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Approach to the patient with bleeding begins with a thorough bleeding, medical, and family history to determine the nature of bleeding and severity of bleeding symptoms. Use of a Bleeding Assessment Tool allows the clinician to obtain a comprehensive bleeding history and ultimately determine the individual bleeding score that reflects bleeding severity and is classifiable as either normal or abnormal. In the absence of significant findings within patient history or presenting symptoms clearly pointing to a specific bleeding pathology, an approach to laboratory investigation is presented that proceeds through first-line, second-line, and third-line testing.	
<b>Laboratory Methods in the Assessment of Hereditary Hemostatic Disorders</b>	<b>1051</b>
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In patients presenting with a suspect hereditary bleeding disorder a detailed bleeding history is first obtained. Testing proceeds in a tiered manner with platelet count, platelet morphology, platelet histogram, PFA-100, fibrinogen, prothrombin time, and activated partial thromboplastin time. More detailed testing includes von Willebrand factor, individual clotting factor assays, and platelet function testing. Next, testing for a dysfibrinogenemia, FXIII, or a fibrinolytic defect is considered. Hemostatic abnormality is not demonstrated in a fraction of patients. An approach to management in these patients, such as desmopressin or antifibrinolytic therapy, may be required and empiric use of blood component therapy is discouraged.	
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Bleeding disorders due to platelet dysfunction are a common hematologic complication affecting patients, and typically present with mucocutaneous bleeding or hemorrhage. An inherited platelet disorder should be suspected in individuals with a suggestive family history and no identified secondary causes of bleeding. Genetic defects have been described at all levels of platelet activation, including receptor binding, signaling, granule release, cytoskeletal remodeling, and platelet hematopoiesis. Management of these disorders is typically supportive, with an emphasis on awareness, patient education, and anticipatory guidance to prevent future episodes of bleeding.	

**Von Willebrand Disease****Von Willebrand Disease: Current Status of Diagnosis and Management 1085**

Angela C. Weyand and Veronica H. Flood

Von Willebrand disease (VWD) is a common bleeding disorder, affecting male and female individuals equally, that often manifests in mucosal bleeding. VWD can be secondary to a quantitative (Type 1 and Type 3) or qualitative (Type 2) defects in Von Willebrand factor (VWF). Initial testing includes VWF antigen, as well as a platelet binding assay to differentiate between qualitative and quantitative defects. Further subtyping requires additional testing and is needed to ensure appropriate treatment. Desmopressin, antifibrinolytics, hormonal treatments for heavy menstrual bleeding, and VWF concentrates are commonly used in the treatment of VWD.

**Acquired von Willebrand Syndrome 1103**

Arielle L. Langer and Nathan T. Connell

Acquired von Willebrand syndrome can occur in the setting of myeloproliferative neoplasms; plasma cell dyscrasias and other lymphoproliferative disorders; autoimmune conditions; and causes of increased shear forces, such as aortic stenosis or other structural heart disease and mechanical circulatory support. The depletion of von Willebrand factor, especially high-molecular-weight multimers, can lead to mucocutaneous bleeding and the formation of arteriovenous malformations, particularly in the gastrointestinal tract. Management focuses on correction of the underlying cause when possible, but may include intravenous immunoglobulins, von Willebrand factor concentrate, rituximab, or antiangiogenic therapy depending on the clinical context.

**Secondary Hemostasis and Fibrinolysis****Hemophilia A (Factor VIII Deficiency) 1117**

Craig D. Seaman, Frederico Xavier, and Margaret V. Ragni

Remarkable changes are occurring in the diagnosis and management of individuals with hemophilia A. Genetic testing, including next-generation sequencing, enables family planning, carrier testing, and prenatal diagnosis. Musculoskeletal ultrasound examination facilitates the early detection of acute bleeds and joint disease in clinic, enabling more rapid bleed resolution and treatment planning. Novel therapies offer simpler weekly or monthly administration, some by subcutaneous injection, with better compliance and quality of life, as well as fewer bleeds. Gene therapy provides a 1-time phenotypic "cure" that is cost effective, but may be complicated by waning levels, vector immune responses, and hepatotoxicity.

