The finding of schistocytes (fragmented erythrocytes) on the peripheral blood smear confirms the diagnosis of MAHA (see Fig. 47-2D). The presence of normal prothrombin and partial thromboplastin times supports a diagnosis of TTP/HUS over that of disseminated intravascular coagulation. Diagnosis and management are described further in Chapter 51.

Infection

Hemolysis can be caused by direct infection of RBCs by parasites, as seen in malaria, babesiosis, and bartonellosis. Severe, overwhelming hemolysis can be seen in clostridial sepsis, in which bacterial toxins directly damage the membrane.

TABLE 47-6 DRUG-INDUCED AUTOIMMUNE HEMOLYTIC ANEMIA

TYPE	MECHANISM	COMMON DRUGS IMPLICATED	DIRECT COOMBS TEST	INDIRECT COOMBS TEST
1	Hapten mediated	Penicillin Cephalothin	IgG positive Complement positive or negative	Positive only in the presence of drug
2	Immune complex mediated	Quinine Quinidine Phenacetin Rifampin Isoniazid Tetracycline Chlorpromazine	IgG negative Complement positive	Positive only in the presence of drug
3	True anti-RBC antibody	Methyldopa Levodopa Procainamide Ibuprofen Interferon-α	IgG positive Complement negative	Positive also in absence of drug

IgG, Immunoglobulin G; RBC, red blood cell.