

is recognized, in most cases, no specific treatment is needed. However, if the anemia is severe, it may be a medical emergency, especially in children, requiring immediate action, including blood transfusion. This has been the case with an antimalarial drug combination containing dapsone (called Lapdap, introduced in 2003) that has caused severe acute hemolytic episodes in children with malaria in several African countries; after a few years, the drug was taken off the market. If there is acute renal failure, hemodialysis may be necessary, but if there is no previous kidney disease, recovery is the rule. The management of NNJ associated with G6PD deficiency is no different from that of NNJ due to other causes.

In cases with CNSHA, if the anemia is not severe, regular folic acid supplements and regular hematologic surveillance will suffice. It will be important to avoid exposure to potentially hemolytic drugs, and blood transfusion may be indicated when exacerbations occur, mostly in concomitance with intercurrent infection. In rare patients, regular blood transfusions may be required, in which case appropriate iron chelation should be instituted. Unlike in HS, there is no evidence of selective red cell destruction in the spleen; however, in practice, splenectomy has proven beneficial in severe cases.

Other abnormalities of the redox system As mentioned above, GSH is a key player in the defense against oxidative stress. Inherited defects of GSH metabolism are exceedingly rare, but each one can give rise to chronic HA (Table 129-4). A rare, peculiar, usually self-limited severe HA of the first month of life, called *infantile poikilocytosis*, may be associated with deficiency of glutathione peroxidase (GSHPX) due not to an inherited abnormality, but to transient nutritional deficiency of selenium, an element essential for the activity of GSHPX.

PYRIMIDINE 5'-NUCLEOTIDASE (P5N) DEFICIENCY P5N is a key enzyme in the catabolism of nucleotides arising from the degradation of nucleic acids that takes place in the final stages of erythroid cell maturation. How exactly its deficiency causes HA is not well understood, but a highly distinctive feature of this condition is a morphologic abnormality of the red cells known as *basophilic stippling*. The condition is rare, but it probably ranks third in frequency among red cell enzyme defects (after G6PD deficiency and PK deficiency). The anemia is lifelong, of variable severity, and may benefit from splenectomy.

Familial (Atypical) Hemolytic-Uremic Syndrome The term *familial (atypical) hemolytic-uremic syndrome* is used to designate a group of rare disorders, mostly affecting children, characterized by microangiopathic HA with presence of fragmented erythrocytes in the peripheral blood smear, thrombocytopenia (usually mild), and acute renal failure. (The word *atypical* is part of the phrase for historical reasons; it was hemolytic-uremic syndrome [HUS] caused by infection with *Escherichia coli* producing the Shiga toxin that was regarded as *typical*). The

genetic basis of atypical HUS (aHUS) has been elucidated. Studies of >100 families have revealed that those family members who developed HUS had mutations in any one of several genes encoding complement regulatory proteins: complement factor H (CFH), CD46 or membrane cofactor protein (MCP), complement factor I (CFI), complement component C3, complement factor B (CFB), and thrombomodulin. Thus, whereas all other inherited HAs are due to intrinsic red cell abnormalities, this group is unique in that hemolysis results from an inherited defect external to red cells (Table 129-1). Because the regulation of the complement cascade has considerable redundancy, in the steady state, any of the above abnormalities can be tolerated. However, when an intercurrent infection or some other trigger activates complement through the alternative pathway, the deficiency of one of the complement regulators becomes critical. Endothelial cells get damaged, especially in the kidney; at the same time, and partly as a result of this, there will be brisk hemolysis (thus, the more common Shiga toxin-related HUS [Chap. 149] can be regarded as a phenocopy of aHUS). aHUS is a severe disease, with up to 15% mortality in the acute phase and up to 50% of cases progressing to end-stage renal disease. Not infrequently, aHUS undergoes spontaneous remission; but because its basis is an inherited abnormality, it is not surprising that, given renewed exposure to a trigger, the syndrome will tend to recur; when it does, the prognosis is always serious. The standard treatment has been plasma exchange, which will supply the deficient complement regulator. The anti-C5 complement inhibitor eculizumab (see below) was found to greatly ameliorate the microangiopathic picture, with improvement in platelet counts and in renal function, thus abrogating the need for plasma exchange. It remains to be seen for how long eculizumab treatment will have to be continued in individual patients and whether it will influence the controversial issue of kidney (and liver) transplantation.

ACQUIRED HEMOLYTIC ANEMIA

Mechanical Destruction of Red Cells Although red cells are characterized by the remarkable deformability that enables them to squeeze through capillaries narrower than themselves for thousands of times in their lifetime, there are at least two situations in which they succumb to shear, if not to wear and tear; the result is intravascular hemolysis, resulting in hemoglobinuria (Table 129-6). One situation is acute and self-inflicted, *march hemoglobinuria*. Why sometimes a marathon runner may develop this complication, whereas on another occasion, this does not happen, we do not know (perhaps her or his footwear needs attention). A similar syndrome may develop after prolonged barefoot ritual dancing or intense playing of bongo drums. The other situation is chronic and iatrogenic (it has been called *microangiopathic hemolytic anemia*). It takes place in patients with prosthetic heart valves, especially when paraprosthetic regurgitation is present. If the hemolysis consequent on mechanical trauma to the red cells is mild, and if the supply of iron is adequate, the loss may be largely compensated; if more

TABLE 129-6 DISEASES AND CLINICAL SITUATIONS WITH PREDOMINANTLY INTRAVASCULAR HEMOLYSIS

	Onset/Time Course	Main Mechanism	Appropriate Diagnostic Procedure	Comments
Mismatched blood transfusion	Abrupt	Nearly always ABO incompatibility	Repeat cross-match	
Paroxysmal nocturnal hemoglobinuria (PNH)	Chronic with acute exacerbations	Complement (C)-mediated destruction of CD59(−) red cells	Flow cytometry to display a CD59(−) red cell population	Exacerbations due to C activation through any pathway
Paroxysmal cold hemoglobinuria (PCH)	Acute	Immune lysis of normal red cells	Test for Donath-Landsteiner antibody	Often triggered by viral infection
Septicemia	Very acute	Exotoxins produced by <i>Clostridium perfringens</i>	Blood cultures	Other organisms may be responsible
Microangiopathic	Acute or chronic	Red cell fragmentation	Red cell morphology on blood smear	Different causes ranging from endothelial damage to hemangioma to leaky prosthetic heart valve
March hemoglobinuria	Abrupt	Mechanical destruction	Targeted history taking	
Favism	Acute	Destruction of older fraction of G6PD-deficient red cells	G6PD assay	Triggered by ingestion of large dish of fava beans, but trigger can be infection or drug instead

Abbreviation: G6PD, glucose 6-phosphate dehydrogenase.