Fast Facts: Bleeding Disorders

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This book is as balanced and as practical as we can make it. Ideas for improvements are always welcome: feedback@fastfacts.com
Glossary of abbreviations

ADAMTS-13: a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13
ADP: adenosine diphosphate
APTT: activated partial thromboplastin time
cAMP: cyclic adenosine monophosphate
cGMP: cyclic guanosine monophosphate
CNS: central nervous system
DIC: disseminated intravascular coagulation
EACA: ε-aminocaproic acid
EDTA: ethylenediamine tetra-acetic acid
FDP: fibrin degradation product
Gp: glycoprotein
HELLP: hemolytic anemia with elevated liver enzymes and low platelet count
HHT: hereditary hemorrhagic telangiectasia
HIT: heparin-induced thrombocytopenia
HIV: human immunodeficiency virus
HLA: human leukocyte antigen
HUS: hemolytic uremic syndrome
ICAM: intercellular adhesion molecule
Ig: immunoglobulin
IL: interleukin
INR: international normalized ratio
ITP: immune thrombocytopenic purpura
LDH: lactic dehydrogenase
LMWH: low molecular weight heparin
MW: molecular weight
NAIT: neonatal alloimmune thrombocytopenia
NSAID: non-steroidal anti-inflammatory drug
PAI: plasminogen activator inhibitor
PFA: platelet function analyzer
PIH: pregnancy-induced hypertension
PT: prothrombin time
raPC: recombinant human activated protein C
TAFI: thrombin activatable fibrinolysis inhibitor
TF: tissue factor
TFPI: tissue factor pathway inhibitor
TGFβ: transforming growth factor β
TNFα: tumor necrosis factor α
tPA: tissue plasminogen activator
TTP: thrombotic thrombocytopenic purpura
VCAM: vascular cell adhesion molecule
vWD: von Willebrand’s disease
vWF: von Willebrand factor
Introduction

Bleeding disorders have had a major impact on world history, beginning with injunctions about practicing ritual circumcision in individuals with a family history of bleeding, to the spread of hemophilia throughout the royal families of Europe by the descendants of Queen Victoria. Bleeding has also been a major cause of mortality after trauma and has dogged surgical procedures. Hemorrhage may be overt or extremely subtle, and may occur unexpectedly in association with a variety of illnesses.

This book begins by describing normal hemostatic mechanisms and suggests how alterations in coagulation may be suspected from the clinical history and examination, and confirmed by laboratory testing. Many bleeding disorders are due to vascular anomalies and vasculitis, and hereditary hemorrhagic telangiectasia (HHT) and Henoch–Schönlein purpura, for example, are discussed in detail. Platelet function disturbances may also promote bleeding, and may be congenital or acquired secondary to exposure to aspirin and other platelet inhibitors used to prevent thrombosis. A simple algorithm is presented to aid the differential diagnosis of thrombocytopenia, and the appropriate use of platelet transfusions and other hemostatic agents is discussed.

The diagnosis and treatment of hemophilia, von Willebrand’s disease (vWD) and other inherited coagulopathies is outlined, and currently available therapeutic products described. Advice on the approach to bleeding that often complicates liver and kidney disorders, which may be multifactorial, is also presented. Bleeding disorders during pregnancy constitute a risk to mother and fetus, and must be recognized promptly and treated effectively. Perioperative bleeding is due to a failure of local hemostasis, or to a variety of systemic causes, including hemodilution, vitamin K deficiency and drugs. Disseminated intravascular coagulation (DIC) complicates acute sepsis, obstetric conditions and malignant disease, and requires accurate diagnosis and appropriate management. Finally, anticoagulants may be pathological proteins that arise in a patient and alter coagulation, or therapeutic agents that cause bleeding.
as an important adverse effect. A wide-ranging discussion of the management of hemorrhage associated with the most commonly used antithrombotic agents completes the text.

