until the platelet count is normal and signs of hemolysis are resolved for at least 2 days. Although never evaluated in clinical trials, the use of glucocorticoids seems a reasonable approach, but should only be used as an adjunct to plasma exchange. Additionally, other immunomodulatory therapies have been reported to be successful in refractory or relapsing TTP, including rituximab, vincristine, cyclophosphamide, and splenectomy. A significant relapse rate is noted; 25–45% of patients relapse within 30 days of initial "remission," and 12–40% of patients have late relapses. Relapses are more frequent in patients with severe ADAMTS13 deficiency at presentation.

**Hemolytic-Uremic Syndrome** HUS is a syndrome characterized by acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. It is seen predominantly in children and in most cases is preceded by an episode of diarrhea, often hemorrhagic in nature. *Escherichia coli* O157:H7 is the most frequent, although not only, etiologic serotype. HUS not associated with diarrhea is more heterogeneous in presentation and course. Atypical HUS (aHUS) due to genetic defects that result in chronic complement activation has been defined, and screening for mutations in complement regulatory genes is available.

## TREATMENT HEMOLYTIC-UREMIC SYNDROME

Treatment of HUS is primarily supportive. In HUS associated with diarrhea, many (~40%) children require at least some period of support with dialysis; however, the overall mortality is <5%. In HUS not associated with diarrhea, the mortality is higher, approximately 26%. Plasma infusion or plasma exchange has not been shown to alter the overall course. ADAMTS13 levels are generally reported to be normal in HUS, although occasionally they have been reported to be decreased. In patients with atypical HUS, eculizumab therapy increases the platelet count and preserves renal function.

### THROMBOCYTOSIS

Thrombocytosis is almost always due to (1) iron deficiency; (2) inflammation, cancer, or infection (reactive thrombocytosis); or (3) an underlying myeloproliferative process (essential thrombocythemia or polycythemia vera) (Chap. 131) or, rarely, the 5q– myelodysplastic process (Chap. 130). Patients presenting with an elevated platelet count should be evaluated for underlying inflammation or malignancy, and iron deficiency should be ruled out. Thrombocytosis in response to acute or chronic inflammation has not been clearly associated with an increased thrombotic risk. In fact, patients with markedly elevated platelet counts (>1.5 million), usually seen in the setting of a myeloproliferative disorder, have an increased risk of bleeding. This appears to be due, at least in part, to acquired von Willebrand disease (VWD) due to platelet-VWF binding and removal from the circulation.

### QUALITATIVE DISORDERS OF PLATELET FUNCTION

**Inherited Disorders of Platelet Function** Inherited platelet function disorders are thought to be relatively rare, although the prevalence of mild disorders of platelet function is unclear, in part because our testing for such disorders is suboptimal. Rare qualitative disorders include the autosomal recessive disorders Glanzmann's thrombasthenia (absence of the platelet Gp IIb/IIIa receptor) and Bernard-Soulier syndrome (absence of the platelet Gp Ib-IX-V receptor). Both are inherited in an autosomal recessive fashion and present with bleeding symptoms in childhood.

Platelet storage pool disorder (SPD) is the classic autosomal dominant qualitative platelet disorder. This results from abnormalities of platelet granule formation. It is also seen as a part of inherited disorders of granule formation, such as Hermansky-Pudlak syndrome. Bleeding symptoms in SPD are variable, but often are mild. The most common inherited disorders of platelet function prevent normal secretion of granule content and are termed *secretion defects*. Few of these abnormalities have been dissected at the molecular level but they likely result from various mutations..

## TREATMENT INHERITED DISORDERS OF PLATELET DYSFUNCTION

Bleeding symptoms or prevention of bleeding in patients with severe platelet dysfunction frequently requires platelet transfusion. Care is taken to limit the risk of alloimmunization by limiting exposure, using HLA-matched leuko-depleted platelet concentrates for transfusion. Platelet disorders associated with milder bleeding symptoms frequently respond to desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]). DDAVP increases plasma VWF and factor VIII levels; it may also have a direct effect on platelet function. Particularly for mucosal bleeding symptoms, antifibrinolytic therapy (ε-aminocaproic acid or tranexamic acid) is used alone or in conjunction with DDAVP or platelet therapy.

**Acquired Disorders of Platelet Function** Acquired platelet dysfunction is common, usually due to medications, either intentionally as with antiplatelet therapy or unintentionally as with high-dose penicillins. Acquired platelet dysfunction occurs in uremia. This is likely multifactorial, but the resultant effect is defective adhesion and activation. The platelet defect is improved most by dialysis but may also be improved by increasing the hematocrit to 27–32%, giving DDAVP (0.3 μg/kg), or use of conjugated estrogens. Platelet dysfunction also occurs with cardiopulmonary bypass due to the effect of the artificial circuit on platelets, and bleeding symptoms respond to platelet transfusion. Platelet dysfunction seen with underlying hematologic disorders can result from nonspecific interference by circulating paraproteins or intrinsic platelet defects in myeloproliferative and myelodysplastic syndromes.

### VON WILLEBRAND DISEASE

VWD is the most common inherited bleeding disorder. Estimates from laboratory data suggest a prevalence of approximately 1%, but data based on symptomatic individuals suggest that it is closer to 0.1% of the population. VWF serves two roles: (1) as the major adhesion molecule that tethers the platelet to the exposed subendothelium; and (2) as the binding protein for factor VIII (FVIII), resulting in significant prolongation of the FVIII half-life in circulation. The platelet-adhesive function of VWF is critically dependent on the presence of large VWF multimers, whereas FVIII binding is not. Most of the symptoms of VWD are "platelet-like" except in more severe VWD when the FVIII is low enough to produce symptoms similar to those found in FVIII deficiency (hemophilia A).

VWD has been classified into three major types, with four subtypes of type 2 (Table 140-2; Fig. 140-5). By far the most common type of VWD is type 1 disease, with a parallel decrease in VWF protein, VWF function, and FVIII levels, accounting for at least 80% of cases. Patients have predominantly mucosal bleeding symptoms, although postoperative bleeding can also be seen. Bleeding symptoms are very uncommon in infancy and usually manifest later in childhood with excessive bruising and epistaxis. Because these symptoms occur commonly in childhood, the clinician should particularly note bruising at sites unlikely to be traumatized and/or prolonged epistaxis requiring medical attention. Menorrhagia is a common manifestation of VWD. Menstrual bleeding resulting in anemia should warrant an evaluation for VWD and, if negative, functional platelet disorders. Frequently, mild type 1 VWD first manifests with dental extractions, particularly wisdom tooth extraction, or tonsillectomy.

Not all patients with low VWF levels have bleeding symptoms. Whether patients bleed or not will depend on the overall hemostatic balance they have inherited, along with environmental influences and the type of hemostatic challenges they experience. Although the inheritance of VWD is autosomal, many factors modulate both VWF levels and bleeding symptoms. These have not all been defined, but include blood type, thyroid hormone status, race, stress, exercise, and hormonal (both endogenous and exogenous) influences. Patients with type O blood have VWF protein levels of approximately one-half that of patients with AB blood type; and, in fact, the normal range for