Bleeding Diatheses

Approach to the Patient Who Bleeds or Has Abnormal Coagulation

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KEYWORDS

• Bleeding disorders • Coagulation • von Willebrand disease • Hemophilia
• Platelet defects

KEY POINTS

- Abnormal bleeding is commonly first encountered in the primary care office and may be due to medication or an underlying bleeding disorder.
- A thorough bleeding history and interpretation of basic laboratory tests, such as complete blood count, prothrombin time, and activated partial thromboplastin time can help elucidate the cause of bleeding.
- Common medications, such as aspirin, vitamin K antagonists (warfarin), or oral anticoagulants, can cause bleeding and can cause abnormal coagulation studies.
- Inherited bleeding conditions, including von Willebrand disease, hemophilia, or platelet disorders, often can be diagnosed in the primary care setting, although diagnosis of a bleeding disorder should prompt referral to a hematologist.

ESTABLISHING A DIAGNOSIS

Understanding bleeding diatheses requires a basic understanding of normal hemostasis and coagulation. Under normal conditions, the free flow of blood is maintained within an intact vascular system by multiple safeguards, including the endothelial lining, which produces anticoagulant factors, such as nitric oxide and prostacyclin, and obscures procoagulant factors, such as tissue factor (TF).[1] However, when there is a hemostatic challenge, as after injury, a complex cascade of coagulation is initiated to prevent excessive blood loss. Various alterations to this system, whether by genetic mutation or taking medication, may prevent normal hemostasis and is discussed in this article.

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Overview of Hemostasis and Coagulation Studies

Primary hemostasis consists initially of platelet adhesion to TF, collagen, von Willebrand factor (vWF), and fibronectin on the subendothelial matrix that becomes exposed during injury or endothelial damage. After this initial contact, the platelets become activated resulting in increased expression of surface proteins and release of granules that contain factors to further enhance coagulation. The platelets then aggregate with each other through binding of fibrinogen with glycoprotein IIb-IIIa to form a platelet plug.[2] Secondary hemostasis refers to the role of the clotting cascade in generating thrombin, which also activates fibrinogen to fibrin and further supports the initial platelet plug. Finally, the newly formed fibrin mesh is cross-linked by factor XIIIa to form a thrombus.

The clotting cascade is divided into the extrinsic, intrinsic, and common pathways (**Fig. 1**). The extrinsic pathway (also known as the TF pathway) is initiated by the binding of TF by factor VII, which generates the prothrombinase complex, composed of the common pathway components factor Xa, factor Va, calcium, and phospholipids. The prothrombinase complex activates prothrombin to thrombin, which in turn converts fibrinogen to fibrin, as discussed previously. The extrinsic pathway is thought to be the primary method of activating the clotting cascade in vivo and is critical for normal hemostasis.[3] This pathway is measured through the prothrombin time (PT) test (**Table 1**).

The intrinsic pathway (so named because in a test tube it does not require the addition of TF to initiate this pathway) is composed of factors XII, XI, IX, and VIII, which generate the prothrombinase complex, as described previously. The intrinsic pathway is initiated in vitro by interaction with a negatively charged surface, such as silica or kaolin, and is measured through the activated partial thromboplastin time (aPTT). In vivo, this process is initiated by the extrinsic pathway, but may also be activated by artificial surfaces and chains of inorganic polyphosphates released from platelet granules on activation.[4]

Thrombin is the key point in the clotting cascade where the pathways converge, and it plays an important role in coagulation, not just through activating fibrinogen and platelets but is also a primary site of regulation of coagulation. Thrombin in part serves as its own regulator through a negative feedback loop initiated by activating protein C, protein S, and antithrombin, which are natural anticoagulants and serve as inhibitors of the clotting cascade (see **Fig. 1**).

Taking a Bleeding History and Physical Examination

When a patient presents for an evaluation of abnormal bleeding, a thorough history is an essential first step. The physician must assess whether the amount of bleeding the patient experiences is truly abnormal. This can be difficult, and formalized approaches have been developed, including bleeding tools. However, multiple studies have shown that it can be difficult to assess severity of bleeding by questionnaire. Several tools, such as the Vincenza bleeding score, ISTH-BAT (International Society on Thrombosis and Hemostasis Bleeding Assessment Tool), or the MCMDM (Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD Bleeding Questionnaire) have been developed to help take an accurate and reproducible bleeding history; however, they have been robustly validated only in von Willebrand disease (vWD).[5–7] In a study of 500 healthy individuals conducted by a trained physician or nurse practitioner, nearly three-quarters of respondents reported bleeding symptoms, including 25% of respondents reporting epistaxis, 18% reporting easy bruising, and 47% of women reporting heavy menses.[8] In children, the frequency of reporting bleeding symptoms may be even higher.[9]