

Fast Facts



Fast Facts: Bleeding Disorders

David Green and Christopher A Ludlam





***Indispensable
Guides to
Clinical
Practice***

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



Fast Facts – Bleeding Disorders

First published July 2004

Text © 2004 David Green, Christopher A Ludlam

© 2004 in this edition Health Press Limited

Health Press Limited, Elizabeth House, Queen Street, Abingdon,
Oxford OX14 3JR, UK

Tel: +44 (0)1235 523233

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Book orders can be placed by telephone or via the website.

For regional distributors or to order via the website, please go to:
www.fastfacts.com

For telephone orders, please call 01752 202301 (UK) or
800 538 1287 (North America, toll free).

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A CIP catalogue record for this title is available from the British Library.

ISBN 1-903734-61-4

Green, D (David)

Fast Facts – Bleeding Disorders/

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Medical illustrations by Dee McLean, London, UK.

Typesetting and page layout by Zed, Oxford, UK.

Printed by Fine Print (Services) Ltd, Oxford, UK.

Printed with vegetable inks on fully biodegradable and
recyclable paper manufactured from sustainable forests.



Low chlorine



Sustainable forests

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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

TGF β : transforming growth factor β

TNF α : 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

TABLE 1.1

Role of endothelial cells in hemostasis

Factors in endothelial cells	Activity
<i>Procoagulant (prothrombotic)</i>	
Tissue factor	Initiates coagulation cascade
von Willebrand factor	Promotes adhesion of platelets
Factors V and VIII	Essential cofactors for coagulation
Plasminogen activator inhibitor-1	Inhibits fibrinolysis
Cytokines (e.g. interleukin-6)	Proinflammatory
Cellular adhesion molecules (e.g. intercellular adhesion molecule, vascular cell adhesion molecule)	Promotes adhesion of neutrophils
<i>Anticoagulant (antithrombotic)</i>	
Tissue factor pathway inhibitor	Inhibits initiation of coagulation
Prostacyclin	Platelet inhibitor and vasodilator
Nitric oxide	Platelet inhibitor and vasodilator
Endothelin-1	Platelet inhibitor and vasoconstrictor
Thrombomodulin and protein C receptor	Redirects thrombin activity towards activating protein C/S anticoagulant system
Tissue plasminogen activator	Promotes fibrinolysis
Heparan sulfate	Binds and enhances the activity of antithrombin

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 (TNF α), 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

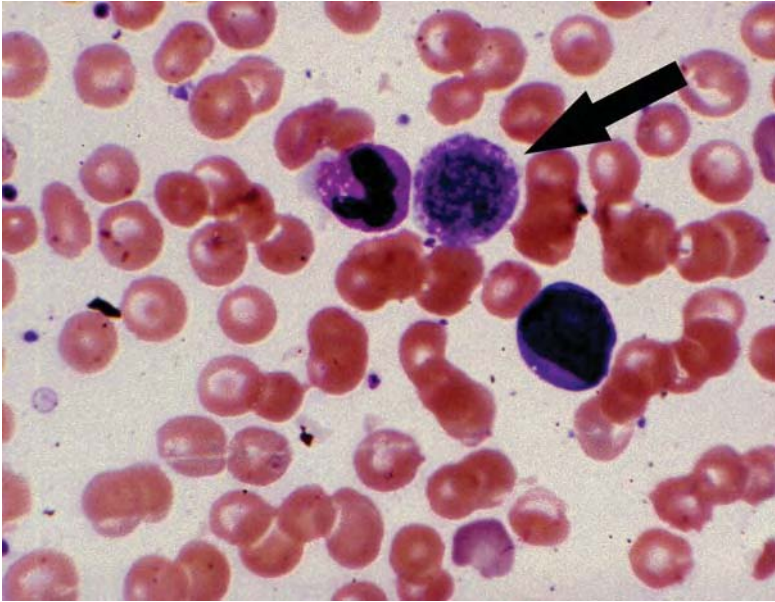


Figure 2.2 Peripheral blood smear showing May-Hegglin disorder with giant platelets and a Döhle body in a leukocyte (arrow). (Wright's stain $\times 400$.)

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.



Figure 2.3 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.