than mild anemia develops, reintervention to correct regurgitation may be required.

Infection By far the most frequent infectious cause of HA, in endemic areas, is malaria (Chap. 248). In other parts of the world, the most frequent direct cause is probably Shiga toxin–producing *E. coli* O157:H7, now recognized as the main etiologic agent of HUS, which is more common in children than in adults (Chap. 149). Life-threatening intravascular hemolysis, due to a toxin with lecithinase activity, occurs with *Clostridium perfringens* sepsis, particularly following open wounds, septic abortion, or as a disastrous accident due to a contaminated blood unit. Rarely, and if at all in children, HA is seen with sepsis or endocarditis from a variety of organisms. In addition, bacterial and viral infections can cause HA by indirect mechanisms (see above section on G6PD deficiency and Table 129-6).

Immune Hemolytic Anemias These can arise through at least two distinct mechanisms. (1) There is a true autoantibody directed against a red cell antigen, i.e., a molecule present on the surface of red cells. (2) When an antibody directed against a certain molecule (e.g., a drug) reacts with that molecule, red cells may get caught in the reaction, whereby they are damaged or destroyed. Because the antibodies involved differ in optimum reactivity temperatures, they are classified in the time-honored categories of "cold" and "warm" (Table 129-7). Autoantibody-mediated HAs may be seen in isolation (when they are called *idiopathic*) or as part of a systemic autoimmune disorder such as systemic lupus erythematosus. Here we discuss the most distinctive clinical pictures.

AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) Once a red cell is coated by an autoantibody (see [1] above), it will be destroyed by one or more mechanisms. In most cases, the Fc portion of the antibody will be recognized by the Fc receptor of macrophages, and this will trigger erythrophagocytosis. Thus, destruction of red cells will take place wherever macrophages are abundant, i.e., in the spleen, liver, or bone marrow; this is called *extravascular hemolysis* (Fig. 129-8). Because of the special anatomy of the spleen, this organ is particularly efficient in trapping antibody-coated red cells, and often this is the predominant site of red cell destruction. In some cases, the nature of the antibody is such (usually an IgM antibody) that the antigen-antibody complex on the surface of red cells is able to activate complement (C); as a result, a large amount of membrane attack complex will form, and the red cells may be destroyed directly; this is known as *intravascular hemolysis*.

Clinical features AIHA is a serious condition; without appropriate treatment, it may have a mortality of approximately 10%. The onset is often abrupt and can be dramatic. The hemoglobin level can drop, within days, to as low as 4 g/dL; the massive red cell removal will produce jaundice; and sometimes the spleen is enlarged. When this triad is present, the suspicion of AIHA must be high. When hemolysis is (in part) intravascular, the telltale sign will be hemoglobinuria, which the patient may report or about which we must enquire or test for. The diagnostic test for AIHA is the direct antiglobulin test developed in 1945 by R. R. A. Coombs and known since by this name. The beauty of this test is that it detects directly the pathogenetic mediator of the disease, i.e., the presence of antibody on the red cells themselves. When the test is positive, it clinches the diagnosis; when it is negative, the diagnosis is unlikely. However, the sensitivity of the Coombs test varies depending on the technique that is used, and in doubtful cases, a repeat in a specialized lab is advisable; the term *Coombs-negative AIHA* is a last resort. In some cases, the autoantibody has a defined identity; it may be specific for an antigen belonging to the Rhesus system (it is often anti-e). In many cases, it is regarded as "nonspecific" because it reacts with virtually all types of red cells.

When AIHA develops in a person who is already known to have, for instance, systemic lupus or chronic lymphocytic leukemia (Table 129-7), we call it a complication; conversely, when AIHA presents on its own, it may be a pointer to an underlying condition that we ought to seek out. In both cases, what brings about AIHA remains, as in other autoimmune disorders, obscure. In some cases, AIHA can be associated, on first presentation or subsequently, with autoimmune thrombocytopenia (Evans' syndrome).

TABLE 129-7 CLASSIFICATION OF ACQUIRED IMMUNE HEMOLYTIC ANEMIAS

	Type of Antibody	
Clinical Setting	**Cold, Mostly IgM, Optimal Temperature 4–30°C**	**Warm, Mostly IgG, Optimal Temperature 37°C; or Mixed**
Primary	CAD	AIHA (idiopathic)
Secondary to viral infection	EBV CMV Other	HIV Viral vaccines
Secondary to other infection	Mycoplasma infection: paroxysmal cold hemoglobinuria	
Secondary to/associated with other disease	CAD in: Waldenström's disease Lymphoma	AIHA in: SLE CLL Other malignancy Chronic inflammatory disorders (e.g., IBD) After allogeneic HSCT
Secondary to drugs: drug-induced immune hemolytic anemia	Small minority (e.g., with lenalidomide)	Majority: currently most common culprit drugs are cefotetan, ceftriaxone, piperacillin
	Drug-dependent: antibody destroys red cells only when drug present (e.g., rarely penicillin)	
	Drug-independent: antibody can destroy red cells even when drug no longer present (e.g., methyldopa)	

Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

TREATMENT AUTOIMMUNE HEMOLYTIC ANEMIA

Severe acute AIHA can be a medical emergency. The immediate treatment almost invariably includes transfusion of red cells. This may pose a special problem because, if the antibody involved is nonspecific, all of the blood units cross-matched will be incompatible. In these cases, it is often correct, paradoxically, to transfuse incompatible blood, with the rationale being that the transfused red cells will be destroyed no less but no more than the patient's own red cells, but in the meantime, the patient stays alive. A situation like this requires close liaison and understanding between the clinical unit treating the patient and the blood transfusion/serology lab. Whenever the anemia is not immediately life-threatening, blood transfusion should be withheld (because compatibility problems may increase with each unit of blood transfused), and medical treatment started immediately with prednisone (1 mg/kg per day), which will produce a remission promptly in at least one-half of patients. Rituximab (anti-CD20) was regarded as second-line treatment, but it is increasingly likely that a relatively low dose (100 mg/wk × 4) of rituximab together with prednisone will become a first-line standard. It is especially encouraging that this approach seems to reduce the rate of relapse, a common occurrence in AIHA. For patients who do relapse or are refractory to medical treatment, one may have to consider splenectomy, which, although it does not cure the disease, can produce significant benefit by removing a major site of hemolysis, thus improving the anemia and/or reducing the need for other therapies (e.g., the dose of prednisone). Since the introduction of rituximab, azathioprine, cyclophosphamide, cyclosporine, and intravenous immunoglobulin have become second- or third-line agents. In very rare severe refractory cases, either autologous or allogeneic hematopoietic stem cell transplantation may have to be considered.