mediated through an increase in inflammatory cytokines and a relative EPO resistance.

Treatment of Normocytic Anemias

The mainstay of therapy for the anemia of chronic inflammation is treatment of the underlying condition and correction of nutritional deficiencies. Iron supplementation should be offered to all patients with a ferritin level lower than 100 ng/mL. Erythroid-stimulating agents (ESAs) have been shown to reduce transfusion needs in many of these patients. However, randomized studies and meta-analyses have shown that their use is associated with an increased incidence of arterial and venous thromboembolic events, an increased risk of mortality from cancer, and a reduced survival time. ESA should be avoided in cancer patients if they are being treated with curative intent, and in all other patients with cancer they should be offered only after a careful discussion of the risks and benefits (grade 1B recommendation).

Anemia of Chronic Kidney Disease

Most patients who have a glomerular filtration rate of less than 30 mL/min have anemia related primarily to low EPO levels. ESAs can help prevent transfusions in this population; however, their use has been associated with an increased risk of stroke, access thrombosis, hypertension, and even mortality in some studies, especially when the hemoglobin levels were normalized. Therefore, most guidelines recommend a target hemoglobin concentration of 10 to 11.5 g/dL when using ESA in patients with chronic kidney disease (grade IB). As in the management of anemia of chronic inflammation, nutritional deficiencies should be corrected before the use of ESAs. The evaluation and treatment of primary marrow failure syndromes and hematologic malignancies are discussed in Chapters 45 and 46, respectively.

EVALUATION OF ANEMIA WITH RETICULOCYTOSIS

An elevated reticulocyte count in the setting of anemia signals a compensatory response by a normal marrow to premature loss of erythrocytes. Hemolysis is the premature destruction of RBCs in the reticuloendothelial system (extrinsic hemolysis) or in blood vessels (intrinsic hemolysis). The only other condition that causes anemia with reticulocytosis is acute bleeding. The differential diagnosis of hemolytic anemia is outlined in Table 47-5.

Whereas examination of the peripheral blood smear is helpful in characterizing any anemia, it is absolutely critical in the evaluation of hemolytic anemia. Morphologic examination of the erythrocytes is helpful in distinguishing immune hemolysis from microangiopathic hemolytic anemia. In addition, other RBC morphologic abnormalities are characteristic for specific diseases such as sickle cell disease (sickled cells), enzyme defects (*bite* cells), and erythrocyte membrane abnormalities (spherocytes and elliptocytes).

Immune Hemolytic Anemia

Immune-mediated hemolysis results from coating of the erythrocyte membrane with antibodies or complement, or both. It may be mediated by immunoglobulin G (IgG) antibodies (*warm* antibody) or by IgM antibodies (*cold* antibody). The designations *warm* and *cold* denote the temperature at which maximal antibody binding takes place, and the clinical syndromes caused by the two types of antibodies are distinct.

TABLE 47-5 DIFFERENTIAL DIAGNOSIS OF HEMOLYTIC ANEMIA

IMMUNE HEMOLYTIC ANEMIA
Immunoglobulin G (warm antibody)–mediated hemolysis
Immunoglobulin M (cold antibody)–mediated hemolysis
HEMOLYSIS FROM CAUSES EXTRINSIC TO THE ERYTHROCYTE
Microangiopathic Hemolysis
Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Preeclampsia, eclampsia, HELLP syndrome
Drugs (mitomycin, cyclosporine, gemcitabine)
Valvular hemolysis
Splenomegaly
Infection (e.g., malaria, babesiosis)
HEMOLYTIC ANEMIA CAUSED BY DISORDERS OF THE ERYTHROCYTE MEMBRANE
Inherited Membrane Abnormalities
Hereditary spherocytosis
Hereditary elliptocytosis
Hereditary pyropoikilocytosis
Acquired Membrane Abnormalities
Paroxysmal nocturnal hemoglobinuria
Spur cell anemia
HEMOLYSIS CAUSED BY ERYTHROCYTE ENZYMOPATHIES
Glucose-6-phosphate dehydrogenase deficiency
Other enzyme deficiencies
HEMOGLOBINOPATHIES
Sickle cell disease
Other sickle syndromes
Thalassemia

HELLP, Hemolysis, elevated liver enzymes, and low-platelet count in association with preeclampsia.

The diagnosis of hemolytic anemia is based on the direct and indirect antiglobulin (Coombs) tests. To perform a direct Coombs test, the patient's erythrocytes are mixed with antisera or monoclonal antibodies directed against human immunoglobulins and human complement. The cells are then monitored for agglutination, the presence of which confirms the presence of antibody or complement on the patient's RBCs. The indirect Coombs test is performed by mixing the patient's serum with ABO-compatible erythrocytes and then combining this mixture with antisera against IgG; the indirect Coombs tests allows for the evaluation of antibody in the patient's serum.

IgG-Mediated (Warm) Hemolytic Anemia

Classic autoimmune hemolytic anemia (AIHA) is caused by IgG antibody directed against erythrocyte antigens. Warm type hemolysis may be primary (idiopathic) or associated with autoimmune disease, lymphoproliferative disorders, or drugs. Patients exhibit acute anemia, jaundice, and an elevated reticulocyte count. Some patients have splenomegaly. The peripheral blood smear demonstrates spherocytes (see Fig. 47-2E). Laboratory analysis confirms the presence of IgG on the erythrocyte membrane, as demonstrated by a positive Coombs test; in some patients, the erythrocytes are also coated with complement.