Essential Guide
to Blood Coagulation
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2nd Edition

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The Swedish edition of this book, *Coagulation News*, has existed for many years. The English edition has been largely rewritten to include additional medical topics and recent developments in the field.

*Essential Guide to Blood Coagulation* is a practical guide to laboratory diagnosis and treatment of hemostatic disorders. The book covers both the stable and the acute stages of hereditary and acquired bleeding and thrombotic disorders. This edition includes a much revised chapter on new anticoagulants and a new chapter on antiplatelet drugs.

The book has been edited in cooperation with physicians now or previously employed at the Karolinska University Hospital and by doctors working at Danderyd Hospital and Södersjukhuset, Stockholm, Sweden.

*Essential Guide to Blood Coagulation* will appeal to interns, hematologists, anesthesiologists, cardiologists, neurologists, pediatricians, laboratory doctors, gynecologists, surgeons, primary care physicians, dentists, and students. It can also be used by nurses, hospital chemists, biomedical technicians, and midwives.

Jovan P. Antovic, Margareta Blombäck
Abbreviations

ACoTS  Acute coagulopathy of trauma and shock
ACS   Acute coronary syndrome
ACT   Activated clotting time
ADH   Antidiuretic hormone
ADP   Adenosine diphosphate
AFLP  Acute fatty liver of pregnancy
APC   Activated protein C
APT   Activated partial thromboplastin
ASA   Acetylsalicylic acid
AUC   Area under the concentration curve
AVK   Anti-vitamin K drugs
BMI   Body mass index
CABG  Coronary artery by-pass grafting
CAD   Coronary artery disease
CRP   C-reactive protein
CT    Computed tomography
DES   Drug-eluting stent
DIC   Disseminated intravascular coagulation
DVT   Deep venous thrombosis
ECT   Ecarin clotting time
EDA   Epidural anesthesia
EDTA  Ethylene-diamine-tetra-acetic acid
eGFR  Estimated glomerular filtration rate
ET    Essential thrombocytosis
ETP   Emergency trauma packages
HELLP Hemolysis, elevated liver enzymes, low platelet counts
HIT   Heparin-induced thrombocytopenia
HRT   Hormone replacement therapy
HUS   Hemolytic uremic syndrome
INR   International normalized ratio
ISI   International sensitivity index
ITP   Idiopathic thrombocytopenic purpura
Abbreviations

IUFD Intrauterine fetal death
IV Intravenous
LA Lupus anticoagulant
LDA Low-dose aspirin
LMH Low molecular weight heparin
MOF Multiple organ failure
MPHV Mechanical prosthetic heart valve
MRA Magnetic resonance angiography
MRI Magnetic resonance imaging
NOAC New oral anticoagulant drug
NSAID Nonsteroidal anti-inflammatory drug
NSTEMI Non ST-elevation myocardial infarction
OC Oral contraceptives
PAI-1 Plasminogen activator inhibitor
PCC Prothrombin-complex concentrate
PCI Percutaneous coronary intervention
PCR Polymerase chain reaction
PE Pulmonary embolism
POCT Point-of-care test
PT Prothrombin time
PTA Percutaneous transluminal angioplasty
PVT Portal vein thrombosis
rt-PA Recombinant tissue plasminogen activator
SC Subcutaneous
SLE Systemic lupus erythematosus
SSRI Selective serotonin re-uptake inhibitor
STEMI ST-elevation myocardial infarction
TAFI Thrombin activatable fibrinolysis inhibitor
TAR Thrombocytopenia with absent radius
TAT Thrombin-antithrombin
TDM Therapeutic drug monitoring
TF Tissue factor
TFPI Tissue factor pathway inhibitor
TIA Transient ischemic attack
TM Thrombomodulin
t-PA Tissue plasminogen activator
TSH Thyroid-stimulating hormone
TTP Thrombotic thrombocytopenic purpura
UFH Unfractionated heparin
VKA Vitamin-K antagonist
VTE Venous thromboembolism
VWD von Willebrand disease
VWF von Willebrand factor
The formation of fibrin via a series of reactions within the coagulation system is central in the hemostatic process (Figure 1.1). Coagulation is initiated in vivo mainly through exposure of tissue factor, TF, on damaged tissue or endothelium. Activated monocytes can also expose TF. TF binds FVII/VIIa (a = activated). The TF-FVIIa complex initiates coagulation by activating FIX and FX. The activated FX transforms prothrombin into thrombin. The process continues, mainly as surface-bound enzymatic reactions, where activated platelets probably offer the phospholipid surface to which coagulation factors (enzymes as well as co-factors) can bind, for example by means of Ca²⁺ bridges. Moreover, the coagulation inhibitors (antithrombin, activated protein C (APC)) quickly react with non-surface connected enzymes and co-factors, which help to limit the spread of fibrin formation. Thrombin cleaves off fibrinopeptides A and B to form fibrin monomers, which then polymerize and cross-link, by the action of FXIII, to form an insoluble fibrin network.