When a physician encounters a bleeding patient, diagnostic and therapeutic steps need to be taken rapidly. It is our hope that *Fast Facts – Bleeding Disorders*, prepared so that information about bleeding disorders is readily accessible, will improve patient management and outcomes.
In health, hemostasis ensures that the blood remains fluid and contained within the vasculature. If a vessel wall is damaged, a number of mechanisms are activated promptly to limit bleeding by a complex series of interrelated reactions involving endothelial cells, plasma coagulation factors, platelets and fibrinolytic proteins. The activities of these components are finely balanced between keeping the blood fluid and preventing excessive activation of the procoagulatory components leading to intravascular thrombosis.

It is helpful to consider the hemostatic process as three distinct phases.

- Primary hemostasis occurs after damage to the vessel wall, and involves vasoconstriction and adhesion of platelets in a monolayer on exposed subendothelial fibrils. Subsequently, further platelets aggregate to form a platelet plug, which stems the flow of blood.
- Secondary hemostasis involves activation of the coagulation system, leading to the generation of fibrin strands, which are laid down between platelets and reinforce the platelet plug.
- Fibrinolysis entails activation of fibrin-bound plasminogen, resulting in clot lysis. Lysis is modulated by inhibitors of fibrinolysis activated by thrombin or released by platelets.

In reality, these processes tend to merge, with the activated platelet and endothelial cell membranes providing the foundation on which the clotting factors can become activated, and fibrin formed and lysed.

**Endothelial cells**

Blood vessels are lined with endothelial cells, which promote hemostasis and keep the blood fluid by preventing excessive deposition of fibrin through the synthesis and secretion of various antithrombotic agents (Table 1.1). Endothelial cells also synthesize proteins that directly promote hemostasis. Von Willebrand factor (vWF) is synthesized by both endothelial cells and megakaryocytes (leading to its presence in platelet α-granules). When the endothelium is damaged, the
subendothelial vessel wall components are exposed, and vWF promotes adhesion of circulating platelets to the exposed microfibrils and collagen. Stimulation of the endothelium by thrombin, following activation of the coagulation cascade, or by cytokines, such as tumor necrosis factor α (TNFα), promotes the synthesis and expression of tissue factor (TF) on the cell surface. This complexes with circulating plasma coagulation factor VII to form TF–VIIa which initiates the coagulation cascade. Stimulated endothelial cells synthesize other
Coagulation screen. A coagulation screen involves measurement of activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen concentration. The APTT clotting test is initiated by activation of factor XII and is therefore prolonged when deficiencies of factors XII, XI, IX, VIII, X and V are present. It should be noted that factor XII deficiency is not associated with a predisposition to bleeding. The PT is performed by adding TF to plasma and is prolonged when levels of factors II, VII, X and V are low. These screening tests are insensitive to small reductions in the levels of clotting factors; therefore, if the clinical possibility of a mild bleeding disorder is high, the level of individual factors must be measured.

If the platelet count and morphology are normal, but a platelet function disorder is suspected, further investigation is necessary. Platelet aggregation can be measured in response to ADP, epinephrine and collagen, and the concentration of ADP in the platelet dense granules can be quantitated.
To determine the bleeding time, two standardized, superficial incisions of 0.5 cm in length and 1 mm in depth are made along the long axis of the forearm, below the antecubital crease. To stress the hemostatic mechanism, venous pressure is increased using a sphygmomanometer cuff on the upper arm inflated to 40 mmHg. The incisions are dabbed with filter paper every 30 seconds and the time taken until bleeding stops is measured; the normal time is less than 8 minutes.

Key points – assessment of bleeding symptoms

- A full and detailed history of personal and family bleeding symptoms often indicates the nature and severity of a potential bleeding diathesis.
- All current and recent drugs should be reviewed as possible causes of a bleeding state.
- Specific inquiry should be made about oral anticoagulant or other antithrombotic therapy (e.g. aspirin).
- Defects of primary hemostasis (i.e. platelet disorders and von Willebrand's disease) present with mucosal bleeding (e.g. epistaxis, gastrointestinal hemorrhage and menorrhagia).
- Defects of secondary hemostasis (i.e. coagulation disorders such as hemophilia) usually present with hemarthroses and muscle hematoma.