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John Bartholomew
Editors

The Coagulation Consult

A Case-Based Guide

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For J. Leon and Beverly Lichtin

—Alan Lichtin

For Kathleen Bartholomew

—John Bartholomew

Preface

The reader might ask, "Why does the world need another coagulation textbook?" In this time of instant access to medical information on the Internet, indeed, one might ask what is the worth of any textbook, with its inherent publication delay.

Many texts in the field of coagulation lean toward an emphasis on basic science. This text does not do that. The goal of this book is to describe clinical scenarios for which the practicing hematologist or vascular medicine expert (either vascular medicine doctor or vascular surgeon) is consulted for bleeding or clotting issue.

Many of us are very comfortable dealing with the spectrum of bleeding and clotting disorders, and yet, these days, many of us feel more comfortable dealing with one or the other. In fact, at many institutions, there are separate departments of hematology (often overly weighted to the malignant hematology side) and vascular medicine/vascular surgery. The bleeding patients tend to be seen by the hematologists, and the thrombotic patients are more frequently evaluated and treated by the vascular medicine doctors.

There are several disorders that present challenges such that both teams are called to the bedside, and cooperation between these two services leads to the best results. This is especially true for the heparin-associated thrombocytopenia (HIT) patients, who do not recover their platelet counts as one might expect. They may remain on a direct thrombin inhibitor, and day after day, the platelets remain frustratingly low. The vascular medicine doctors will call the hematologists to make sure that there is not some other reason for the thrombocytopenia. Likewise, the severely affected antiphospholipid patient may present with thrombocytopenia and be seen by the hematologists first, and the thrombotic aspect of the disorder will be of more paramount importance, and the hematologist may call the vascular medicine colleague to help. Another common scenario where one service calls the other is when there is a patient with a thrombosis in an unusual location and is first seen by the vascular medicine doctor and work-up suggests a primary hematologic reason for the thrombosis, such as a myeloproliferative disorder or paroxysmal nocturnal hemoglobinuria. That is when the hematologist might be called.

This book is divided into chapters whose titles are the typical reasons we are consulted to see patients. Our non-hematologic colleagues will call us for a patient with a prolonged PT, a prolonged PTT, bleeding with surgery, easy bruising, etc. The reader should look over the chapter headings and realize

that many of the reasons we are consulted are listed there. Also, chapters are devoted to special categories of patients, such as the patient with postoperative bleeding, the patient with thrombosis around catheters, the individual with heparin-induced thrombocytopenia, and the pregnant woman.

We wish to acknowledge many individuals who have made this text possible. The team of editors at Springer, especially Michael Wilt, have been most helpful. The photography in the chapter on Easy Bruising was made possible by Janine Sot. This book obviously could not have been written without the help of our authors, and we appreciate their efforts. Also, we have been blessed to have an exceptional secretary, Marge Dvorsack, to prepare the manuscripts for the publisher. She has done a phenomenal job.

Cleveland, OH

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Laboratory Analysis of Coagulation

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List of Abbreviations

AA	Arachidonic acid
ACA	Anticardiolipin antibody
ADP	Adenosine diphosphate
APA	Antiphospholipid antibody
APC	Activated protein C
APC-R	APC resistance
APS	Antiphospholipid syndrome
aPTT	Activated partial thromboplastin time
AR	Autosomal recessive
AS	Allele-specific
ASA	Aspirin (acetyl salicylic acid)
AT	Antithrombin
ATP	Adenosine triphosphate
B2GPI	Beta2 glycoprotein 1
BT	Bleeding time
BU	Bethesda unit
C4bBP	C4b-binding protein
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments
COX1	Cyclooxygenase 1
CT	Closure time
DIC	Disseminated intravascular coagulation
DRVVT	Dilute Russell's viper venom test
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
ELISA	Enzyme-linked immunosorbent assay
ELT	Euglobulin lysis time
EM	Electron microscopy
ET	Essential thrombocythemia
FDP	Fibrin degradation product
FII	Prothrombin
FIIa	Thrombin
FVIIa	Activated factor VII
FVIII	Factor VIII
FVL	Factor V Leiden
FRET	Fluorescence resonance energy transfer
GP	Glycoprotein
HMWK	High-molecular-weight kininogen
INR	International normalized ratio
ISI	International sensitivity index
ISTH	International Society for Thrombosis and Haemostasis
LA	Lupus anticoagulant
LMW	Low molecular weight
MPN	Myeloproliferative neoplasms
MPV	Mean platelet volume

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MTHFR	Methylenetetrahydrofolate reductase
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAI	Plasminogen activator inhibitor
PCR	Polymerase chain reaction
PDW	Platelet distribution width
PE	Pulmonary embolism
PFA	Platelet function analyzer
PK	Prekallikrein
PRP	Platelet rich plasma
PT	Prothrombin time
RFLP	Restriction fragment length polymorphism
RIPA	Ristocetin-induced platelet aggregation
RT	Reptilase time
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
TAFI	Thrombin-activatable fibrinolysis inhibitor
TAR	Thrombocytopenia with absent radii
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TM	Thrombomodulin
tPA	Tissue plasminogen activator
TT	Thrombin time
TxA_2	Thromboxane A_2
uPA	Urokinase plasminogen activators
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	von Willebrand factor
XR	X-linked recessive

Introduction of Hemostasis and Thrombosis

The goal of physiologic hemostasis is to stop any bleeding that occurs and, ultimately, to return the vessel wall back to its original state. This is achieved through a dynamic interaction of pro- and anticoagulant elements. Early studies of hemostasis focused primarily on the process of clot formation. Originally described as a coagulation "cascade," the model for in vivo hemostasis subsequently evolved to incorporate the more complex contributions of elements beyond the traditional coagulation factors (Roberts et al. 1998; Hoffman and Monroe 2001; Schmaier and Miller 2011). Although it is now well established that the classic coagulation cascade does not accurately depict in vivo events, it remains particularly relevant with regard to understanding the in vitro process of hemostasis reflected by widely used coagulation screening tests such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT).

Physiology of Hemostasis

Following an insult to the vascular wall, hemostasis is initiated by platelet adhesion at the site of injury. This is followed by platelet aggregation and degranulation, with release of multiple mediators and procoagulant factors by the activated platelets. At the same time, tissue factor expressed at the site of injury initiates serial activation of coagulation factors. These events culminate in the formation of a fibrin thrombus which incorporates the activated platelets into its structure. In order to prevent the clot from growing uncontrollably, antithrombotic mechanisms are activated to maintain the balance of pro- and anticoagulant processes. Clot remodeling by fibrinolysis occurs over time, while cellular elements move in to repair the underlying tissue damage. The remainder of the clot is eventually eliminated and vascular patency and integrity restored. Thrombin plays a key role in virtually every step of the hemostatic process. Derangements of one or more pro- or anticoagulant elements of hemostasis may result in an increased risk of bleeding, an increased risk of clotting, or, rarely, both.

Initiation of Hemostasis by Platelet Plug Formation

The role of platelets in hemostasis and laboratory evaluation of platelet function are discussed in section of this chapter.

Initiation and Propagation of Clotting Through Activation of Coagulation Factors

Clotting factors are proenzymes or inactive precursor proteins (zymogens), enzyme cofactors, and substrates that are sequentially activated to form a fibrin clot. All of these factors are made