**Acquired Hemophilia A 1131**

Menaka Pai

Acquired hemophilia A is a potentially severe bleeding disorder caused by antibodies against the patient's own factor VIII. Acquired hemophilia A is rare. It is most commonly diagnosed in older individuals; about one-half

of cases of acquired hemophilia are associated with underlying conditions, including autoimmune disease, cancer, and pregnancy. The diagnosis of acquired hemophilia A can be suspect with an isolated activated partial thromboplastin time elevation, and confirmed with demonstration of reduced factor VIII activity and the presence of a specific factor VIII inhibitor. Treatment of acquired hemophilia A involves control of bleeding, and eradication of the inhibitor.

### **Hemophilia B (Factor IX Deficiency)**

1143

Robert F. Sidonio Jr and Lynn Malec

The biology of factor IX deficiency leading to hemophilia B has important distinctions from factor VIII deficiency that leads to hemophilia A. In this article, the authors explore the unique biology of factor IX in hemostasis, including the importance of FIX distribution to the extravascular space and the implications on dosing of factor concentrates. The authors review basic treatment principles of hemophilia B, including extended half-life products, and highlight areas of ongoing therapeutic innovation for hemophilia B prophylaxis.

### **Factor XI Deficiency**

1157

Magdalena Dorota Lewandowska and Jean Marie Connors

Factor XI (FXI) deficiency (hemophilia C or Rosenthal disease) was first described in the 1950s in a multigenerational family experiencing bleeding related to surgery and dental procedures. Managing patients with FXI deficiency presents several challenges, including a lack of correlation of bleeding symptoms with FXI activity levels, the large volume of fresh frozen plasma required to achieve hemostatic FXI levels, lack of availability of FXI concentrate in certain regions of the world, and the inherent thrombotic risk associated with replacement therapy. This article summarizes presentation, diagnosis, and management of patients with FXI deficiency in a variety of clinical settings.

### **Factor XIII Deficiency: A Review of Clinical Presentation and Management**

1171

Ari Pelcovits, Fred Schiffman, and Rabin Niroula

Factor XIII (FXIII) deficiency is a rare autosomal recessive disorder that can result in life-threatening bleeding and early fetal loss. FXIII not only is responsible for cross-linking fibrinogen to stabilize and strengthen clot formation but also facilitates wound healing and angiogenesis and plays an important role in fetal vitality. Modern therapeutics allow for prophylactic treatment that can prevent most major bleeding and increasing fetal viability. Early diagnosis is paramount due to the high risk of intracranial bleeding.

### **Rare Coagulation Factor Deficiencies (Factors VII, X, V, and II)**

1181

Glaivy Batsuli and Peter Kouides

Although rare clotting factor deficiencies primarily referred to as rare bleeding disorders (RBD), including factors II, V, VII, and X, make up ~5% of all inherited bleeding disorders worldwide, each of these clotting

factors play a critical role in the coagulation cascade. Incomplete bleeding evaluation or misinterpretation of laboratory studies can result in delayed diagnoses that ultimately affect patient outcomes. Bleeding manifestations can range from mild to severe, but the most common are mucocutaneous bleeding. The ideal treatment in RBD is dedicated single-factor concentrates that can be used for acute bleeding events, surgical management, and prophylaxis.

**Disorders of Fibrinogen and Fibrinolysis**

**1197**

Jori E. May, Alisa S. Wolberg, and Ming Yeong Lim

Fibrinogen plays a fundamental role in coagulation through its support for platelet aggregation and its conversion to fibrin. Fibrin stabilizes clots and serves as a scaffold and immune effector before being broken down by the fibrinolytic system. Given its importance, abnormalities in fibrin(ogen) and fibrinolysis result in a variety of disorders with hemorrhagic and thrombotic manifestations. This review summarizes (i) the basic elements of fibrin(ogen) and its role in coagulation and the fibrinolytic system; (ii) the laboratory evaluation for fibrin(ogen) disorders, including the use of global fibrinolysis assays; and (iii) the management of congenital and acquired disorders of fibrinogen and fibrinolysis.