The formation of thrombin is accelerated initially by a positive feedback, whereby the thrombin activates FVIII and FV in order to produce more thrombin. Thrombin also promotes coagulation by activating platelets and endothelium.

The physiological importance of the contact activation system for blood coagulation is partly unclear. It has been suggested that when the FXII initiated coagulation is activated in vivo it could lead to excessive fibrin formation resulting in thromboembolic manifestations.

The thrombin specificity is modified by its binding to the endothelial receptor thrombomodulin (TM). The TM–thrombin complexes then
Figure 1.1 Cell and tissue injury.
activate protein C into APC, which then decomposes FVIIIa and FVα. Consequently, thrombin is involved both in the *stimulation and inhibition* of the hemostatic process.

A model for cell-associated blood coagulation has also been proposed where the reaction sequence has been divided into three stages:

1. **The initiation phase** where a small amount of thrombin is generated via the TF-induced pathway to activate platelets and coagulation co-factors FV and FVIII to their activated forms.

2. **The priming phase (amplification phase)** where coagulation factors bind to receptors and phosphatidylserine-enriched surfaces such as activated platelets.

3. **The propagation phase** where thrombin is formed via both the contact and TF pathways in order to generate large amounts of thrombin that will transform fibrinogen to fibrin.

Antithrombin and APC are the most important coagulation inhibitors. Another is tissue factor pathway inhibitor (TFPI) but its physiological role is not yet entirely clear. Antithrombin inhibits thrombin by irreversible complex binding, thrombin-antithrombin (TAT) complexes. In a similar way, antithrombin also inhibits most of the activated coagulation factors, except for FVIIa, with different affinities. Heparin accelerates the reaction about 500 times.

It has recently been discovered that thrombin also has antifibrinolytic effects. It activates thrombin activatable fibrinolysis inhibitor (TAFI) to its active form, thereby inhibiting fibrinolysis.

The activation of fibrinolysis is probably secondary to the activation of coagulation. Tissue plasminogen activator (t-PA) is released from the endothelium and transforms plasminogen into plasmin. The reaction is substantially accelerated by the presence of fibrin, and plasmin formation normally occurs only locally on and in a fibrin clot. Plasmin breaks down fibrin and fibrinogen into a number of fragments, fibrin(ogen) degradation products, for example X, Y, D and E fragments, and cross-linked fibrin fragments, fibrin D-dimers. t-PA is inhibited by the release of plasminogen activator inhibitor (PAI-1) from the endothelium. Free plasmin, not bound to fibrin, is rapidly inhibited by the plasmin inhibitor. Plasmin inhibitor and plasmin form an enzymatically inactive complex.
Proposals for sampling instructions
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Points to note prior to sampling

The concentrations of components of the hemostatic system often vary with the patient’s condition, for example infection, emotional stress, physical exertion (e.g. rush to keep an appointment), lipid concentration in plasma, etc. Sampling conditions should be standardized as far as possible to minimize sources of error (see [1] and following).

• **Sitting up/lying down.** Due to changes in hydrostatic pressure, the concentrations of high molecular proteins and blood cells vary according to whether the patient is sitting up or lying down (hematocrit is as much as 15% higher when sitting up). A new balance is reached fairly quickly (after 15–20 min).

• **Diurnal variations** occur for several factors such as PAI-1, which peaks late at night.

• **Acute phase reactants.** Many hemostatic components, such as FVIII, von Willebrand Factor (VWF), PAI-1 and fibrinogen, are acute phase reactants (i.e. increased by inflammation, infection, surgery, etc.).

• **Intraindividual variations** occur mainly for FVIII and VWF but also for FVII. Thus, mental stress and physical activity increase the concentrations of FVIII and VWF many times over.

• **Smoking and age** affect the levels of several coagulation factors (e.g. VWF and fibrinogen are increased).

• **Estrogen.** High-dose contraceptives (and other hormone drugs) also affect coagulation and fibrinolysis (e.g. FVIII, VWF and fibrinogen are